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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 31, 1996

FROM: Thomas P. Laughren, M.D. TPL
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Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for Paxil (paroxetine) for Panic Disorder (PD)

TO: File NDA 20-031/S-009
[Note: This overview should be filed with the 3-29-95 original submission.]

1.0 BACKGROUND

Paxil (paroxetine) is a selective serotonin reuptake inhibitor (SSRI) that was approved for the treatment of depression in December, 1992 (NDA 20-031). Supplement S-009 includes data from clinical trials supporting the use of paroxetine in the treatment of panic disorder (PD), in a dose range of 40-60 mg/day [Note: The maximum recommended dose in currently approved labeling is 50 mg/day.].

Since the proposal is to use the currently marketed paroxetine formulations for this new indication, there was no need for substantial chemistry, pharmacology, or biopharmaceutics reviews of this supplement. Consequently, the focus was on clinical data. The safety and efficacy data were reviewed by James Knudsen, M.D. The efficacy data were also examined by Japo Choudhury, Ph.D. from the Division of Biometrics.

The original supplement for PD was submitted 3-29-95. The review was based on the original submission plus amendments containing responses to requests for additional information, including a 7-7-95 amendment providing data for extension study 222.

At the present time, Xanax (alprazolam), a triazolobenzodiazepine, is the only drug approved for the panic disorder indication in the US. However, a number of other drugs are believed to be effective and are widely used for the treatment of this indication, including other benzodiazepines, the tricyclic antidepressants, MAOIs (phenelzine in particular), and other SSRIs.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

Paxil is a marketed product, and there were no chemistry issues requiring review for this supplement.

3.0 PHARMACOLOGY

Paxil is a marketed product, and there were no pharmacology issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

Paxil is a marketed product, and there were no biopharmaceutics issues requiring review for this supplement.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Summary of Studies Pertinent to Efficacy

Our review of the effectiveness of Paxil in the treatment of PD focused on 4 short-term, placebo-controlled studies for which we had full study reports (i.e., 120, 108, 187, and 223). Data from double-blind extensions were available for 2 of these studies, i.e., extension 228 for Study 187 and extension 222 for Study 120.

Statistical Methods: I will make general comments here on the statistical methodology used in analyzing the data for these studies, rather than providing detailed comments on these methods in each of the sections that follow.

Dichotomous variables (proportions of patients achieving zero panic attacks or experiencing a reduction of $\geq$ 50% in panic attacks) were analyzed using nonparametric categorical approaches. For other measures (# panic attacks, MSPS subscales, SDS subscales, anticipatory anxiety measures, and CGI-Severity) change from baseline values were analyzed using ANOVA methods, unless the data appeared non-normally distrubuted, in which case, nonparametric methods were used.

The models included effects for treatment, investigator, and the interaction, however, interaction terms were dropped from the model if non-significant ($P > 0.10$). Investigator effect was not included in study 187. Analyses were not weighted by site.

All p-value data presented refer to 2-sided p-values. Alpha was set at 0.05, except for study 120, where Dunnet's test was used, and the criterion p-value was set at p , 0.019.

5.1.1.1 Study 120

This was a randomized, 20-center (US and Canada), double-blind, parallel group, 10 week, fixed-dose study comparing paroxetine at 3 fixed doses [10, 20, and 40 mg/day; titration up to the two higher dose groups by adding 10 mg/day at week 2 (for the 20 mg and 40 mg groups) and 20 mg/day at week 3 (for the 40 mg group); qd schedule] and placebo for the treatment of PD in adult outpatients meeting DSMIIIR criteria for PD. Patients were required to have at least 2 full panic attacks (i.e., ≥4 of the DSMIIIR criteria for a panic attack) in the 2 week period between screening and baseline. Patients could have sufficient depressive symptoms to meet criteria for major depressive disorder, providing the panic disorder symptoms were considered primary.

Patients completed a Panic Diary and an Anticipatory Anxiety Assessment (AAA) daily. Patients were rated at baseline and the ends of weeks 1, 2, 3, 4, 6, 8, and 10 on the following: Panic Diary and AAA (investigator summarized the information from these instruments); and CGI [range 1-7, for both improvement (I) and severity (S) scales]. Patients were rated at baseline and the ends of weeks 4 and 10 on the following: Marks-Sheehan Phobia Scale (MSPS); Sheehan Disability Scale (SDS).

Reduction in the number of full panic attacks was identified as the primary efficacy variable, using 3 approaches (all with reference to an interval of the previous 2 weeks): (1) proportion of patients having zero full panic attacks, (2) proportion of patients having ≥ 50% reduction from baseline in the mean number of full panic attacks, and (3) mean change from baseline in the number of full panic attacks.

The following variables (mean change from baseline) were derived from the secondary assessments:

- MSPS-Fear Score
- MSPS-Avoidance Score
- AAA-% Time Worrying
- AAA-Intensity of Attacks
- SDS-Work Score
- SDS-Social Life Score
- SDS-Family Life Score

Patients were predominantly female (approximately 2/3), predominantly Caucasian, and the mean age was mid 30's. The treatment groups were comparable at baseline on the demographic and the key efficacy variables.

Study Results

The intent-to-treat dataset was as follows:

paroxetine 10 mg/day	(67)
paroxetine 20 mg/day	(70)
paroxetine 40 mg/day	(72)
placebo	(69)

Completion rates to 10 weeks were as follows:

paroxetine 10 mg/day	45/67 (67%)
paroxetine 20 mg/day	47/70 (67%)
paroxetine 40 mg/day	50/72 (69%)
placebo	46/69 (67%)

Summary of Significance Levels[1] (2-Sided) for Pairwise Comparisons (Paroxetine vs Placebo) in Study 120

Key Outcome Variables	Paroxetine Dose Groups														
	10 mg					20 mg					40 mg				
	Week[2]					Week					Week				
	2	4	6	8	10	2	4	6	8	10	2	4	6	8	10
No. Panic Attacks															
Proportion Zero															
LOCF	-	-	-	-	-	-	-	-	-	-	-	*	-	*	*
OC	-	-	-	-	-	-	-	-	-	-	-	*	-	-	*
Proportion ≥ 50% ↓															
LOCF	-	-	-	-	-	-	-	-	-	-	t	t	-	-	-
OC	-	-	-	-	-	-	-	-	-	-	t	t	t	-	-
Mean Δ Baseline															
LOCF	-	-	-	-	-	-	-	-	*	*	-	*	*	*	*
OC	-	-	-	-	-	-	t	-	t	-	-	*	*	*	*
CGI Severity															
LOCF	-	-	-	-	-	-	-	-	-	-	-	-	-	t	*
OC	-	-	-	-	-	-	-	-	-	-	-	-	t	t	*
MSPS-Fear Score															
LOCF		-		-			-			*		*			*
OC		-		-			-			*		*			*
MSPS-Avoidance Score															
LOCF		-		-			-			-		-			*
OC		-		-			-			-		-			-
AA-% Time Worrying															
LOCF	-	-	-	-	-	t	-	-	-	-	*	-	-	-	t
OC	-	-	-	-	-	t	-	-	-	-	*	-	*	-	-
AA-Intensity															
LOCF	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SDS-Work Score															
LOCF		-		-			-			*		-			*
OC		-		-			-			-		-			-
SDS-Social Life Score															
LOCF		-		-			-			t		-			t
OC		-		-			t			t		-			t
SDS-Family Life Score															
LOCF		-		-			-			*		-			-
OC		-		-			-			-		-			-

1 * = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$
* = $p \leq 0.019$ (criterion p-value for Dunnett's Test)

2 End of weeks 2, 4, 6, 8, and 10

Size of Treatment Effect in Study 120			
Proportion of Patients with Panic Attacks ↓ to Zero			
Group	Baseline[1]	Wk 9-10	Difference[2]
Placebo	-	44%	
Parox. 10 mg	-	56%	12%
Parox. 20 mg	-	57%	13%
Parox. 40 mg	-	76%	32%
Proportion of Patients with ≥ 50% ↓ in Panic Attacks			
Group	Baseline[1]	Wk 9-10	Difference[2]
Placebo	-	74%	
Parox. 10 mg	-	81%	7%
Parox. 20 mg	-	85%	11%
Parox. 40 mg	-	89%	15%
Number of Full Panic Attacks/2 Weeks			
Group	Baseline[3]	BL - Wk 10[4]	Difference[5]
Placebo	11.6	- 5.5	
Parox. 10 mg	10.2	- 5.9	0.4
Parox. 20 mg	9.5	- 5.7	0.2
Parox. 40 mg	9.6	- 8.2	2.7
CGI Severity Score			
Group	Baseline[3]	BL - Wk 10[4]	Difference[5]
Placebo	4.4	- 1.3	
Parox. 10 mg	4.4	- 1.3	0
Parox. 20 mg	4.4	- 1.5	0.2
Parox. 40 mg	4.4	- 1.8	0.5

1 Baseline score not relevant for this variable
2 Difference between drug and placebo in proportion of patients meeting criteria for weeks 9-10
3 Mean score at baseline
4 Mean Change from baseline to week 10 (LOCF)
5 Difference in mean change from baseline to week 10 endpoint (LOCF) between paroxetine and placebo

Impression: I considered this study positive on 2 of the 3 panic attack variables and also for CGI severity and the MSPS fear score, but only for the 40 mg/day dose. [Note: Technically, this study didn't make it for zero panic attacks and CGI-Severity in the LOCF analyses at endpoint. However, in both cases, the p-values missed the Dunnet's criterion value by only a few hundredths of a percent, and I consider these results close enough. In support of this finding, in both cases there was a significant linear relationship between dose and response.] There was no demonstrable effect on the other secondary variables, however, this is not too surprising. The study duration may have been too short to expect to see behavioral changes, e.g., in avoidance and overall functioning (SDS). In addition, the assessment for anticipatory anxiety may not have been sensitive enough to detect change. The effect size seen in terms of change in panic attack frequency was actually quite impressive, with drug treated patients (40 mg/day) going from an average of about 10 attacks/2 weeks at baseline to about 2 attacks/2 weeks at endpoint, compared to a reduction from about 10 to 5 for placebo patients. I consider that a clinically meaningful effect and I consider this a positive study in support of the 40 mg/day dose.

5.1.1.2 Study 108

This was a randomized, 7-center (Danish), double-blind, parallel group, 12-week, flexible-dose study comparing paroxetine in a dose range of 20-60 mg/day (on a qd schedule) and placebo for the treatment of PD in adult outpatients meeting DSMIIIR criteria for PD. All patients also received standard cognitive behavior therapy. Patients were required to have at least 3 panic attacks (type not specified) in the 4 week period between screening and baseline. Patients could have sufficient depressive symptoms to meet criteria for major depressive disorder, providing the panic disorder symptoms were considered primary.

Patients completed a Panic Diary daily. Patients were rated at baseline and the ends of weeks 3, 6, 9, and 12 on the Panic Diary (investigator summarized the information from this instrument) and the CGI.

Reduction in the number of panic attacks was identified as the primary efficacy variable, using 3 approaches (all with reference to an interval of the previous 3 weeks): (1) proportion of patients having zero or 1 panic attack, (2) proportion of patients having ≥ 50% reduction from baseline in the mean number of panic attacks, and (3) mean change from baseline in the number of panic attacks.

Patients were predominantly female (approximately 3/4), and the mean age was mid 30's. The treatment groups were comparable at baseline on the demographic and the key efficacy variables. The mean paroxetine dose at 12 weeks in completers was 40 mg/day.

Study Results

The intent-to-treat dataset was as follows:

paroxetine	(60)
placebo	(60)

Completion rates to 10 weeks were as follows:

paroxetine	55/60 (92%)
placebo	52/60 (87%)

Summary of Significance Levels[1] (2-sided) for Pairwise Comparisons (Paroxetine vs Placebo) in Study 108

Key Outcome Variables	Paroxetine vs Placebo			
	Week[2] 3	6	9	12
No. Panic Attacks				
Proportion Zero or 1				
LOCF	-	-	-	*
OC	-	-	-	*
Proportion ≥ 50% ↓				
LOCF	-	*	*	*
OC	-	*	*	*
Mean Δ Baseline				
LOCF	-	-	-	-
OC	-	-	-	t
CGI Severity				
LOCF	-	*	t	*
OC	-	*	*	*

1 * = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$

2 End of weeks 3, 6, 9, and 12

Size of Treatment Effect in Study 108			
Proportion of Patients with Panic Attacks ↓ to Zero or 1			
Group	Baseline[1]	Wks 9-12	Difference[2]
Placebo	-	14%	
Paroxetine	-	33%	19%
Proportion of Patients with ≥ 50% ↓ in Panic Attacks			
Group	Baseline[1]	Wks 9-12	Difference[2]
Placebo	-	47%	
Paroxetine	-	79%	32%
Number of Panic Attacks/3 Weeks			
Group	Baseline[3]	BL - Wk 12[4]	Difference[5]
Placebo	26.4	- 10.0	
Parox. 10 mg	21.2	- 15.0	5.0
CGI Severity Score			
Group	Baseline[3]	BL - Wk 12[4]	Difference[5]
Placebo	4.3	- 1.3	
Parox. 10 mg	4.3	- 2.1	0.8

1 Baseline score not relevant for this variable
2 Difference between drug and placebo in proportion of patients meeting criteria in weeks 9-12
3 Mean score at baseline
4 Mean Change from baseline to week 12 (LOCF)
5 Difference in mean change from baseline to week 12 endpoint (LOCF) between paroxetine and placebo

Impression: I considered this study positive on 2 of the 3 panic attack variables and also for CGI severity. It isn't clear why this study didn't make it on mean change from baseline in panic attack frequency. It may have been underpowered for this variable. In any case, the results were significant and clinically meaningful for both of the other panic attack variables. Thus, I consider this a second positive study in support of paroxetine in a dose range of 20-60 mg/day.

5.1.1.3 Study 187

This was a randomized, 39-center (international, mostly European), double-blind, parallel group, 12-week, flexible-dose study

comparing paroxetine (in a dose range of 20-60 mg/day; qd schedule), clomipramine (in a dose range of 50-150 mg/day; bid schedule), and placebo for the treatment of PD in adult outpatients meeting DSMIIIR criteria for PD. Patients were required to have at least 3 full panic attacks (i.e., ≥4 of the DSMIIIR criteria for a panic attack) in the 3 week period between screening and baseline. Patients could have sufficient depressive symptoms to meet criteria for major depressive disorder, providing the panic disorder symptoms were considered primary.

Patients completed a Panic Diary daily. Patients were rated at baseline and the ends of weeks 1, 2, 3, 4, 6, 9, and 12 on the following: Panic Diary (investigator summarized the information from this instrument); Marks-Sheehan Phobia Scale (MSPS); and Sheehan Disability Scale (SDS). CGI was obtained at the end of weeks 3, 6, 9, and 12.

Reduction in the number of full panic attacks was identified as the primary efficacy variable, using 3 approaches (all with reference to an interval of the previous 3 weeks): (1) proportion of patients having zero full panic attacks, (2) proportion of patients having ≥ 50% reduction from baseline in the mean number of full panic attacks, and (3) mean change from baseline in the number of full panic attacks.

The following variables (mean change from baseline) were derived from the secondary assessments:

MSPS-Fear Score
MSPS-Avoidance Score
SDS-Work Score
SDS-Social Life Score
SDS-Family Life Score

Patients were approximately 60% female, almost exclusively Caucasian, and the mean age was mid 30's. The treatment groups were generally comparable at baseline on the demographic and the key efficacy variables. Mean doses for completers at 12 weeks were 43 mg/day for paroxetine and 103 mg/day for clomipramine.

Study Results

The intent-to-treat dataset was as follows:

paroxetine	(123)
clomipramine	(121)
placebo	(123)

Completion rates to 12 weeks were as follows:

paroxetine	89/123	(72%)
clomipramine	91/121	(75%)
placebo	81/123	(66%)

Summary of Significance Levels[1] (2-sided) for Pairwise Comparisons (Parox. & Clomip. vs Placebo) in Study 187

Key Outcome Variables	Parox. vs Pbo. Week[2] 3 6 9 12	Clomip. vs Pbo Week 3 6 9 12
No. Panic Attacks		
Proportion Zero		
LOCF	- * * *	- - - *
OC	- t * -	- - - t
Proportion ≥ 50% ↓		
LOCF	- t * *	- - - -
OC	- - - -	- - - -
Mean Δ Baseline		
LOCF	- - t *	- - - -
OC	- - - -	- - - -
CGI Severity		
LOCF	t * * *	- * * *
OC	* * * *	- * * *
MSPS-Fear Score		
LOCF	- t * *	- * * *
OC	- * * *	- * - *
MSPS-Avoidance Score		
LOCF	- * t *	- - t *
OC	- * - *	- - t *
SDS-Work Score		
LOCF	* * * *	- * * *
OC	* * * *	- * * *
SDS-Social Life Score		
LOCF	* * * *	- * * *
OC	* * * *	- * * *
SDS-Family Life Score		
LOCF	* * * *	* * * *
OC	* * * *	* * * *

1 * = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$

2 End of weeks 3, 6, 9, and 12

Size of Treatment Effect in Study 187			
Proportion of Patients with Panic Attacks ↓ to Zero			
Group	Baseline[1]	Wks 9-12	Difference[2]
Placebo	-	33%	
Paroxetine	-	51%	18%
Clomipramine	-	50%	17%
Proportion of Patients with ≥ 50% ↓ in Panic Attacks			
Group	Baseline[1]	Wks 9-12	Difference[2]
Placebo	-	62%	
Paroxetine	-	80%	18%
Clomipramine	-	68%	6%
Number of Full Panic Attacks/3 Weeks			
Group	Baseline[3]	BL - Wk 12[4]	Difference[5]
Placebo	18.5	- 8.5	
Paroxetine	17.9	- 12.2	3.7
Clomipramine	15.3	- 8.7	0.2
CGI Severity Score			
Group	Baseline[3]	BL - Wk 12[4]	Difference[5]
Placebo	4.5	- 1.0	
Paroxetine	4.6	- 1.9	0.9
Clomipramine	4.6	- 1.6	0.6

1 Baseline not relevant to this variable
2 Difference between drug and placebo in proportion of patients meeting criteria in weeks 9-12 (LOCF)
3 Mean score at baseline
4 Mean Change from baseline to week 12 (LOCF)
5 Difference in mean change from baseline to week 12 endpoint (LOCF) between drug and placebo

Impression: I considered this study positive, not only for the primary panic attack variables, but also for CGI severity, the MSPS scores and the SDS scores. [Note: One concern here was the failure for the OC results on the panic attack variable to meet the p ≤ 0.05 cirterion. The explanation proposed was a higher dropout rate for lack of effect in placebo (14%) vs paroxetine (4%). While I

would like to have seen an analyses of scores on these variables for dropouts from each of these groups (e.g., were paroxetine dropouts doing better than placebo dropouts?), I am not particularly troubled by this discrepancy, given the overwhelmingly positive findings on the CGI-Severity and all the secondary variables.] Consequently, I believe this study provides additional support for the effectiveness of paroxetine in panic disorder.

5.1.1.4 Study 223

This was a randomized, 16-center (US), double-blind, parallel group, 10-week, flexible-dose study comparing paroxetine (in a dose range of 10-60 mg/day; qd schedule), alprazolam (in a dose range of 1-6 mg/day; bid schedule), and placebo for the treatment of PD in adult outpatients meeting DSMIIIR criteria for PD. Patients were required to have at least 2 full panic attacks (i.e., ≥4 of the DSMIIIR criteria for a panic attack) in the 2 week period between screening and baseline. Patients could have sufficient depressive symptoms to meet criteria for major depressive disorder, providing the panic disorder symptoms were considered primary.

Patients completed a Panic Diary and an Anticipatory Anxiety Assessment (AAA) daily. Patients were rated at baseline and the ends of weeks 1, 2, 3, 4, 6, 8, and 10 on the following: Panic Diary and AAA (investigator summarized the information from these instruments); and CGI. Patients were rated at baseline and the ends of weeks 4 and 10 on the following: Marks-Sheehan Phobia Scale (MSPS); Sheehan Disability Scale (SDS).

Reduction in the number of full panic attacks was identified as the primary efficacy variable, using 3 approaches (all with reference to an interval of the previous 2 weeks): (1) proportion of patients having zero full panic attacks, (2) proportion of patients having ≥ 50%reduction from baseline in the mean number of full panic attacks, and (3) mean change from baseline in the number of full panic attacks.

The following variables (mean change from baseline) were derived from the secondary assessments:

MSPS-Fear Score
MSPS-Avoidance Score
AA-% Time Worrying
AA-Intensity
SDS-Work Score
SDS-Social Life Score
SDS-Family Life Score

Patients were approximately 2/3 female, predominantly Caucasian, and the mean age was late 30's. The treatment groups were generally comparable at baseline on the demographic and the key

efficacy variables. Mean doses for completers at 10 weeks were 39 mg/day for paroxetine and 3.6 mg/day for alprazolam.

Study Results

The intent-to-treat dataset was as follows:

paroxetine	(77)
alprazolam	(77)
placebo	(68)

Completion rates to 12 weeks were as follows:

paroxetine	48/77 (62)
alprazolam	60/77 (78%)
placebo	50/68 (69%)

Summary of Significance Levels[1] (2-sided) for Pairwise Comparisons (Parox. & Alpraz. vs Placebo) in Study 223

Key Outcome Variables	Parox. vs Pbc					Alpraz. vs Pbo				
	Week[2] 2	4	6	8	10	Week 2	4	6	8	10
No. Panic Attacks										
Proportion Zero										
LOCF	-	t	-	-	-	-	-	-	-	-
OC	-	t	-	-	-	-	-	-	-	-
Proportion ≥ 50% ↓										
LOCF	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-
Mean Δ Baseline										
LOCF	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-
CGI Severity										
LOCF	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-
MSPS-Fear Score										
LOCF	-				t	*				-
OC	-				-	t				-
MSPS-Avoidance Score										
LOCF	-				-	*				-
OC	-				-	*				-
AA-% Time Worrying										
LOCF	-	-	-	-	-	*	-	*	*	-
OC	-	-	-	-	-	*	-	*	-	-
AA-Intensity										
LOCF	-	-	-	-	-	*	-	*	t	-
OC	-	-	-	-	-	*	-	-	-	-
SDS-Work Score										
LOCF	*				t	-				-
OC	t				-	-				-
SDS-Social Life Score										
LOCF	t				*	-				-
OC	t				-	-				-
SDS-Family Life Score										
LOCF	*				*	-				-
OC	*				-	-				-

1 * = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$

2 End of weeks 2, 4, 6, 8, and 10

Size of Treatment Effect in Study 223			
Proportion of Patients with Panic Attacks ↓ to Zero			
Group	**Baseline[1]**	**Wks 9-10**	**Difference[2]**
Placebo	-	63%	
Paroxetine	-	59%	-4%
Alprazolam	-	62%	-1%
Proportion of Patients with ≥ 50% ↓ in Panic Attacks			
Group	**Baseline[1]**	**Wks 9-10**	**Difference[2]**
Placebo	-	78%	
Paroxetine	-	79%	1%
Alprazolam	-	87%	9%
Number of Full Panic Attacks/2 Weeks			
Group	Baseline[3]	BL - Wk 10[4]	Difference[5]
Placebo	7.9	- 4.7	
Paroxetine	8.8	- 6.7	2.0
Alprazolam	9.8	- 7.8	3.1
CGI Severity Score			
Group	Baseline[3]	BL - Wk 10[4]	Difference[5]
Placebo	4.5	- 1.5	
Paroxetine	4.4	- 1.8	0.3
Alprazolam	4.4	- 1.8	0.3

1 Baseline not relevant to this variable
2 Difference between drug and placebo in proportion of patients meeting criteria in weeks 9-10 (LOCF)
3 Mean score at baseline
4 Mean Change from baseline to week 10 (LOCF)
5 Difference in mean change from baseline to week 10 endpoint (LOCF) between drug and placebo

Impression: Although there were some scattered positive findings in this study, especially for alprazolam, overall neither active drug was shown to be superior to placebo. The prominent placebo response may have contributed to this outcome. In any case, this can be considered a failed study, since neither active drug beat placebo.

5.1.1.5 Study 228

This was an extension of study 187. Patients from any of the 3 treatment groups who completed study 187 and had no significant adverse events could be continued for up to 9 months, on a double-blind basis, on the same treatment and dose as in the short-term phase. Assessments were the same as in the short-term phase, but at 6-week intervals. In addition, definitions were provided for categorizing patients as having had partial or full relapse during the extension phase.

A major problem with this study was the fact that the original randomization was violated, in that only completers meeting the identified criteria were continued. Consequently, it is of descriptive value only, and I will not provide detailed comments. However, overall the results did not substantially favor paroxetine over placebo. There were few relapses and no statistically significant differences between groups in number of relapses or time to relapse.

5.1.1.6 Study 222

This was an extension of study 120. Patients who completed study 120, had no significant adverse events, and met criteia for being either partial or full responders could be entered into study 222. [Partial response = ≥ 50% reduction in full panic attacks during weeks 9-10; full response = no full panic attacks during weeks 9-10.]

The first 3 months of study 222 was a double-blind maintenance phase during which patients were continued on their previously assigned treatment and dose. Patients who were responders during the last 2 weeks of the maintenance phase and had not "relapsed" during that 3 month period could enter the 3-month re-randomization phase, which involved randomization to either their previous treatment and dose (placebo or paroxetine 10, 20, or 40 mg/day), or to placebo. The key outcomes during this phase were percent relapse and time to relapse. [A patient relapsed if frequency of full panic attacks per two weeks was ≥ that observed at baseline for study 120, or there was an increase of ≥ 2 points on CGI severity, relative to the score at week 12 of the maintenance phase.]

For the primary analysis, patients randomized from placebo to placebo were not included (not planned this way in protocol). The relapse rates for the remaining groups were as follows:

10 mg to pbo	2/12 (17%)
20 mg to pbo	2/12 (17%)
40 mg to pbo	7/13 (54%)
Total Parox to pbo	11/37 (30%)
10 mg to 10 mg	0/12 (0%)

20 mg to 20 mg	1/13 (8%)
40 mg to 40 mg	1/18 (6%)
Total parox to parox	2/43 (5%)

These results are certainly suggestive of a maintenance effect for paroxetine. However, this can be considered only a pilot study without any clearly defined prospective analysis plan, and would need replication in a more definitive trial to justify a claim for maintenance effectiveness.

5.1.2 Comment on Other Important Clinical Issues Regarding the Efficacy of Paxil for Panic Disorder

Evidence Bearing on the Question of Dose/Response for Efficacy

Of the 3 positive studies supporting the anti-panic effectiveness of Paxil, only 1 (Study 120) involved a fixed dose design. In that fixed dose study, only the highest dose (40 mg/day) was shown to be effective. The other 2 positive studies involved titration within a paroxetine range of 20-60 mg/day, and for both, the mean paroxetine dose for completers was approximately 40 mg/day. Thus, it seems reasonable to suggest 40 mg/day as the initial target dose for anti-panic therapy with paroxetine. However, since higher doses have not been specifically studied, and some patients in the flexible dose studies seemed to need doses at the higher end of the paroxetine dose range, it also seems reasonable to propose 60 mg/day as the maximum recommended dose and suggest that, although not proven, some patients may benefit from these higher doses.

Clinical Predictors of Response

The sponsor conducted subgroup analyses on the basis of gender and baseline severity for the 3 panic attack variables in each of the 4 short-term studies. There were no differences for paroxetine on the basis of gender. As might be expected, patients with a greater severity of illness at entry, as based on number of panic attacks, improved more than less ill patients. An analysis using age as a continuous variable revealed no significant age effect on response.

Size of Treatment Effect

An approach to estimating treatment effect size is to examine the differences between paroxetine and placebo in the proportions of patients meeting criteria for response or on mean change from baseline for other key effectiveness measures in the 3 positive studies in this development program, as follows:

Size of Treatment Effect in Three Panic Disorder Studies for Key Efficacy Variables at 10- or 12-Week Endpoint (LOCF)			
Study 120			
Variables	Paroxetine[1,2]	Placebo[2]	Difference[3]
# Panic Attack			
↓ to Zero	76%	44%	32%
≥ 50% ↓	89%	74%	15%
# Full PA	- 8.2	- 5.5	2.7
CGI Severity	- 1.8	- 1.3	0.5
Study 108			
Variables	Paroxetine[1,2]	Placebo[2]	Difference[3]
# Panic Attack			
↓ to 0/1	33%	14%	19%
≥ 50% ↓	79%	47%	32%
# Full PA	- 15.0	- 10.0	5.0
CGI Severity	- 2.1	- 1.3	0.8
Study 187			
Variables	Paroxetine[1,2]	Placebo[2]	Difference[3]
# Panic Attack			
↓ to Zero	51%	33%	18%
≥ 50% ↓	80%	62%	18%
# Full PA	- 12.2	- 8.5	3.7
CGI Severity	- 1.9	- 1.0	0.9

1 Data from 40 mg/day group

2 Proportions of patients meeting criteria for response in last observation interval, for zero panic attacks and ≥ 50% ↓ variables; mean change from baseline to 10- or 12-week endpoint for # panic attacks and CGI-Severity

3 Difference between paroxetine and placebo in proportions meeting criteria for zero panic attacks and ≥ 50% ↓ variables; difference between paroxetine and placebo in mean change from baseline to 10- or 12-week endpoint for # panic attacks and CGI-Severity

I consider these effects to be clinically meaningful and sufficient support to justify the approvability of the panic disorder indication for paroxetine.

Duration of Treatment Effect

As noted earlier, there were extension phases for 2 of the short-term trials. Study 228 generated data that was of descriptive value only, and those results were not partucularly supportive of a maintenance effect for paroxetine. Study 222 did involve a re-randomization of patients who were considered responders, and data from that study were suggestive of a maintenance effect. However, for the reasons noted, study 222 cannot be considered a sufficient basis for a definitive judgement on this matter. In the meantime, we have taken the same approach in labeling for this indication that we have for other chronic illnesses, i.e., acknowledge the absence of sufficient relapse prevention data, yet suggest that it would not be unreasonable to continue responding patients beyond the acute treatment phase.

5.1.3 Conclusions Regarding Efficacy Data

In my view, three of the four studies in this development program support the short-term effectiveness of paroxetine in the treatment of PD.

5.2 Safety Data

The safety data for Paxil/PD were reviewed by James Knudsen, M.D. (review completed and signed 12-28-95). Since Paxil has been widely available in the US and elsewhere for approximately 2 years for the treatment of depression, a major part of our approach to the safety data was to compare the findings from the relatively small PD database with the database for depression. Dr. Knudsen concluded that Paxil is acceptably safe for use in the treatment of PD, and I agree with that conclusion.

The four studies for which data were available for the integrated database (120, 108, 187, and 223) were briefly described under 5.1 (efficacy). These were 10-12 week, placebo-controlled trials. The cutoff date for the integrated database for these four studies was 5-1-94, and this database included 469 patients exposed to paroxetine. The cutoff date for serious events was 12-31-94. Patients from two of those studies (120 and 187) had additional exposure in extension phases of those studies for up to 9 months. The above four studies and the two extensions were completed prior to submission of this supplement, thus, all adverse event data were included in the supplement, and no additional data are expected for any of these patients. The supplement also included an update on spontaneous reports for Paxil worldwide. Apparently, all the spontaneous reports provided were for patients being treated for

depression, and no reports were available for patients identified as being treated with paroxetine for Panic Disorder.

For the integrated PD database, paroxetine-exposed patients ranged in age from 18-74 (mean=36), were 65% female, and were 78% caucasian. The exposure tended to be short-term, however, about 29% were exposed for greater than 6 months. About 75% of patients received mean doses in a range of 16-60 mg/day.

There were no deaths among the paroxetine-exposed patients in the integrated database for the panic disorder studies.

A search of the integrated database for serious events yielded a total of 13 among paroxetine-exposed patients. Neither the numbers nor types of events were unexpected for this population. A search for suicidality also did not reveal any indication of a paroxetine-associated risk for suicidal behavior.

The common and drug-related adverse events leading to dropout (incidence ≥ 1% and at least twice the placebo rate) included: nausea, insomnia, and somnolence. This list overlapped with comparable lists for depression and OCD databases, however, included fewer adverse events overall.

The common and drug-related adverse events overall (from the integrated database; incidence ≥ 5% and at least twice the placebo rate) included: asthenia, decreased appetite, tremor, sweating, abnormal ejaculation, impotence, libido decreased, and female genital disorders (mostly anorgasmia or difficulty reaching orgasm). This list was also similar to the adverse events associated with paroxetine in the depression and OCD databases.

Three of the 4 short-term trials had a run-out phase during which assigned treatments were tapered and withdrawn (periods ranged from 3-6 weeks). Overall, 390 patients were discontinued in this manner, including 155 from paroxetine, 60 from alprazolam, 27 from clomipramine, and 148 from placebo. The incidence of dropout from this tapered withdrawl for adverse events was as follows:

Paroxetine	6/155	(4%)
Alprazolam	1/60	(2%)
Clomipramine	1/27	(4%)
Placebo	0	

The most common reasons for paroxetine patients leaving the scheduled tapering were headache, agitation, and depression.

Explorations of the integrated database for laboratory and vital signs variables, including analyses of change from baseline, analyses of proportions of patients meeting criteria for potentially clinically significant change on these variables, and

dropouts for changes in any of these variables did not reveal any new or clinically important findings.

In conclusion, the safety experience for paroxetine (dosed in a range of 20 to 60 mg/day) in patients with PD did not reveal any adverse findings that are unique for this population, and none that would preclude its use in this population. We have requested a safety update in the approvable letter.

5.3 Clinical Sections of Labeling

We have rewritten some of the proposed changes in the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

Dr. Knudsen reviewed the published literature for Paxil included in the NDA and did not discover any previously unrecognized important safety concerns for this drug.

7.0 FOREIGN REGULATORY ACTIONS

Paxil is marketed in a number of countries around the world for the treatment of depression. To my knowledge, it is not yet marketed anywhere for the treatment of PD. We will ask for an update on the regulatory status of Paxil in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this supplement to the PDAC.

9.0 DSI INSPECTIONS

DSI inspections were requested but no responses have been received as yet. It is the current policy of DSI not to do routine inspections for supplements.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made some changes to the sponsor's draft dated 3-29-95.

10.2 Foreign Labeling

To my knowledge, Paxil is not approved for PD anywhere at this time.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a safety update, a literature update, a regulatory status update, and a commitment to conduct a relapse prevention trial.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that SKB has submitted sufficient data to support the conclusion that Paxil is effective and acceptably safe in the treatment of Panic Disorder. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

cc:
Orig NDA
HFD-120
HFD-120/TLaughren/PLeber/GDubitsky/JKnudsen/MMille

DOC: MEMPAXPD.AE1

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S-009
1/31/96
memo

Mille

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 31, 1996

FROM: Thomas P. Laughren, M.D. TPL
Group Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for
Paxil (paroxetine) for Panic Disorder (PD)

TO: File NDA 20-031/S-009
[Note: This overview should be filed with the 3-29-95 original submission.]

1.0 BACKGROUND

Paxil (paroxetine) is a selective serotonin reuptake inhibitor (SSRI) that was approved for the treatment of depression in December, 1992 (NDA 20-031). Supplement S-009 includes data from clinical trials supporting the use of paroxetine in the treatment of panic disorder (PD), in a dose range of 40-60 mg/day [Note: The maximum recommended dose in currently approved labeling is 50 mg/day.].

Since the proposal is to use the currently marketed paroxetine formulations for this new indication, there was no need for substantial chemistry, pharmacology, or biopharmaceutics reviews of this supplement. Consequently, the focus was on clinical data. The safety and efficacy data were reviewed by James Knudsen, M.D. The efficacy data were also examined by Japo Choudhury, Ph.D. from the Division of Biometrics.

The original supplement for PD was submitted 3-29-95. The review was based on the original submission plus amendments containing responses to requests for additional information, including a 7-7-95 amendment providing data for extension study 222.

At the present time, Xanax (alprazolam), a triazolobenzodiazepine, is the only drug approved for the panic disorder indication in the US. However, a number of other drugs are believed to be effective and are widely used for the treatment of this indication, including other benzodiazepines, the tricyclic antidepressants, MAOIs (phenelzine in particular), and other SSRIs.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

Paxil is a marketed product, and there were no chemistry issues requiring review for this supplement.

3.0 PHARMACOLOGY

Paxil is a marketed product, and there were no pharmacology issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

Paxil is a marketed product, and there were no biopharmaceutics issues requiring review for this supplement.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Summary of Studies Pertinent to Efficacy

Our review of the effectiveness of Paxil in the treatment of PD focused on 4 short-term, placebo-controlled studies for which we had full study reports (i.e., 120, 108, 187, and 223). Data from double-blind extensions were available for 2 of these studies, i.e., extension 228 for Study 187 and extension 222 for Study 120.

Statistical Methods: I will make general comments here on the statistical methodology used in analyzing the data for these studies, rather than providing detailed comments on these methods in each of the sections that follow.

Dichotomous variables (proportions of patients achieving zero panic attacks or experiencing a reduction of $\geq$ 50% in panic attacks) were analyzed using nonparametric categorical approaches. For other measures (# panic attacks, MSPS subscales, SDS subscales, anticipatory anxiety measures, and CGI-Severity) change from baseline values were analyzed using ANOVA methods, unless the data appeared non-normally distrubuted, in which case, nonparametric methods were used.

The models included effects for treatment, investigator, and the interaction, however, interaction terms were dropped from the model if non-significant ($P > 0.10$). Investigator effect was not included in study 187. Analyses were not weighted by site.

All p-value data presented refer to 2-sided p-values. Alpha was set at 0.05, except for study 120, where Dunnet's test was used, and the criterion p-value was set at p , 0.019.

5.1.1.1 Study 120

This was a randomized, 20-center (US and Canada), double-blind, parallel group, 10-week, fixed-dose study comparing paroxetine at 3 fixed doses [10, 20, and 40 mg/day; titration up to the two higher dose groups by adding 10 mg/day at week 2 (for the 20 mg and 40 mg groups) and 20 mg/day at week 3 (for the 40 mg group); qd schedule] and placebo for the treatment of PD in adult outpatients meeting DSMIIIR criteria for PD. Patients were required to have at least 2 full panic attacks (i.e., ≥4 of the DSMIIIR criteria for a panic attack) in the 2 week period between screening and baseline. Patients could have sufficient depressive symptoms to meet criteria for major depressive disorder, providing the panic disorder symptoms were considered primary.

Patients completed a Panic Diary and an Anticipatory Anxiety Assessment (AAA) daily. Patients were rated at baseline and the ends of weeks 1, 2, 3, 4, 6, 8, and 10 on the following: Panic Diary and AAA (investigator summarized the information from these instruments); and CGI [range 1-7, for both improvement (I) and severity (S) scales]. Patients were rated at baseline and the ends of weeks 4 and 10 on the following: Marks-Sheehan Phobia Scale (MSPS); Sheehan Disability Scale (SDS).

Reduction in the number of full panic attacks was identified as the primary efficacy variable, using 3 approaches (all with reference to an interval of the previous 2 weeks): (1) proportion of patients having zero full panic attacks, (2) proportion of patients having ≥ 50% reduction from baseline in the mean number of full panic attacks, and (3) mean change from baseline in the number of full panic attacks.

The following variables (mean change from baseline) were derived from the secondary assessments:

- MSPS-Fear Score
- MSPS-Avoidance Score
- AAA-% Time Worrying
- AAA-Intensity of Attacks
- SDS-Work Score
- SDS-Social Life Score
- SDS-Family Life Score

Patients were predominantly female (approximately 2/3), predominantly Caucasian, and the mean age was mid 30's. The treatment groups were comparable at baseline on the demographic and the key efficacy variables.

Study Results

The intent-to-treat dataset was as follows:

paroxetine 10 mg/day	(67)
paroxetine 20 mg/day	(70)
paroxetine 40 mg/day	(72)
placebo	(69)

Completion rates to 10 weeks were as follows:

paroxetine 10 mg/day	45/67 (67%)
paroxetine 20 mg/day	47/70 (67%)
paroxetine 40 mg/day	50/72 (69%)
placebo	46/69 (67%)

Summary of Significance Levels[1] (2-Sided) for Pairwise Comparisons (Paroxetine vs Placebo) in Study 120

Key Outcome Variables	Paroxetine Dose Groups														
	10 mg					20 mg					40 mg				
	Week[2]					Week					Week				
	2	4	6	8	10	2	4	6	8	10	2	4	6	8	10
No. Panic Attacks															
Proportion Zero															
LOCF	-	-	-	-	-	-	-	-	-	-	-	*	-	*	*
OC	-	-	-	-	-	-	-	-	-	-	-	*	-	-	*
Proportion ≥ 50% ↓															
LOCF	-	-	-	-	-	-	-	-	-	-	t	t	-	-	-
OC	-	-	-	-	-	-	-	-	-	-	t	t	t	-	-
Mean Δ Baseline															
LOCF	-	-	-	-	-	-	-	-	*	*	-	*	*	*	*
OC	-	-	-	-	-	-	t	-	t	-	-	*	*	*	*
CGI Severity															
LOCF	-	-	-	-	-	-	-	-	-	-	-	-	-	t	*
OC	-	-	-	-	-	-	-	-	-	-	-	-	t	t	*
MSPS-Fear Score															
LOCF		-		-			-		*			*			*
OC		-		-			-		*			*			*
MSPS-Avoidance Score															
LOCF		-		-			-		-			-			*
OC		-		-			-		-			-			-
AA-% Time Worrying															
LOCF	-	-	-	-	-	t	-	-	-	-	*	-	-	-	t
OC	-	-	-	-	-	t	-	-	-	-	*	-	*	-	-
AA-Intensity															
LOCF	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SDS-Work Score															
LOCF		-		-			-		*			-			*
OC		-		-			-		-			-			-
SDS-Social Life Score															
LOCF		-		-			-		t			-			t
OC		-		-			t		t			-			t
SDS-Family Life Score															
LOCF		-		-			-		*			-			-
OC		-		-			-		-			-			-

1 * = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$
* = $p \leq 0.019$ (criterion p-value for Dunnett's Test)

2 End of weeks 2, 4, 6, 8, and 10

Size of Treatment Effect in Study 120			
Proportion of Patients with Panic Attacks ↓ to Zero			
Group	Baseline[1]	Wk 9-10	Difference[2]
Placebo	-	44%	
Parox. 10 mg	-	56%	12%
Parox. 20 mg	-	57%	13%
Parox. 40 mg	-	76%	32%
Proportion of Patients with ≥ 50% ↓ in Panic Attacks			
Group	Baseline[1]	Wk 9-10	Difference[2]
Placebo	-	74%	
Parox. 10 mg	-	81%	7%
Parox. 20 mg	-	85%	11%
Parox. 40 mg	-	89%	15%
Number of Full Panic Attacks/2 Weeks			
Group	Baseline[3]	BL - Wk 10[4]	Difference[5]
Placebo	11.6	- 5.5	
Parox. 10 mg	10.2	- 5.9	0.4
Parox. 20 mg	9.5	- 5.7	0.2
Parox. 40 mg	9.6	- 8.2	2.7
CGI Severity Score			
Group	Baseline[3]	BL - Wk 10[4]	Difference[5]
Placebo	4.4	- 1.3	
Parox. 10 mg	4.4	- 1.3	0
Parox. 20 mg	4.4	- 1.5	0.2
Parox. 40 mg	4.4	- 1.8	0.5

1 Baseline score not relevant for this variable
2 Difference between drug and placebo in proportion of patients meeting criteria for weeks 9-10
3 Mean score at baseline
4 Mean Change from baseline to week 10 (LOCF)
5 Difference in mean change from baseline to week 10 endpoint (LOCF) between paroxetine and placebo

Impression: I considered this study positive on 2 of the 3 panic attack variables and also for CGI severity and the MSPS fear score, but only for the 40 mg/day dose. [Note: Technically, this study didn't make it for zero panic attacks and CGI-Severity in the LOCF analyses at endpoint. However, in both cases, the p-values missed the Dunnet's criterion value by only a few hundredths of a percent, and I consider these results close enough. In support of this finding, in both cases there was a significant linear relationship between dose and response.] There was no demonstrable effect on the other secondary variables, however, this is not too surprising. The study duration may have been too short to expect to see behavioral changes, e.g., in avoidance and overall functioning (SDS). In addition, the assessment for anticipatory anxiety may not have been sensitive enough to detect change. The effect size seen in terms of change in panic attack frequency was actually quite impressive, with drug treated patients (40 mg/day) going from an average of about 10 attacks/2 weeks at baseline to about 2 attacks/2 weeks at endpoint, compared to a reduction from about 10 to 5 for placebo patients. I consider that a clinically meaningful effect and I consider this a positive study in support of the 40 mg/day dose.

5.1.1.2 Study 108

This was a randomized, 7-center (Danish), double-blind, parallel group, 12-week, flexible-dose study comparing paroxetine in a dose range of 20-60 mg/day (on a qd schedule) and placebo for the treatment of PD in adult outpatients meeting DSMIIIR criteria for PD. All patients also received standard cognitive behavior therapy. Patients were required to have at least 3 panic attacks (type not specified) in the 4 week period between screening and baseline. Patients could have sufficient depressive symptoms to meet criteria for major depressive disorder, providing the panic disorder symptoms were considered primary.

Patients completed a Panic Diary daily. Patients were rated at baseline and the ends of weeks 3, 6, 9, and 12 on the Panic Diary (investigator summarized the information from this instrument) and the CGI.

Reduction in the number of panic attacks was identified as the primary efficacy variable, using 3 approaches (all with reference to an interval of the previous 3 weeks): (1) proportion of patients having zero or 1 panic attack, (2) proportion of patients having $\geq$ 50% reduction from baseline in the mean number of panic attacks, and (3) mean change from baseline in the number of panic attacks.

Patients were predominantly female (approximately 3/4), and the mean age was mid 30's. The treatment groups were comparable at baseline on the demographic and the key efficacy variables. The mean paroxetine dose at 12 weeks in completers was 40 mg/day.

Study Results

The intent-to-treat dataset was as follows:

paroxetine	(60)
placebo	(60)

Completion rates to 10 weeks were as follows:

paroxetine	55/60 (92%)
placebo	52/60 (87%)

Summary of Significance Levels[1] (2-sided) for Pairwise Comparisons (Paroxetine vs Placebo) in Study 108

Key Outcome Variables	Paroxetine vs Placebo Week[2] 3 6 9 12
No. Panic Attacks	
Proportion Zero or 1	
LOCF	- - - *
OC	- - - *
Proportion ≥ 50% ↓	
LOCF	- * * *
OC	- * * *
Mean Δ Baseline	
LOCF	- - - -
OC	- - - t
CGI Severity	
LOCF	- * t *
OC	- * * *

1 * = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$

2 End of weeks 3, 6, 9, and 12

Size of Treatment Effect in Study 108			
Proportion of Patients with Panic Attacks ↓ to Zero or 1			
Group	Baseline[1]	Wks 9-12	Difference[2]
Placebo	-	14%	
Paroxetine	-	33%	19%
Proportion of Patients with ≥ 50% ↓ in Panic Attacks			
Group	Baseline[1]	Wks 9-12	Difference[2]
Placebo	-	47%	
Paroxetine	-	79%	32%
Number of Panic Attacks/3 Weeks			
Group	Baseline[3]	BL - Wk 12[4]	Difference[5]
Placebo	26.4	- 10.0	
Parox. 10 mg	21.2	- 15.0	5.0
CGI Severity Score			
Group	Baseline[3]	BL - Wk 12[4]	Difference[5]
Placebo	4.3	- 1.3	
Parox. 10 mg	4.3	- 2.1	0.8

1 Baseline score not relevant for this variable
2 Difference between drug and placebo in proportion of patients meeting criteria in weeks 9-12
3 Mean score at baseline
4 Mean Change from baseline to week 12 (LOCF)
5 Difference in mean change from baseline to week 12 endpoint (LOCF) between paroxetine and placebo

Impression: I considered this study positive on 2 of the 3 panic attack variables and also for CGI severity. It isn't clear why this study didn't make it on mean change from baseline in panic attack frequency. It may have been underpowered for this variable. In any case, the results were significant and clinically meaningful for both of the other panic attack variables. Thus, I consider this a second positive study in support of paroxetine in a dose range of 20-60 mg/day.

5.1.1.3 Study 187

This was a randomized, 39-center (international, mostly European), double-blind, parallel group, 12-week, flexible-dose study

comparing paroxetine (in a dose range of 20-60 mg/day; qd schedule), clomipramine (in a dose range of 50-150 mg/day; bid schedule), and placebo for the treatment of PD in adult outpatients meeting DSMIIIR criteria for PD. Patients were required to have at least 3 full panic attacks (i.e., ≥4 of the DSMIIIR criteria for a panic attack) in the 3 week period between screening and baseline. Patients could have sufficient depressive symptoms to meet criteria for major depressive disorder, providing the panic disorder symptoms were considered primary.

Patients completed a Panic Diary daily. Patients were rated at baseline and the ends of weeks 1, 2, 3, 4, 6, 9, and 12 on the following: Panic Diary (investigator summarized the information from this instrument); Marks-Sheehan Phobia Scale (MSPS); and Sheehan Disability Scale (SDS). CGI was obtained at the end of weeks 3, 6, 9, and 12.

Reduction in the number of full panic attacks was identified as the primary efficacy variable, using 3 approaches (all with reference to an interval of the previous 3 weeks): (1) proportion of patients having zero full panic attacks, (2) proportion of patients having ≥ 50% reduction from baseline in the mean number of full panic attacks, and (3) mean change from baseline in the number of full panic attacks.

The following variables (mean change from baseline) were derived from the secondary assessments:

MSPS-Fear Score
MSPS-Avoidance Score
SDS-Work Score
SDS-Social Life Score
SDS-Family Life Score

Patients were approximately 60% female, almost exclusively Caucasian, and the mean age was mid 30's. The treatment groups were generally comparable at baseline on the demographic and the key efficacy variables. Mean doses for completers at 12 weeks were 43 mg/day for paroxetine and 103 mg/day for clomipramine.

Study Results

The intent-to-treat dataset was as follows:

paroxetine	(123)
clomipramine	(121)
placebo	(123)

Completion rates to 12 weeks were as follows:

paroxetine	89/123	(72%)
clomipramine	91/121	(75%)
placebo	81/123	(66%)

Summary of Significance Levels[1] (2-sided) for Pairwise Comparisons (Parox. & Clomip. vs Placebo) in Study 187		
Key Outcome Variables	Parox. vs Pbo.	Clomip. vs Pbo
	Week[2] 3 6 9 12	Week 3 6 9 12
No. Panic Attacks		
Proportion Zero		
LOCF	- * * *	- - - *
OC	- t * -	- - - t
Proportion ≥ 50% ↓		
LOCF	- t * *	- - - -
OC	- - - -	- - - -
Mean Δ Baseline		
LOCF	- - t *	- - - -
OC	- - - -	- - - -
CGI Severity		
LOCF	t * * *	- * * *
OC	* * * *	- * * *
MSPS-Fear Score		
LOCF	- t * *	- * * *
OC	- * * *	- * - *
MSPS-Avoidance Score		
LOCF	- * t *	- - t *
OC	- * - *	- - t *
SDS-Work Score		
LOCF	* * * *	- * * *
OC	* * * *	- * * *
SDS-Social Life Score		
LOCF	* * * *	- * * *
OC	* * * *	- * * *
SDS-Family Life Score		
LOCF	* * * *	* * * *
OC	* * * *	* * * *

1 * = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$

2 End of weeks 3, 6, 9, and 12

Size of Treatment Effect in Study 187			
Proportion of Patients with Panic Attacks ↓ to Zero			
Group	**Baseline[1]**	**Wks 9-12**	**Difference[2]**
Placebo	-	**33%**	
Paroxetine	-	**51%**	**18%**
Clomipramine	-	**50%**	**17%**
Proportion of Patients with ≥ 50% ↓ in Panic Attacks			
Group	**Baseline[1]**	**Wks 9-12**	**Difference[2]**
Placebo	-	**62%**	
Paroxetine	-	**80%**	**18%**
Clomipramine	-	**68%**	**6%**
Number of Full Panic Attacks/3 Weeks			
Group	Baseline[3]	BL - Wk 12[4]	Difference[5]
Placebo	18.5	- 8.5	
Paroxetine	17.9	- 12.2	3.7
Clomipramine	15.3	- 8.7	0.2
CGI Severity Score			
Group	Baseline[3]	BL - Wk 12[4]	Difference[5]
Placebo	4.5	- 1.0	
Paroxetine	4.6	- 1.9	0.9
Clomipramine	4.6	- 1.6	0.6

1 Baseline not relevant to this variable
2 Difference between drug and placebo in proportion of patients meeting criteria in weeks 9-12 (LOCF)
3 Mean score at baseline
4 Mean Change from baseline to week 12 (LOCF)
5 Difference in mean change from baseline to week 12 endpoint (LOCF) between drug and placebo

Impression: I considered this study positive, not only for the primary panic attack variables, but also for CGI severity, the MSPS scores and the SDS scores. [Note: One concern here was the failure for the OC results on the panic attack variable to meet the $p \leq 0.05$ cirterion. The explanation proposed was a higher dropout rate for lack of effect in placebo (14%) vs paroxetine (4%). While I

would like to have seen an analyses of scores on these variables for dropouts from each of these groups (e.g., were paroxetine dropouts doing better than placebo dropouts?), I am not particularly troubled by this discrepancy, given the overwhelmingly positive findings on the CGI-Severity and all the secondary variables.] Consequently, I believe this study provides additional support for the effectiveness of paroxetine in panic disorder.

5.1.1.4 Study 223

This was a randomized, 16-center (US), double-blind, parallel group, 10-week, flexible-dose study comparing paroxetine (in a dose range of 10-60 mg/day; qd schedule), alprazolam (in a dose range of 1-6 mg/day; bid schedule), and placebo for the treatment of PD in adult outpatients meeting DSMIIIR criteria for PD. Patients were required to have at least 2 full panic attacks (i.e., ≥4 of the DSMIIIR criteria for a panic attack) in the 2 week period between screening and baseline. Patients could have sufficient depressive symptoms to meet criteria for major depressive disorder, providing the panic disorder symptoms were considered primary.

Patients completed a Panic Diary and an Anticipatory Anxiety Assessment (AAA) daily. Patients were rated at baseline and the ends of weeks 1, 2, 3, 4, 6, 8, and 10 on the following: Panic Diary and AAA (investigator summarized the information from these instruments); and CGI. Patients were rated at baseline and the ends of weeks 4 and 10 on the following: Marks-Sheehan Phobia Scale (MSPS); Sheehan Disability Scale (SDS).

Reduction in the number of full panic attacks was identified as the primary efficacy variable, using 3 approaches (all with reference to an interval of the previous 2 weeks): (1) proportion of patients having zero full panic attacks, (2) proportion of patients having ≥ 50%reduction from baseline in the mean number of full panic attacks, and (3) mean change from baseline in the number of full panic attacks.

The following variables (mean change from baseline) were derived from the secondary assessments:

MSPS-Fear Score
MSPS-Avoidance Score
AA-% Time Worrying
AA-Intensity
SDS-Work Score
SDS-Social Life Score
SDS-Family Life Score

Patients were approximately 2/3 female, predominantly Caucasian, and the mean age was late 30's. The treatment groups were generally comparable at baseline on the demographic and the key

efficacy variables. Mean doses for completers at 10 weeks were 39 mg/day for paroxetine and 3.6 mg/day for alprazolam.

Study Results

The intent-to-treat dataset was as follows:

paroxetine	(77)
alprazolam	(77)
placebo	(68)

Completion rates to 12 weeks were as follows:

paroxetine	48/77 (62)
alprazolam	60/77 (78%)
placebo	50/68 (69%)

Summary of Significance Levels[1] (2-sided) for Pairwise Comparisons (Parox. & Alpraz. vs Placebo) in Study 223

Key Outcome Variables	Parox. vs Pbo.					Alpraz. vs Pbo				
	Week[2] 2	4	6	8	10	Week 2	4	6	8	10
No. Panic Attacks										
Proportion Zero										
LOCF	-	t	-	-	-	-	-	-	-	-
OC	-	t	-	-	-	-	-	-	-	-
Proportion ≥ 50% ↓										
LOCF	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-
Mean Δ Baseline										
LOCF	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-
CGI Severity										
LOCF	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-
MSPS-Fear Score										
LOCF	-				t	*				-
OC	-				-	t				-
MSPS-Avoidance Score										
LOCF	-				-	*				-
OC	-				-	*				-
AA-% Time Worrying										
LOCF	-	-	-	-	-	*	-	*	*	-
OC	-	-	-	-	-	*	-	*	-	-
AA-Intensity										
LOCF	-	-	-	-	-	*	-	*	t	-
OC	-	-	-	-	-	*	-	-	-	-
SDS-Work Score										
LOCF	*				t	-				-
OC	t				-	-				-
SDS-Social Life Score										
LOCF	t				*	-				-
OC	t				-	-				-
SDS-Family Life Score										
LOCF	*				*	-				-
OC	*				-	-				-

1 * = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$

2 End of weeks 2, 4, 6, 8, and 10

Size of Treatment Effect in Study 223			
Proportion of Patients with Panic Attacks ↓ to Zero			
Group	**Baseline[1]**	**Wks 9-10**	**Difference[2]**
Placebo	-	**63%**	
Paroxetine	-	**59%**	**-4%**
Alprazolam	-	**62%**	**-1%**
Proportion of Patients with ≥ 50% ↓ in Panic Attacks			
Group	**Baseline[1]**	**Wks 9-10**	**Difference[2]**
Placebo	-	**78%**	
Paroxetine	-	**79%**	**1%**
Alprazolam	-	**87%**	**9%**
Number of Full Panic Attacks/2 Weeks			
Group	Baseline[3]	BL - Wk 10[4]	Difference[5]
Placebo	7.9	- 4.7	
Paroxetine	8.8	- 6.7	2.0
Alprazolam	9.8	- 7.8	3.1
CGI Severity Score			
Group	Baseline[3]	BL - Wk 10[4]	Difference[5]
Placebo	4.5	- 1.5	
Paroxetine	4.4	- 1.8	0.3
Alprazolam	4.4	- 1.8	0.3

1 Baseline not relevant to this variable
2 Difference between drug and placebo in proportion of patients meeting criteria in weeks 9-10 (LOCF)
3 Mean score at baseline
4 Mean Change from baseline to week 10 (LOCF)
5 Difference in mean change from baseline to week 10 endpoint (LOCF) between drug and placebo

Impression: Although there were some scattered positive findings in this study, especially for alprazolam, overall neither active drug was shown to be superior to placebo. The prominent placebo response may have contributed to this outcome. In any case, this can be considered a failed study, since neither active drug beat placebo.

5.1.1.5 Study 228

This was an extension of study 187. Patients from any of the 3 treatment groups who completed study 187 and had no significant adverse events could be continued for up to 9 months, on a double-blind basis, on the same treatment and dose as in the short-term phase. Assessments were the same as in the short-term phase, but at 6-week intervals. In addition, definitions were provided for categorizing patients as having had partial or full relapse during the extension phase.

A major problem with this study was the fact that the original randomization was violated, in that only completers meeting the identified criteria were continued. Consequently, it is of descriptive value only, and I will not provide detailed comments. However, overall the results did not substantially favor paroxetine over placebo. There were few relapses and no statistically significant differences between groups in number of relapses or time to relapse.

5.1.1.6 Study 222

This was an extension of study 120. Patients who completed study 120, had no significant adverse events, and met criteia for being either partial or full responders could be entered into study 222. [Partial response = ≥ 50% reduction in full panic attacks during weeks 9-10; full response = no full panic attacks during weeks 9-10.]

The first 3 months of study 222 was a double-blind maintenance phase during which patients were continued on their previously assigned treatment and dose. Patients who were responders during the last 2 weeks of the maintenance phase and had not "relapsed" during that 3 month period could enter the 3-month re-randomization phase, which involved randomization to either their previous treatment and dose (placebo or paroxetine 10, 20, or 40 mg/day), or to placebo. The key outcomes during this phase were percent relapse and time to relapse. [A patient relapsed if frequency of full panic attacks per two weeks was ≥ that observed at baseline for study 120, or there was an increase of ≥ 2 points on CGI severity, relative to the score at week 12 of the maintenance phase.]

For the primary analysis, patients randomized from placebo to placebo were not included (not planned this way in protocol). The relapse rates for the remaining groups were as follows:

10 mg to pbo	2/12 (17%)
20 mg to pbo	2/12 (17%)
40 mg to pbo	7/13 (54%)
Total Parox to pbo	11/37 (30%)
10 mg to 10 mg	0/12 (0%)

20 mg to 20 mg	1/13 (8%)
40 mg to 40 mg	1/18 (6%)
Total parox to parox	2/43 (5%)

These results are certainly suggestive of a maintenance effect for paroxetine. However, this can be considered only a pilot study without any clearly defined prospective analysis plan, and would need replication in a more definitive trial to justify a claim for maintenance effectiveness.

5.1.2 Comment on Other Important Clinical Issues Regarding the Efficacy of Paxil for Panic Disorder

Evidence Bearing on the Question of Dose/Response for Efficacy

Of the 3 positive studies supporting the anti-panic effectiveness of Paxil, only 1 (Study 120) involved a fixed dose design. In that fixed dose study, only the highest dose (40 mg/day) was shown to be effective. The other 2 positive studies involved titration within a paroxetine range of 20-60 mg/day, and for both, the mean paroxetine dose for completers was approximately 40 mg/day. Thus, it seems reasonable to suggest 40 mg/day as the initial target dose for anti-panic therapy with paroxetine. However, since higher doses have not been specifically studied, and some patients in the flexible dose studies seemed to need doses at the higher end of the paroxetine dose range, it also seems reasonable to propose 60 mg/day as the maximum recommended dose and suggest that, although not proven, some patients may benefit from these higher doses.

Clinical Predictors of Response

The sponsor conducted subgroup analyses on the basis of gender and baseline severity for the 3 panic attack variables in each of the 4 short-term studies. There were no differences for paroxetine on the basis of gender. As might be expected, patients with a greater severity of illness at entry, as based on number of panic attacks, improved more than less ill patients. An analysis using age as a continuous variable revealed no significant age effect on response.

Size of Treatment Effect

An approach to estimating treatment effect size is to examine the differences between paroxetine and placebo in the proportions of patients meeting criteria for response or on mean change from baseline for other key effectiveness measures in the 3 positive studies in this development program, as follows:

Size of Treatment Effect in Three Panic Disorder Studies for Key Efficacy Variables at 10- or 12-Week Endpoint (LOCF)			
Study 120			
Variables	**Paroxetine[1,2]**	**Placebo[2]**	**Difference[3]**
# Panic Attack			
↓ to Zero	76%	44%	32%
≥ 50% ↓	89%	74%	15%
# Full PA	- 8.2	- 5.5	2.7
CGI Severity	- 1.8	- 1.3	0.5
Study 108			
Variables	**Paroxetine[1,2]**	**Placebo[2]**	**Difference[3]**
# Panic Attack			
↓ to 0/1	33%	14%	19%
≥ 50% ↓	79%	47%	32%
# Full PA	- 15.0	- 10.0	5.0
CGI Severity	- 2.1	- 1.3	0 8
Study 187			
Variables	**Paroxetine[1,2]**	**Placebo[2]**	**Difference[3]**
# Panic Attack			
↓ to Zero	51%	33%	18%
≥ 50% ↓	80%	62%	18%
# Full PA	- 12.2	- 8.5	3.7
CGI Severity	- 1.9	- 1.0	0.9

1 Data from 40 mg/day group

2 Proportions of patients meeting criteria for response in last observation interval, for zero panic attacks and ≥ 50% ↓ variables; mean change from baseline to 10- or 12-week endpoint for # panic attacks and CGI-Severity

3 Difference between paroxetine and placebo in proportions meeting criteria for zero panic attacks and ≥ 50% ↓ variables; difference between paroxetine and placebo in mean change from baseline to 10- or 12-week endpoint for # panic attacks and CGI-Severity

I consider these effects to be clinically meaningful and sufficient support to justify the approvability of the panic disorder indication for paroxetine.

Duration of Treatment Effect

As noted earlier, there were extension phases for 2 of the short-term trials. Study 228 generated data that was of descriptive value only, and those results were not partucularly supportive of a maintenance effect for paroxetine. Study 222 did involve a re-randomization of patients who were considered responders, and data from that study were suggestive of a maintenance effect. However, for the reasons noted, study 222 cannot be considered a sufficient basis for a definitive judgement on this matter. In the meantime, we have taken the same approach in labeling for this indication that we have for other chronic illnesses, i.e., acknowledge the absence of sufficient relapse prevention data, yet suggest that it would not be unreasonable to continue responding patients beyond the acute treatment phase.

5.1.3 Conclusions Regarding Efficacy Data

In my view, three of the four studies in this development program support the short-term effectiveness of paroxetine in the treatment of PD.

5.2 Safety Data

The safety data for Paxil/PD were reviewed by James Knudsen, M.D. (review completed and signed 12-28-95). Since Paxil has been widely available in the US and elsewhere for approximately 2 years for the treatment of depression, a major part of our approach to the safety data was to compare the findings from the relatively small PD database with the database for depression. Dr. Knudsen concluded that Paxil is acceptably safe for use in the treatment of PD, and I agree with that conclusion.

The four studies for which data were available for the integrated database (120, 108, 187, and 223) were briefly described under 5.1 (efficacy). These were 10-12 week, placebo-controlled trials. The cutoff date for the integrated database for these four studies was 5-1-94, and this database included 469 patients exposed to paroxetine. The cutoff date for serious events was 12-31-94. Patients from two of those studies (120 and 187) had additional exposure in extension phases of those studies for up to 9 months. The above four studies and the two extensions were completed prior to submission of this supplement, thus, all adverse event data were included in the supplement, and no additional data are expected for any of these patients. The supplement also included an update on spontaneous reports for Paxil worldwide. Apparently, all the spontaneous reports provided were for patients being treated for

depression, and no reports were available for patients identified as being treated with paroxetine for Panic Disorder.

For the integrated PD database, paroxetine-exposed patients ranged in age from 18-74 (mean=36), were 65% female, and were 78% caucasian. The exposure tended to be short-term, however, about 29% were exposed for greater than 6 months. About 75% of patients received mean doses in a range of 16-60 mg/day.

There were no deaths among the paroxetine-exposed patients in the integrated database for the panic disorder studies.

A search of the integrated database for serious events yielded a total of 13 among paroxetine-exposed patients. Neither the numbers nor types of events were unexpected for this population. A search for suicidality also did not reveal any indication of a paroxetine-associated risk for suicidal behavior.

The common and drug-related adverse events leading to dropout (incidence ≥ 1% and at least twice the placebo rate) included: nausea, insomnia, and somnolence. This list overlapped with comparable lists for depression and OCD databases, however, included fewer adverse events overall.

The common and drug-related adverse events overall (from the integrated database; incidence ≥ 5% and at least twice the placebo rate) included: asthenia, decreased appetite, tremor, sweating, abnormal ejaculation, impotence, libido decreased, and female genital disorders (mostly anorgasmia or difficulty reaching orgasm). This list was also similar to the adverse events associated with paroxetine in the depression and OCD databases.

Three of the short-term trials had a run-out phase during which assigned treatments were tapered and withdrawn (periods ranged from 3-6 weeks). Overall, 390 patients were discontinued in this manner, including 155 from paroxetine, 60 from alprazolam, 27 from clomipramine, and 148 from placebo. The incidence of dropout from this tapered withdrawl for adverse events was as follows:

Paroxetine	6/155	(4%)
Alprazolam	1/60	(2%)
Clomipramine	1/27	(4%)
Placebo	0	

The most common reasons for paroxetine patients leaving the scheduled tapering were headache, agitation, and depression.

Explorations of the integrated database for laboratory and vital signs variables, including analyses of change from baseline, analyses of proportions of patients meeting criteria for potentially clinically significant change on these variables, and

dropouts for changes in any of these variables did not reveal any new or clinically important findings.

In conclusion, the safety experience for paroxetine (dosed in a range of 20 to 60 mg/day) in patients with PD did not reveal any adverse findings that are unique for this population, and none that would preclude its use in this population. We have requested a safety update in the approvable letter.

5.3 Clinical Sections of Labeling

We have rewritten some of the proposed changes in the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

Dr. Knudsen reviewed the published literature for Paxil included in the NDA and did not discover any previously unrecognized important safety concerns for this drug.

7.0 FOREIGN REGULATORY ACTIONS

Paxil is marketed in a number of countries around the world for the treatment of depression. To my knowledge, it is not yet marketed anywhere for the treatment of PD. We will ask for an update on the regulatory status of Paxil in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this supplement to the PDAC.

9.0 DSI INSPECTIONS

DSI inspections were requested but no responses have been received as yet. It is the current policy of DSI not to do routine inspections for supplements.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made some changes to the sponsor's draft dated 3-29-95.

10.2 Foreign Labeling

To my knowledge, Paxil is not approved for PD anywhere at this time.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a safety update, a literature update, a regulatory status update, and a commitment to conduct a relapse prevention trial.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that SKB has submitted sufficient data to support the conclusion that Paxil is effective and acceptably safe in the treatment of Panic Disorder. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

cc:
Orig NDA
HFD-120
HFD-120/TLaughren/PLeber/GDubitsky/JKnudsen/MMille

DOC: MEMPAXPD.AE1

NDA 20031
S001 OCD
S009 Paxil

PAXIL

(PAROXETINE HYDROCHLORIDE)
NDA 20-031/S-007/S-009

VOLUME 1 of 3

APPROVAL PACKAGE

INDICATION: OBSESSIVE-COMPULSIVE DISORDER (S-007) & PANIC DISORDER (S-009)

CLASS: SELECTIVE SEROTONIN REUPTAKE INHIBITOR (SSRI)

CATEGORY: SE1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-031/S-007/S-009

MAY 7 1996

SmithKline Beecham Pharmaceuticals
Attention: Michael J. Brennan, Ph.D.
1250 S. Collegeville Road
P.O. Box 5089
Collegeville, Pennsylvania 19426-0989

Dear Dr. Brennan:

Please refer to your supplemental New Drug Applications dated December 6, 1994 (S-007), and March 29, 1995 (S-009), submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil® (paroxetine hydrochloride) 10, 20, 30, and 40 mg tablets.

Reference is also made to Agency approvable letters dated October 12, 1995 (S-007), and March 15, 1996 (S-009), and to facsimile transmissions from this Division to your firm on April 22, and May 2, 1996. We additionally refer to telephone conversations dated April 30, and May 3, 1996.

We acknowledge receipt of your amendments dated January 18, and February 8, April 5, and April 12, 1996, providing for responses to our approvable letters.

The above efficacy supplemental applications provide for the use of Paxil® to treat obsessive compulsive disorder (S-007), and panic disorder (S-009).

We note that your firm agreed on April 30, and May 3, 1996, to the minor labeling revisions to your draft labeling submitted on April 5, 1996. Additionally, we note that you intend to market Paxil® 10 mg and 40 mg tablets strengths with the issuance of the proposed labeling submitted on April 5, 1996. These tablets strengths were included in the approval of the original application.

We have completed our review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling (see ATTACHMENT). Accordingly, these supplemental applications are approved effective on the date of this letter.

The labeling accompanying this letter should be used for marketing this drug product. This labeling is identical to the draft labeling "faxed" to you on April 22, except for the minor revisions agreed upon in telephone conversations dated April 30, and May 3, 1996. For convenience, all labeling changes made since the approval of the last labeling supplement (SLR- 008, Label Code - PX:L8) on February 23, 1995, appear as shaded text (redlined) in the attached labeling.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. These revisions are terms of the supplemental NDA approvals. Marketing the product before making the agreed upon revisions in the product's labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDAs 20-031/S-007/S-009. Approval of this labeling by FDA is not required before it is used.

We remind you of your Phase 4 commitment agreed upon in your submission dated January 18, 1996. This commitment is listed below. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocols, data, and final reports to this NDA as correspondence. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments".

Phase 4 Commitments

> We note that your commitment, in correspondence dated January 18, 1996, to initiate a protocol to study the efficacy and safety in adolescents with obsessive compulsive disorder within the first quarter of 1996. We also note that your correspondence dated February 8, 1996, indicates that you expect to complete this study by fourth quarter of 1997.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions concerning this NDA, please contact Mr. Paul David, Project Manager, at (301) 594-2777.

Sincerely yours,

5/7/96

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ATTACHMENT

ATTACHMENT

FINAL LABELING

Note: This final labeling is based on your 4-5-96 draft labeling proposal. For ease in supervisory review of the labeling modifications regarding the OCD indication, panic disorder indication, and other labeling revisions, we have shaded ('redline font') all the changes to the current existing labeling.

ATTACHMENT

PRESCRIBING INFORMATION

PAXIL®
brand of
paroxetine hydrochloride tablets

DESCRIPTION

Paxil (paroxetine hydrochloride) is an orally administered antidepressant with a chemical structure unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic or other available antidepressant agents. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-trans-4R-(4'-fluorophenyl)-3S-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3HCl$ $1/2H_2O$. The molecular weight is 374.8 (329.4 as free base). The structural formula is:

[Insert structural formula here]
paroxetine hydrochloride

Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of 120° to 138°C and a solubility of 5.4 mg/mL in water.

Each film-coated tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: 10 mg-yellow; 20-mg pink

(scored); 30 mg-blue, 40mg-green. Inactive ingredients consist of dibasic calcium phosphate dihydrate, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide and one or more of the following: D&C Red No. 30, D&C Yellow No. 10, FD&C Blue No. 2, FD&C Yellow No. 6.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The antidepressant action of paroxetine and its efficacy in the treatment of obsessive compulsive disorder (OCD) and panic disorder (PD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* radioligand binding studies indicate that paroxetine has little affinity for muscarinic, alpha$_1$-, alpha$_2$-, beta-adrenergic-, dopamine (D_2)-, 5-HT_1-, 5-H_2T - and histamine (H)-receptors; antagonism of muscarinic, histaminergic and alpha$_1$-adrenergic receptors has been associated with various anticholinergic, sedative and cardiovascular effects for other psychotropic drugs.

Because the relative potencies of paroxetine's major metabolites are at most 1/50 of the parent compound, they are essentially inactive.

Pharmacokinetics

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male subjects (n=15) received 30 mg tablets daily for 30 days, steady-state paroxetine concentrations were achieved by approximately 10 days for most subjects, although it may take substantially longer in an occasional patient. At steady state,

mean values of C_{max}, T_{max}, C_{min} and $T_{1/2}$ were 61.7 ng/mL (CV 45%), 5.2 hr. (CV 10%), 30.7 ng/mL (CV 67%) and 21.0 hr. (CV 32%), respectively. The steady-state C_{max} and C_{min} values were about 6 and 14 times what would be predicted from single-dose studies. Steady-state drug exposure based on AUC_{0-24} was about 8 times greater than would have been predicted from single-dose data in these subjects. The excess accumulation is a consequence of the fact that one of the enzymes that metabolizes paroxetine is readily saturable.

In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of 20 to 40 mg daily for the elderly and 20 to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{min} values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than doubled.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by cytochrome $P_{450}IID_6$. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see PRECAUTIONS).

Approximately 64% of a 30 mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.

Distribution

Paroxetine distributes throughout the body, including the CNS, with

only 1% remaining in the plasma.

Protein Binding

Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/mL. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.

Renal and Liver Disease

Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below 30 mL/min was approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30 to 60 mL/min and patients with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, C_{max}).

The initial dosage should therefore be reduced in patients with severe renal or hepatic impairment, and upward titration, if necessary, should be at increased intervals (see DOSAGE AND ADMINISTRATION).

Elderly Patients

In a multiple-dose study in the elderly at daily paroxetine doses of 20, 30 and 40 mg, C_{min} concentrations were about 70% to 80% greater than the respective C_{min} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced. (See DOSAGE AND ADMINISTRATION.)

Clinical Trials

Depression

The efficacy of Paxil as a treatment for depression has been established in 6 placebo-controlled studies of patients with depression (ages 18 to 73). In these studies Paxil was shown to be significantly more effective than placebo in treating depression by

at least 2 of the following measures: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI) Severity of Illness. Paxil was significantly better than placebo in improvement of the HDRS sub-factor scores, including the depressed mood item, sleep disturbance factor and anxiety factor.

A study of depressed outpatients who had responded to Paxil (HDRS total score <8) during an initial 8-week open-treatment phase and were then randomized to continuation on Paxil or placebo for 1 year demonstrated a significantly lower relapse rate for patients taking Paxil (15%) compared to those on placebo (39%). Effectiveness was similar for male and female patients.

Obsessive Compulsive Disorder

The effectiveness of Paxil in the treatment of obsessive compulsive disorder (OCD) was demonstrated in two 12-week multicenter placebo-controlled studies of adult outpatients (Studies 1 and 2). Patients in all studies had moderate to severe OCD (DSM-IIIR) with mean baseline ratings on the Yale Brown Obsessive Compulsive Scale (YBOCS) total score ranging from 23 to 26. Study 1, a dose range finding study where patients were treated with fixed doses of 20, 40 or 60 mg of paroxetine/day demonstrated that daily doses of paroxetine 40 and 60 mg are effective in the treatment of OCD. Patients receiving doses of 40 and 60 mg paroxetine experienced a mean reduction of approximately 6 and 7 points respectively on the YBOCS total score which was significantly greater than the approximate 4 point reduction at 20 mg and a 3 point reduction in the placebo-treated patients. Study 2 was a flexible dose study comparing paroxetine (20 to 60 mg daily) with clomipramine (25 to 250 mg daily). In this study, patients receiving paroxetine experienced a mean reduction of approximately 7 points on the YBOCS total score which was significantly greater than the mean reduction of approximately 4 points in placebo-treated patients.

The following table provides the outcome classification by treatment group on Global Improvement items of the Clinical Global Impressions (CGI) scale for study 1.

Outcome Classification (%) on CGI Global Improvement Item for Completers in Study 1				
Outcome Classification	Placebo (N=74)	Paxil 20mg (N=75)	Paxil 40mg (N=66)	Paxil 60mg (N=65)
Worse	14%	7%	7%	3%
No Change	44%	35%	22%	19%
Minimally Improved	24%	33%	29%	34%
Much Improved	11%	18%	22%	24%
Very Much Improved	7%	7%	20%	20%

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

The long-term maintenance effects of Paxil in OCD were demonstrated in a long-term extension to Study 1. Patients who were responders on paroxetine during the 3-month double-blind phase and a 6-month extension on open-label paroxetine (20 to 60 mg/day) were randomized to either paroxetine or placebo in a 6-month double-blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Panic Disorder

The effectiveness of Paxil in the treatment of panic disorder was demonstrated in three 10 to 12 week multicenter, placebo-controlled studies of adult outpatients (Studies 1-3). Patients in all studies had panic disorder (DSM-IIIR), with or without agoraphobia. In these studies, Paxil was shown to be significantly more effective than placebo in treating panic disorder by at least 2 out of 3 measures of panic attack frequency and on the Clinical Global Impression Severity of Illness score.

Study 1 was a 10-week dose-range finding study: patients were treated with fixed paroxetine doses of 10, 20, or 40 mg/day or placebo. A significant difference from placebo was observed only

for the 40 mg/day group. At endpoint, 76% of patients receiving paroxetine 40 mg/day were free of panic attacks, compared to 36% of placebo-treated patients.

Study 2 was a 12-week flexible-dose study comparing paroxetine (10 to 60 mg daily) and placebo. At endpoint, 51% of paroxetine patients were free of panic attacks compared to 33% of placebo treated patients.

Study 3 was a 12-week flexible-dose study comparing paroxetine (10 to 60 mg daily) to placebo in patients concurrently receiving standardized cognitive behavioral therapy. At endpoint, 38% of the paroxetine-treated patients showed a reduction to 0 or 1 panic attacks compared to 14% of placebo patients.

In both Studies 2 and 3, the mean paroxetine dose for completers at endpoint was approximately 40 mg/day of paroxetine.

Long-term maintenance effects of Paxil in panic disorder were demonstrated in an extension to Study 1. Patients who were responders during the 10-week double-blind phase and during a 3-month double-blind extension phase were randomized to either paroxetine (10, 20, or 40 mg/day) or placebo in a 3-month double blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

INDICATIONS AND USAGE

Depression

Paxil (paroxetine hydrochloride) is indicated for the treatment of depression.

The efficacy of Paxil in the treatment of a major depressive episode was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category

of major depressive disorder (see CLINICAL PHARMACOLOGY). A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant action of Paxil in hospitalized depressed patients has not been adequately studied.

The efficacy of Paxil in maintaining an antidepressant response for up to 1 year was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use Paxil for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Obsessive Compulsive Disorder

Paxil is indicated for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD) as defined in the DSM-IV. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of Paxil was established in two 12-week trials with obsessive compulsive outpatients whose diagnoses corresponded most closely to the DSM-IIIR category of obsessive compulsive disorder (see CLINICAL PHARMACOLOGY-Clinical Trials).

Obsessive compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients assigned to paroxetine showed a lower relapse rate compared to patients on

placebo (see Clinical Pharmacology). Nevertheless, the physician who elects to use Paxil for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Panic Disorder

Paxil is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attack.

The efficacy of Paxil was established in three 10 to 12 week trials in panic disorder patients whose diagnoses corresponded to the DSM-IIIR category of panic disorder (see Clinical Pharmacology-Clinical Trials).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes [(1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.]

Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who prescribes Paxil for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS and **PRECAUTIONS**).

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving another serotonin reuptake inhibitor drug in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with *Paxil*, limited animal data on the effects of combined use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Paxil (paroxetine hydrochloride) not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. At least 2 weeks should be allowed after stopping *Paxil* before starting a MAOI.

PRECAUTIONS

General

Activation of Mania/Hypomania

During premarketing testing, hypomania or mania occurred in approximately 1.0% of Paxil-treated unipolar patients compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for Paxil and 11.6% for the combined active-control groups. As with all antidepressants, Paxil should

be used cautiously in patients with a history of mania.

Seizures

During premarketing testing, seizures occurred in 0.1% of Paxil-treated patients, a rate similar to that associated with other antidepressants. Paxil should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Suicide

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Paxil should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Hyponatremia

Several cases of hyponatremia have been reported. The hyponatremia appeared to be reversible when Paxil was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Abnormal Bleeding

There have been several reports of abnormal bleeding (mostly ecchymosis and purpura) associated with paroxetine treatment, including a report of impaired platelet aggregation. While a causal relationship to paroxetine is unclear, impaired platelet aggregation may result from platelet serotonin depletion and contribute to such occurrences.

Use in Patients with Concomitant Illness

Clinical experience with Paxil in patients with certain concomitant systemic illness is limited. Caution is advisable in using Paxil in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Paxil has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. Evaluation of electrocardiograms of 682 patients who received Paxil in double-blind, placebo-controlled trials, however, did not indicate that Paxil is associated with the development of significant ECG abnormalities. Similarly, Paxil (paroxetine hydrochloride) does not cause any clinically important changes in heart rate or blood pressure.

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance <30 mL/min.) or severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Paxil:

Interference with Cognitive and Motor Performance

Any psychoactive drug may impair judgment, thinking or motor skills. Although in controlled studies Paxil has not been shown to impair psychomotor performance, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Paxil therapy does not affect their ability to engage in such activities.

Completing Course of Therapy

While patients may notice improvement with Paxil therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant Medication

Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Although Paxil has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking Paxil.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing

Patients should be advised to notify their physician if they are breast-feeding an infant. (See PRECAUTIONS-Nursing Mothers.)

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

Tryptophan

As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are co-administered. Adverse experiences, consisting primarily of headache, nausea, sweating and dizziness, have been reported when tryptophan was administered to patients taking Paxil (paroxetine hydrochloride). Consequently, concomitant use of Paxil with tryptophan is not recommended.

Monoamine Oxidase Inhibitors

See CONTRAINDICATIONS and WARNINGS.

Warfarin

Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the face of unaltered prothrombin time) between paroxetine and

warfarin. Since there is little clinical experience, the concomitant administration of Paxil and warfarin should be undertaken with caution.

Drugs Affecting Hepatic Metabolism

The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug-metabolizing enzymes.

Cimetidine - Cimetidine inhibits many cytochrome P_{450} (oxidative) enzymes. In a study where Paxil (30 mg q.d.) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during co-administration with oral cimetidine (300 mg t.i.d.) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of Paxil after the 20 mg starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

Phenobarbital - Phenobarbital induces many cytochrome P_{450} (oxidative) enzymes. When a single oral 30 mg dose of Paxil was administered at phenobarbital steady state (100 mg q.d. for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since Paxil exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed. No initial Paxil dosage adjustment is considered necessary when co-administered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

Phenytoin - When a single oral 30 mg dose of Paxil was administered at phenytoin steady state (300 mg q.d. for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 50% and 35%, respectively) compared to Paxil administered alone. In a separate study, when a single oral 300 mg dose of phenytoin was administered at paroxetine steady state (30 mg q.d. for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the 2 drugs are both being

chronically dosed. No initial dosage adjustments are considered necessary when these drugs are co-administered; any subsequent adjustments should be guided by clinical effect. (see ADVERSE REACTIONS-Postmarketing Reports).

Drugs Metabolized by Cytochrome $P_{450}IID_6$

Many drugs, including most antidepressants (paroxetine, other SSRIs, and many tricyclics), are metabolized by the cytochrome P450 isozyme P450IID6. Like other agents that are metabolized by P450IID6, paroxetine may significantly inhibit the activity of this isozyme. In most patients (>90%), the P450IID6 isozyme is saturated early during PAXIL dosing. In one study, daily dosing of PAXIL (20 mg q.d.) under steady-state conditions increased single dose desipramine (100 mg) Cmax, AUC, and $T_{1/2}$ by an average of approximately two-, five-, and three-fold respectively. Concomitant use of PAXIL with other drugs metabolized by cytochrome P450IID6 has not been formally studied but may require lower doses than usually prescribed for either PAXIL or the other drug.

Therefore, co-administration of Paxil with other drugs that are metabolized by this isozyme, including certain antidepressants (e.g., nortriptyline, amitriptyline, imipramine, desipramine and fluoxetine), phenothiazines (e.g., thioridazine) and Type 1C anti-arrhythmics (e.g., propafenone, flecainide and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

At steady state, when the $P_{450}IID_6$ pathway is essentially saturated, paroxetine clearance is governed by alternative P_{450} isozymes which, unlike $P_{450}IID_6$, show no evidence of saturation. (see PRECAUTIONS-Tricyclic Antidepressants).

Drugs Metabolized by Cytochrome P450IIIA4

An in vivo interaction study involving the co-administration under steady-state conditions of paroxetine and terfenadine, a substrate for cytochrome $P_{450}3A4$, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of cytochrome $P_{450}3A4$, to be at least 100 times more potent than paroxetine as an inhibitor of

the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporin. Based on the assumption that the relationship between paroxetine's in vitro Ki and its lack of effect on terfenadine's in vivo clearance predicts its effect on other 3A4 substrates, paroxetine's extent of inhibition of 3A4 activity is not likely to be of clinical significance.

Tricyclic Antidepressants (TCA)

Caution is indicated in the co-administration of tricyclic antidepressants (TCAs) with PAXIL, because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is co-administered with PAXIL (see PRECAUTIONS-Drugs Metabolized by Cytochrome $P_{450}IID_6$).

Drugs Highly Bound to Plasma Protein

Because paroxetine is highly bound to plasma protein, administration of *Paxil* to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

Alcohol

Although Paxil does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking Paxil (paroxetine hydrochloride).

Lithium

A multiple-dose study has shown that there is no pharmacokinetic interaction between Paxil and lithium carbonate. However, since there is little clinical experience, the concurrent administration of paroxetine and lithium should be undertaken with caution.

Digoxin

The steady-state pharmacokinetics of paroxetine was not altered

when administered with digoxin at steady state. Mean digoxin AUC at steady state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of paroxetine and digoxin should be undertaken with caution.

Diazepam

Under steady-state conditions, diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

Procyclidine

Daily oral dosing of *Paxil* (30 mg q.d.) increased steady-state AUC_{0-24}, C_{max} and C_{min} values of procyclidine (5 mg oral q.d.) by 35%, 37% and 67%, respectively, compared to procyclidine alone at steady state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

Beta-Blockers

In a study where propranolol (80 mg b.i.d.) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during co-administration with Paxil (30 mg q.d.) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated. (see **ADVERSE REACTIONS-Postmarketing Reports**).

Theophylline

Reports of elevated theophylline levels associated with Paxil treatment have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

Electroconvulsive Therapy (ECT)

There are no clinical studies of the combined use of ECT and Paxil.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 2.5, 10 and 20 mg/kg/day (rats). These doses are up to 2.4 (mouse) and 3.9 (rat) times the maximum recommended human dose (MRHD) for depression on a mg/m² basis. Because the MRHD for depression is slightly less than that for OCD (50 mg vs. 60 mg), the doses used in these carcinogenicity studies were only 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50 and 4/50 for control, low-, middle- and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis

Paroxetine produced no genotoxic effects in a battery of 5 *in vitro* and 2 *in vivo* assays that included the following: bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes and in a dominant lethal test in rats.

Impairment of Fertility

A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day which is 2.9 times the MRHD for depression or 2.4 times the MRHD for OCD on a mg/m² basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (9.8 and

4.9 times the MRHD for depression; 8.2 and 4.1 times the MRHD for OCD and PD on a mg/m² basis).

Pregnancy

Teratogenic Effects - Pregnancy Category C

Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during [redacted]. These doses are equivalent to 9.7 (rat) and 2.2 (rabbit) times the maximum recommended human dose (MRHD) for depression (50 mg) and 8.1 (rat) and 1.9 (rabbit) times the MRHD for OCD, on a mg/m² basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or 0.19 times (mg/m²) the MRHD for depression and at 0.16 times (mg/m²) the MRHD for OCD. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of paroxetine on labor and delivery in humans is unknown.

Nursing Mothers

Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when Paxil (paroxetine hydrochloride) is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

Geriatric Use

In worldwide premarketing Paxil clinical trials, 17% of *Paxil*-treated patients (approximately 700) were 65 years of age or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Twenty percent of (1,199/6,145) of Paxil patients in worldwide clinical trials in depression and 11.8% (64/542) and 9.4% (44/469) of Paxil patients in worldwide trials in OCD and panic disorder, respectively, discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for Paxil compared to placebo) included the following:

	Depression		OCD		Panic Disorder	
	Paxil	Placebo	Paxil	Placebo	Paxil	Placebo
CNS						
Somnolence	2.3%	0.7%	-		1.9%	0.3%
Insomnia	-	-	1.7%	0%	1.3%	0.3%
Agitation	1.1%	0.5%	-			
Tremor	1.1%	0.3%	-			
Anxiety	-	-	-			
Dizziness	-	-	1.5%	0%		
Gastrointestinal						
Constipation	-		1.1%	0%		
Nausea	3.2%	1.1%	1.9%	0%	3.2%	1.2%
Diarrhea	1.0%	0.3%	-			
Dry mouth	1.0%	0.3%	-			
Vomiting	1.0%	0.3%	-			
Other						
Asthenia	1.6%	0.4%	1.9%	0.4%		
Abnormal ejaculation[1]	1.6%	0%	2.1%	0%		
Sweating	1.0%	0.3%	-			
Impotence[1]	-		1.5%	0%		

Where numbers are not provided the incidence of the adverse events in PAXIL patients was not >1% or was greater than or equal to two times the incidence of placebo.

1. Incidence corrected for gender.

Commonly Observed Adverse Events

Depression

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo, derived from Table 1 below) were: asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance and other male genital disorders.

Obsessive Compulsive Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for Paxil at least twice that of placebo, derived from Table 2 below) were: nausea, dry mouth, decreased appetite, constipation, dizziness, somnolence, tremor, sweating, impotence and abnormal ejaculation.

Panic Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for Paxil at least twice that for placebo, derived from Table 2 below were: asthenia, sweating, decreased appetite, libido decreased, tremor, abnormal ejaculation, female genital disorders and impotence.

Incidence in Controlled Clinical Trials

Depression

Table 1 enumerates adverse events that occurred at an incidence of 1% or more among paroxetine-treated patients who participated in short term (6-week) placebo-controlled trials in which patients were dosed in a range of 20 to 50 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors

differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Depression[1]

Body System	Preferred Term	*Paxil* (n=421)	Placebo (n=421)
Body as a Whole	Headache	18%	17%
	Asthenia	15%	6%
Cardiovascular	Palpitation	3%	1%
	Vasodilation	3%	1%
Dermatologic	Sweating	11%	2%
	Rash	2%	1%
Gastrointestinal	Nausea	26%	9%
	Dry Mouth	18%	12%
	Constipation	14%	9%
	Diarrhea	12%	8%
	Decreased Appetite	6%	2%
	Flatulence	4%	2%
	Oropharynx Disorder[2]	2%	0%
	Dyspepsia	2%	1%
Musculoskeletal	Myopathy	2%	1%
	Myalgia	2%	1%
	Myasthenia	1%	0%
Nervous System	Somnolence	23%	9%
	Dizziness	13%	6%
	Insomnia	13%	6%
	Tremor	8%	2%
	Nervousness	5%	3%
	Anxiety	5%	3%
	Paresthesia	4%	2%
	Libido Decreased	3%	0%
	Drugged Feeling	2%	1%
	Confusion	1%	0%
Respiration	Yawn	4%	0%
Special Senses	Blurred Vision	4%	1%
	Taste Perversion	2%	0%
Urogenital System	Ejaculatory Disturbance[3,4]	13%	0%

Other Male Genital Disorders[3,5]	10%	0%
Urinary Frequency	3%	1%
Urination Disorder[6]	3%	0%
Female Genital Disorders[3,7]	2%	0%

1. Events reported by at least 1% of patients treated with Paxil (paroxetine hydrochloride) are included, except the following: events which had an incidence on placebo ≥ *Paxil*: abdominal pain, agitation, back pain, chest pain, CNS stimulation, fever, increased appetite, myoclonus, pharyngitis, postural hypotension, respiratory disorder (includes mostly "cold symptoms" or "URI"), trauma and vomiting.
2. Includes mostly "lump in throat" and "tightness in throat."
3. Percentage corrected for gender.
4. Mostly "ejaculatory delay."
5. Includes "anorgasmia", "erectile difficulties", "delayed ejaculation/orgasm", and "sexual dysfunction," and "impotence."
6. Includes mostly "difficulty with micturition" and "urinary hesitancy."
7. Includes mostly "anorgasmia" and "difficulty reaching climax/orgasm."

Obsessive-Compulsive Disorder and Panic Disorder

Table 2 enumerates adverse events that occurred at a frequency of 2% or more among OCD patients on Paxil who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 to 60 mg/day or among patients with panic disorder on Paxil who participated in placebo controlled trials of 10 to 12 weeks duration in which patients were dosed in a range of 10 to 60 mg/day.

Table 2
Treatment Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Obsessive Compulsive Disorder and Panic Disorder[1]

		Obsessive Compulsive Disorder		Panic Disorder	
Body System	**Preferred Term**	**Paxil (n=542)**	**Placebo (n=265)**	**Paxil (n=469)**	**Placebo (n=324)**
Body as a Whole	Asthenia	22%	14%	14%	5%
	Abdominal Pain	-	-	4%	3%
	Chest Pain	3%	2%	-	-
	Back Pain	-	-	3%	2%
	Chills	2%	1%	2%	1%
Cardiovascular	Vasodilation	4%	1%	-	-
	Palpitation	2%	0%	-	-
Dermatologic	Sweating	9%	3%	14%	6%
	Rash	3%	2%	-	-
Gastrointestinal	Nausea	23%	10%	23%	17%
	Dry Mouth	18%	9%	18%	11%

	Constipation	16%	6%	8%	5%
	Diarrhea	10%	10%	12%	7%
	Decreased Appetite	9%	3%	7%	3%
	Increased Appetite	4%	3%	2%	1%
Nervous System	Insomnia	24%	13%	18%	10%
	Somnolence	24%	7%	19%	11%
	Dizziness	12%	6%	14%	10%
	Tremor	11%	1%	9%	1%
	Nervousness	9%	8%	-	-
	Libido Decreased	7%	4%	9%	1%
	Agitation	-	-	5%	4%
	Anxiety	-	-	5%	4%
	Abnormal Dreams	4%	1%	-	-
	Concentration Impaired	3%	2%	-	-
	Depersonalization	3%	0%	-	-
	Myoclonus	3%	0%	3%	2%
	Amnesia	2%	1%	-	-
Respiratory System	Rhinitis	-	-	3%	0%
Special Senses	Abnormal Vision	4%	2%	-	-
	Taste Perversion	2%	0%	-	-
Urogenital System	Abnormal Ejaculation[2]	23%	1%	21%	1%
	Female Genital Disorder[2]	3%	0%	9%	1%
	Impotence[2]	8%	1%	5%	0%
	Urinary Frequency	3%	1%	2%	0%
	Urination Impaired	3%	0%	-	-
	Urinary Tract Infection	2%	1%	2%	1%

1. Events reported by at least 2% of OCD or panic disorder Paxil-treated patients are included, except the following events which had an incidence on placebo≥Paxil: [OCD]: abdominal pain, agitation, anxiety, back pain, cough increased, depression, headache, hyperkinesia, infection, paresthesia, pharyngitis, respiratory disorder, rhinitis and sinusitis. [panic disorder]: abnormal dreams, abnormal vision, chest pain, cough increased, depersonalization, depressions, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, myalgia, nervousness, palpitation, paresthesia, pharyngitis, rash, respiratory disorder, sinusitis, taste perversion, trauma, urination impaired and vasodilation.

2. Percentage corrected for gender.

Dose Dependency of Adverse Events

A comparison of adverse event rates in a fixed-dose study comparing Paxil 10, 20, 30 and 40 mg/day with placebo in the treatment of depression revealed a clear dose dependency for some of the more common adverse events associated with Paxil use, as shown in the following table:

Table 3 Treatment-Emergent Adverse Experience Incidence in a Depression Dose-Comparison Trial*

	Placebo	Paxil			
Body System/ Preferred Term		10 mg	20 mg	30 mg	40 mg
	n=51	n=102	n=104	n=101	n=102
Body as a Whole					
Asthenia	0.0%	2.9%	10.6%	13.9%	12.7%
Dermatology					
Sweating	2.0%	1.0%	6.7%	8.9%	11.8%
Gastrointestinal					
Constipation	5.9%	4.9%	7.7%	9.9%	12.7%
Decreased Appetite	2.0%	2.0%	5.8%	4.0%	4.9%
Diarrhea	7.8%	9.8%	19.2%	7.9%	14.7%
Dry Mouth	2.0%	10.8%	18.3%	15.8%	20.6%
Nausea	13.7%	14.7%	26.9%	34.7%	36.3%
Nervous System					
Anxiety	0.0%	2.0%	5.8%	5.9%	5.9%
Dizziness	3.9%	6.9%	6.7%	8.9%	12.7%
Nervousness	0.0%	5.9%	5.8%	4.0%	2.9%
Paresthesia	0.0%	2.9%	1.0%	5.0%	5.9%
Somnolence	7.8%	12.7%	18.3%	20.8%	21.6%
Tremor	0.0%	0.0%	7.7%	7.9%	14.7%
Special Senses					
Blurred Vision	2.0%	2.9%	2.9%	2.0%	7.8%
Urogenital System					
Abnormal Ejaculation	0.0%	5.8%	6.5%	10.6%	13.0%
Impotence	0.0%	1.9%	4.3%	6.4%	1.9%
Male Genital Disorders	0.0%	3.8%	8.7%	6.4%	3.7%

*Rule for including adverse events in table: incidence at least 5% for one of paroxetine groups and ≥ twice the placebo incidence for at least one paroxetine group.

In a fixed-dose study comparing placebo and Paxil 20, 40 and 60 mg in the treatment of OCD, there was no clear relationship between adverse events and the dose of Paxil to which patients were assigned. No new adverse events were observed in the Paxil 60 mg dose group compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and *Paxil* 10, 20 and 40 mg in the treatment of panic disorder, there was no clear relationship between adverse events and the dose of *Paxil* to which patients were assigned, except for asthenia, dry mouth, anxiety, libido decreased, tremor and abnormal ejaculation. In flexible dose studies, no new adverse

events were observed in patients receiving *Paxil* 60 mg compared to any of the other treatment groups.

Adaptation to Certain Adverse Events

Over a 4- to 6-week period, there was evidence of adaptation to some adverse events with continued therapy (e.g., nausea and dizziness), but less to other effects (e.g., dry mouth, somnolence and asthenia).

Weight and Vital Sign Changes

Significant weight loss may be an undesirable result of treatment with *Paxil* for some patients but, on average, patients in controlled trials had minimal (about 1 pound) weight loss vs. smaller changes on placebo and active control. No significant changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were observed in patients treated with *Paxil* in controlled clinical trials.

ECG Changes

In an analysis of ECGs obtained in 682 patients treated with *Paxil* and 415 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests

In placebo-controlled clinical trials, patients treated with *Paxil* exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients. In particular, the *Paxil*-vs.-placebo comparisons for alkaline phosphatase, SGOT, SGPT and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

Other Events Observed During the Premarketing Evaluation of Paxil (paroxetine hydrochloride)

During its premarketing assessment in depression, multiple doses of *Paxil* were administered to 6,145 patients in phase 2 and 3 studies. The conditions and duration of exposure to

Paxil varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. During premarketing clinical trials in OCD and panic disorder, 542 and 399 patients, respectively, received multiple doses of Paxil. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 7,156 patients exposed to multiple doses of Paxil (paroxetine hydrochloride) who experienced an event of the type cited on at least one occasion while receiving *Paxil*. All reported events are included except those already listed in Tables 1 and 2, those reported in terms so general as to be uninformative and those events where a drug cause was remote. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

Body as a Whole: *frequent:* chills, malaise; *infrequent:* allergic reaction, carcinoma, face edema, moniliasis, neck pain; *rare:* abscess, adrenergic syndrome, cellulitis, neck rigidity, pelvic pain, peritonitis, ulcer.

Cardiovascular System: *frequent:* hypertension, syncope, tachycardia; *infrequent:* bradycardia, conduction abnormalities, electrocardiogram abnormal, hematoma, hypotension, migraine, peripheral vascular disorder; *rare:* angina pectoris, arrhythmia, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

Digestive System: *infrequent:* bruxism, colitis, dysphagia, eructation, gastroenteris, gingivitis, glossitis, increased salivation, liver function tests abnormal, mouth ulceration, rectal hemorrhage, ulcerative stomatitis; *rare:* aphthous stomatitis, bloody diarrhea, bulimia, choleithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gastritis, gum hemorrhage, hematemesis, hepatitis, ileus, intestinal obstruction, jaundice, melena, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries, tooth malformation.

Endocrine System: *rare:* diabetes mellitus, hyperthyroidism, hypothyroidism, thyroiditis.

Hemic and Lymphatic Systems: *infrequent:* anemia, leukopenia, lymphadenopathy, purpura; *rare:* abnormal erythrocytes, basophilia, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

Metabolic and Nutritional: *frequent:* edema, weight gain, weight loss; *infrequent:* hyperglycemia, peripheral edema, SGOT increased, SGPT increased, thirst; *rare:* alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic dehydrogenase increased.

Musculoskeletal System: *frequent:* arthralgia; *infrequent:* arthritis; *rare:* arthrosis, bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany.

Nervous System: *frequent:* amnesia, CNS stimulation, concentration impaired, depression, emotional lability, vertigo; *infrequent:* abnormal thinking, akinesia, alcohol abuse, ataxia, convulsion, depersonalization, dystonia, hallucinations, hostility, hyperkinesia, hypertonia, hypesthesia, incoordination, lack of emotion, manic reaction, neurosis, paralysis, paranoid reaction; *rare:* abnormal electroencephalogram, abnormal gait, antisocial reaction, aphasia, choreoathetosis, circumoral parasthesias, delirium, delusions, diplopia, drug dependence, dysarthria, dyskinesia, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, hypokinesia, hysteria, libido increased, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus, withdrawal syndrome.

Respiratory System: *frequent:* cough increased, rhinitis; *infrequent:* asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu, sinusitis, voice alteration; *rare:* emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased.

Skin and Appendages: *frequent:* pruritus; *infrequent:* acne, alopecia, dry skin, ecchymosis, eczema, furunculosis, urticaria; *rare:* angioedema, contact dermatitis, erythema nodosum, erythema multiforme, fungal dermatitis, herpes simplex, herpes zoster, hirsutism, maculopapular rash, photosensitivity, seborrhea, skin discoloration, skin hypertrophy, skin ulcer, vesiculobullous rash.

Special Senses: *frequent:* tinnitus; *infrequent:* abnormality of accommodation, conjunctivitis, ear pain, eye pain, mydriasis, otitis media, taste loss, visual field defect; *rare:* amblyopia, anisocroia, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, keratoconjunctivitis, night blindness, otitis externa, parosmia, photophobia, ptosis, retinal hemorrhage.

Urogenital System: *infrequent:* abortion, amenorrhea, breast pain, cystitis, dysmenorrhea, dysuria, hematuria, menorrhagia, nocturia, polyuria, urethritis, urinary incontinence, urinary retention, urinary urgency, vaginitis; *rare:* breast atrophy, breast carcinoma, breast enlargement, breast neoplasm, epididymitis, female lactation, fibrocystic breast, kidney calculus, kidney function abnormal, kidney pain, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, prostatic carcinoma, pyuria, urethritis, uterine spasm, urolith, vaginal moniliasis, vaginal hemorrhage.

Postmarketing Reports

Voluntary reports of adverse events in patients taking *Paxil* that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barre syndrome, toxic epidermal necrolysis, priapism, thrombocytopenia, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and trismus; and serotonin syndrome, associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired *Paxil* metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor). There have been spontaneous reports that abrupt discontinuation may lead to symptoms such as dizziness, sensory disturbances, agitation or anxiety, nausea and sweating; these events are generally self-limiting. There has been a case report of an elevated phenytoin level after 4 weeks of Paxil and phenytoin co-administration. There has been a case report of severe hypotension when Paxil was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Paxil (paroxetine hydrochloride) is not a controlled substance.

Physical and Psychologic Dependence

Paxil has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of *Paxil* misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

No deaths were reported following acute overdose with *Paxil* alone or in combination with other drugs and/or alcohol (18 cases, with doses up to 850 mg) during premarketing clinical trials in depression, OCD, and panic disorder. Signs and symptoms of overdose with *Paxil* included: nausea, vomiting, drowsiness, sinus tachycardia and dilated pupils. There were no reports of ECG abnormalities, coma or convulsions following overdosage with *Paxil* alone.

Overdosage Management

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. There are no specific antidotes for *Paxil*. Establish and maintain an airway; ensure adequate oxygenation and ventilation. Gastric evacuation either by the induction of emesis or lavage or both should be performed. In most

cases, following evacuation, 20 to 30 grams of activated charcoal may be administered every 4 to 6 hours during the first 24 to 48 hours after ingestion. An ECG should be taken and monitoring of cardiac function instituted if there is any evidence of abnormality. Supportive care with frequent monitoring of vital signs and careful observation is indicated. Due to the large volume of distribution of Paxil, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

A specific caution involves patients taking or recently having taken paroxetine who might ingest by accident or intent excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and its active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation.

In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Depression

Usual Initial Dosage

Paxil (paroxetine hydrochloride) should be administered as a single daily dose, usually in the morning. The recommended initial dose is 20 mg/day. Patients were dosed in a range of 20 to 50 mg/day in the clinical trials demonstrating the antidepressant effectiveness of Paxil. As with all antidepressants, the full antidepressant effect may be delayed. Some patients not responding to a 20 mg dose may benefit from dose increases, in 10 mg/day increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least 1 week.

Maintenance Therapy

There is no body of evidence available to answer the question of how long the patient treated with Paxil should remain on it. It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of Paxil (paroxetine hydrochloride) has shown that efficacy is maintained for periods of up to 1 year with doses that averaged about 30 mg.

Obsessive Compulsive Disorder

Usual Initial Dosage

Paxil should be administered as a single daily dose, usually in the morning. The recommended dose of Paxil in the treatment of OCD is 40 mg daily. Patients should be started on 20 mg/day and the dose can be increased in 10 mg/day increments. Dose changes should occur at intervals of at least 1 week. Patients were dosed in a range of 20 to 60 mg/day in the clinical trials demonstrating the effectiveness of Paxil in the treatment of OCD. The maximum dosage should not exceed 60 mg/day.

Maintenance Therapy

Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients with OCD assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see Clinical Pharmacology). OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Panic Disorder

Usual Initial Dosage

Paxil should be administered as a single daily dose, usually in the morning. The target dose of Paxil in the treatment of panic disorder is 40 mg/day. Patients should be started on 10 mg/day. Dose changes should occur in 10 mg/week increments and at intervals of at least 1 week. Patients were dosed in a range of 10 to 60 mg/day in the clinical trials demonstrating the effectiveness of Paxil. The maximum dosage should not exceed 60 mg/day.

Maintenance Therapy

Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY). Panic disorder is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Dosage for Elderly or Debilitated, and Patients with Severe Renal or Hepatic Impairment

The recommended initial dose is 10 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 40 mg/day.

Switching Patients to or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of a MAOI and initiation of Paxil therapy. Similarly, at least 14 days should be allowed after stopping Paxil before starting a MAOI.

HOW SUPPLIED

Paxil is supplied as film-coated, modified-oval tablets as follows:

10 mg yellow tablets engraved on the front with PAXIL and on the back with 10.
NDC 0029-3210-13 Bottles of 30

20 mg pink, scored tablets engraved on the front with PAXIL and on the back with 20.
NDC 0029-3211-13 Bottles of 30
NDC 0029-3211-20 Bottles of 100
NDC 0029-3211-21 SUP 100's (intended for institutional use only)

30 mg blue tablets engraved on the front with PAXIL and on the back with 30.
NDC 0029-3212-13 Bottles of 30

40 mg green tablets engraved on the front with PAXIL and on the back with 40.
NDC 0029-3213-13 Bottles of 30

Store between (15° and 30°C; (59° and 86°F).
DATE OF ISSUANCE MONTH YEAR

SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101
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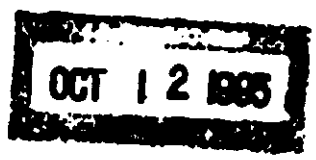

SmithKline Beecham Pharmaceuticals
Attention: Michael J. Brennan, Ph.D.
Four Falls Corporate Center, FF-0415
Route 23 & Woodmont Avenue, P.O. Box 1510
King of Prussia, Pennsylvania 19406-0939

Dear Dr. Brennan:

Please refer to your supplemental New Drug Application dated December 6, 1994, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act providing for the use of Paxil® (paroxetine hydrochloride) 20 and 30 mg tablets in obsessive compulsive disorder (OCD).

We acknowledge receipt of your amendments dated February 17, April 4, May 3, May 15, June 9, July 6, and July 15, 1995 submitted to your NDA, a well as your amendment dated July 24, 1995, providing for a final study report of long term treatment with Paxil in patients with OCD submitted to your IND.

We have completed the review of this supplemental application and it is APPROVABLE. Before the application may be approved, however, it will be necessary for you to submit the following information and respond to the following issues:

CLINICAL

1. Labeling

Accompanying this letter (Attachment) is the Agency's proposal for the labeling of Paxil®. Our proposal is based on your labeling proposal submitted in your original supplement.

We have proposed a number of changes to your draft labeling, and explanations for these changes are provided in the bracketed comments embedded within the proposed text. In certain instances, we have asked you to further modify labeling. Division staff would be happy to meet with you to discuss any disagreements you might have with any part of the proposed labeling format or content.

We have additionally highlighted, in the attached labeling, revisions requested by the Division in previous correspondences. It is our intention that all of these pending revisions can be resolved as part of a final action on this supplement.

2. Safety Update

Our review of the safety of paroxetine in the treatment of OCD was based on data accumulated through 12-10-93 for the integrated database and through 5-31-94 for serious events. You will need to submit a final safety update including safety data accumulated since these cutoff dates.

The safety update should include an update on spontaneous reports for Paxil worldwide. We note that in your earlier safety submission, you did not segregate and report separately on reports in patients being treated for OCD. We ask that, as part of this safety update, you provide such a report, for the entire postmarketing experience for Paxil thus far.

In addition, we ask that you conduct analyses to explore for age and gender effects on adverse event incidence.

3. World Literature Update

Prior to the approval of paroxetine for OCD we require an updated report on the world's archival literature pertaining to the safety of paroxetine in this population. This report should cover all relevant published papers, including clinical or preclinical data, that were not submitted with the original NDA or in subsequent amendments.

We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of paroxetine in this population. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any new finding be judged important, a copy (translated as required) should be submitted for review.

4. Foreign Regulatory Update/Labeling

We require a review of the status of all actions with regard to paroxetine in the treatment of OCD, either taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. If paroxetine is approved for use in OCD in any countries, we ask that you provide us current labeling for paroxetine in those countries, along with English translations when needed.

5. Efficacy Data

We ask that you perform and provide to us the results of exploratory analyses of the efficacy data for interactions on the basis of age and gender.

6. Pediatric OCD Studies

Another deficiency in your development program for this indication was the absence of safety and efficacy data for children and adolescents. This is a potentially important problem for OCD because of the very early age of onset for this disorder (peak age of onset is 9 for males and 12 for females). In fact, it is likely that many children and adolescents are already being treated with paroxetine for OCD, and it would be expected that such treatment would increase with the approval of this new indication. Although it is true that you have not specifically sought approval for this indication in these age groups, ideally, data would be available to support (or refute) what is already occurring in clinical practice. We would like your commitment as well as a proposed completion date to conduct such studies following the approval of Paxil® for this indication.

PHARMACOLOGY

As with other serotonin reuptake inhibitors, we find it necessary to request that the decreased survival of rat pups in reproduction toxicology studies receive more emphasis in labeling. Because it is not clear whether this finding was related to effects of the drug on the developing fetus *in utero* or was secondary to postnatal drug effects on the dams and/or pups, we have labeled PAXIL® pregnancy category C. If you were to conduct a cross-fostering study that clearly established that the adverse effect on pup survival occurred as a result of a postnatal effect rather than an *in utero* effect of drug on the fetus, the labeling may be changed from pregnancy category C to pregnancy category B. We recommend that you submit the protocol for this study for our concurrence before initiating it.

Please submit fifteen copies of the printed labels and other labeling, ten of which are individually mounted on heavy weight paper or similar paper.

In addition, please submit three copies of the introductory promotional and/or advertising campaign that you propose to use for this new indication. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert, directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications
HFD-240, Room 17B-17
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action on your part, the FDA may proceed to withdraw the application.

In accordance with the policy described in 21 CFR 314.102(d) and in the Center for Drug Evaluation and Research Staff Manual Guide CDB 4820.6, you may request an informal conference with the Division to discuss what further steps you need to secure approval. The meeting is to be requested at least 15 days in advance. Alternatively, you may choose to receive such a report via a telephone call. Should you wish this conference or a telephone report, or should any questions arise concerning this NDA, please contact Mr. Paul David, Regulatory Management Officer, at (301) 594-2777.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of this invoice.

This drug may not be legally marketed for the indication provided by this application until you have been notified in writing that the application is approved.

Sincerely yours,

10/12/95

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ATTACHMENT

ATTACHMENT

DRAFT LABELING PROPOSAL

Note: This draft of labeling is based on your 12-6-94 labeling proposal. Brackets [] embedded within the text that follows include comments, explanations, and requests concerning the proposed draft labeling. For some sections, few changes were proposed, while others required more extensive modification. In some instances, we are asking you to provide additional data for a future draft of labeling. For ease in review of the labeling modifications regarding the OCD indication and also unrelated changes proposed in recent FDA correspondence, we have shaded in additions ('redline font') and lined out ('strikeout' font) all the proposed changes to the current existing labeling. In your next labeling proposal, please use this exact document as the starting document. Please use the 'strikeout' font to indicate the material you wish to delete and the 'redline' font to indicate the material you wish to add.

PRESCRIBING INFORMATION

PAXIL®
brand of
paroxetine hydrochloride tablets

DESCRIPTION

Paxil (paroxetine hydrochloride) is an orally administered antidepressant with a chemical structure unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic or other available antidepressant agents. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-trans-4R-(4'-fluorophenyl)-3S-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3HCl\ 1/2H_2O$. The molecular weight is 374.8 (329.4 as free base). The structural formula is:

[Insert structural formula here]

Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of 120° to 138°C and a solubility of 5.4 mg/mL in water.

Each film-coated tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: 20 mg pink (scored); 30 mg blue. Inactive ingredients consist of dibasic calcium phosphate dihydrate, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide and one or more of the following: D&C Red No. 30, FD&C Blue No. 2.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The antidepressant and antiobsessive compulsive action of paroxetine is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* radioligand binding studies indicate that paroxetine has little affinity for muscarinic, alpha$_1$-, alpha$_2$-, beta-adrenergic-, dopamine (D_2)-, 5-HT_1-, 5-HT_2- and histamine (H_1)-receptors; antagonism of muscarinic, histaminergic and alpha$_1$-adrenergic receptors has been associated with various anticholinergic, sedative and cardiovascular effects for other psychotropic drugs.

Because the relative potencies of paroxetine's major metabolites are at most 1/50 of the parent compound, they are essentially inactive.

Pharmacokinetics

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male subjects (n=15) received 30 mg tablets daily for 30 days, steady-state paroxetine concentrations were achieved by approximately 10 days for most subjects, although it may take substantially longer in an occasional patient. At steady state, mean values of C_{max}, T_{max}, C_{min} and $T_{1/2}$ were 61.7 ng/mL (CV 45%), 5.2 hr. (CV 10%), 30.7 ng/mL (CV 67%) and 21.0 hr. (CV 32%), respectively. The steady-state C_{max} and C_{min} values were about 6 and 14 times what would be predicted from single-dose studies. Steady-state drug exposure based on AUC_{0-24} was about 8 times greater than would have been predicted from single-dose data in these subjects. The excess accumulation is a consequence of the fact that one of the enzymes that metabolizes paroxetine is readily saturable.

In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of 20 to 40 mg daily for the elderly and 20 to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{min} values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than doubled.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates

with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by cytochrome $P_{450}IID_6$. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see PRECAUTIONS).

Approximately 64% of a 30 mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.

Distribution

Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.

Protein Binding

Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/mL. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.

Renal and Liver Disease

Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below 30 mL/min was approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30 to 60 mL/min and patients with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, C_{max}).

The initial dosage should therefore be reduced in patients with severe renal or hepatic impairment, and upward titration, if necessary, should be at increased intervals (see DOSAGE AND ADMINISTRATION).

Elderly Patients

In a multiple-dose study in the elderly at daily paroxetine doses of 20, 30 and 40 mg, C_{min} concentrations were about 70% to 80% greater than the respective C_{min} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced. (See DOSAGE AND ADMINISTRATION.)

Clinical Trials

Depression

The efficacy of Paxil as a treatment for depression has been established in 6 placebo-controlled studies of patients with depression (ages 18 to 73). In these studies Paxil was shown to be significantly more effective than placebo in treating depression by at least 2 of the following measures: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI) Severity of Illness. Paxil was significantly better than placebo in improvement of the HDRS sub-factor scores, including the depressed mood item, sleep disturbance factor and anxiety factor.

A study of depressed outpatients who had responded to Paxil (HDRS total score <8) during an initial 8-week open-treatment phase and were then randomized to continuation on Paxil or placebo for 1 year demonstrated a significantly lower relapse rate for patients taking Paxil (15%) compared to those on placebo (39%). Effectiveness was similar for male and female patients.

Obsessive Compulsive Disorder

[We have made slight editorial changes to the following paragraph, and we have added a table illustrating the effect for study 116. In addition, we have noted where a statement is needed regarding the results of the exploratory analyses for age and gender effects.]

The effectiveness of Paxil in the treatment of obsessive compulsive disorder (OCD) was demonstrated in two 12-week multicenter placebo-controlled studies of adult outpatients (Studies 1 and 2). Patients in all studies had moderate to severe OCD (DSM-IIIR), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS) total score ranging from 23 to 26. Study 1, a dose-range finding study where patients were treated with fixed doses of 20, 40 or 60 mg/day demonstrated that daily doses of paroxetine 40 and 60 mg are effective in the treatment of OCD. [redacted]

The following table provides the outcome classification by treatment group on the Global Improvement item of the Clinical

Global Impressions (CGI) scale for study 1.

Outcome Classification (%) on CGI-Global Improvement Item for Completers in Study 1				
Outcome Classification	Placebo (N=74)	Paxil 20mg (N=75)	Paxil 40mg (N=66)	Paxil 60mg (N=65)
Worse	14%	7%	7%	3%
No Change	44%	35%	22%	19%
Minimally Improved	24%	33%	27%	34%
Much Improved	11%	16%	22%	24%
Very Much Improved	7%	7%	20%	20%

[A statement is needed here regarding the results of the exploratory analyses for age and gender effect on outcomes.]

INDICATIONS AND USAGE

Depression

Paxil (paroxetine hydrochloride) is indicated for the treatment of depression.

The efficacy of Paxil in the treatment of a major depressive episode was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see CLINICAL PHARMACOLOGY).
A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of in rest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant ac on of Paxil in hospitalized depressed patients has not been adequately studied.

The efficacy of Paxil in maintaining an antidepressant response for up to 1 year was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use Paxil for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Obsessive Compulsive Disorder

[We have made slight editorial changes to this section. We acknowledge the long-term data submitted in your 7-24-95 amendment. Since we are aware that additional long-term data for the remaining two studies are yet to be submitted, we will await these data before reaching a final judgement on long-term efficacy and before making any additional modifications to this section.]

Paxil is indicated for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD) as defined in the DSM-IV. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of Paxil was established in two 12-week trials with obsessive compulsive outpatients whose diagnoses corresponded most closely to the DSM-IIIR category of obsessive compulsive disorder (see Clinical Trials under CLINICAL PHARMACOLOGY).

Obsessive compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The effectiveness of Paxil in long-term use, i.e., for more than 12 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use Paxil for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

[The following paragraph has been added on the basis of findings communicated to you in our August 30, 1995 letter.]

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS and PRECAUTIONS).

Co-administration of terfenadine, astemizole, or cisapride with PAXIL Tablets is contraindicated (see WARNINGS and PRECAUTIONS).

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving another serotonin reuptake inhibitor drug in combination with a monoamine oxidase inhibitor (MAOI), there have

been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with *Paxil*, limited animal data on the effects of combined use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Paxil (paroxetine hydrochloride) not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. At least 2 weeks should be allowed after stopping *Paxil* before starting a MAOI.

[The following paragraph has been added on the basis of findings communicated to you in our August 30, 1995 letter.]

Potential Terfenadine, Astemizole, and Cisapride Interactions

Terfenadine, astemizole, and cisapride are all metabolized by the cytochrome P450IIIA4 isozyme, and it has been demonstrated that ketoconazole, a potent inhibitor of IIIA4, blocks the metabolism of these drugs, resulting in increased plasma concentrations of parent drug. Increased plasma concentrations of terfenadine, astemizole, and cisapride cause QT prolongation and have been associated with torsades de pointes-type ventricular tachycardia, sometimes fatal. It has been shown that the metabolism of alprazolam, a IIIA4 substrate, is inhibited under in vitro conditions by paroxetine. Although it has not been definitively demonstrated that paroxetine is a potent IIIA4 inhibitor, it may be, based on this data. Consequently, it is recommended that paroxetine not be used in combination with terfenadine, astemizole, or cisapride (see CONTRAINDICATIONS and PRECAUTIONS).

PRECAUTIONS

General

Activation of Mania/Hypomania

During premarketing testing, hypomania or mania occurred in approximately 1.0% of Paxil-treated unipolar patients compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for Paxil and 11.6% for the combined active-control groups. As with all antidepressants, Paxil should be used cautiously in patients with a history of mania.

Seizures

During premarketing testing, seizures occurred in 0.1% of Paxil-treated patients, a rate similar to that associated with other antidepressants. Paxil should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Suicide

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Paxil should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Hyponatremia

Several cases of hyponatremia have been reported. The hyponatremia appeared to be reversible when Paxil was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

[[The following paragraph has been added on the basis of findings communicated to you in our May 12, 1995 letter.]

Abnormal Bleeding

There have been several reports of abnormal bleeding (mostly ecchymosis and purpura) associated with paroxetine treatment, including a report of impaired platelet aggregation. While a causal relationship to paroxetine is unclear, impaired platelet aggregation may result from platelet serotonin depletion and contribute to such occurrences.

Use in Patients with Concomitant Illness

Clinical experience with Paxil in patients with certain concomitant systemic illness is limited. Caution is advisable in using Paxil in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Paxil has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. Evaluation of electrocardiograms of 682 depression patients who received Paxil in double-blind, placebo-controlled trials, however, did not indicate that Paxil is associated with the development of significant ECG abnormalities. Similarly, Paxil (paroxetine hydrochloride) does not cause any clinically important changes in

heart rate or blood pressure.

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance <30 mL/min.) or severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Paxil:

Interference with Cognitive and Motor Performance

Any psychoactive drug may impair judgment, thinking or motor skills. Although in controlled studies Paxil has not been shown to impair psychomotor performance, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Paxil therapy does not affect their ability to engage in such activities.

Completing Course of Therapy

While patients may notice improvement with Paxil therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant Medication

Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Although Paxil has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking Paxil.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing

Patients should be advised to notify their physician if they are breast-feeding an infant. (See PRECAUTIONS Nursing Mothers.)

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

[[The following paragraph has been added on the basis of findings communicated to you in our August 30, 1995 letter.]

Theophylline

Multiple reports of elevated theophylline levels associated with Paxil treatment have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

Tryptophan

As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are co-administered. Adverse experiences, consisting primarily of headache, nausea, sweating and dizziness, have been reported when tryptophan was administered to patients taking Paxil (paroxetine hydrochloride). Consequently, concomitant use of Paxil with tryptophan is not recommended.

Monoamine Oxidase Inhibitors

See CONTRAINDICATIONS and WARNINGS.

Warfarin

Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the face of unaltered prothrombin time) between paroxetine and warfarin. Since there is little clinical experience, the concomitant administration of Paxil and warfarin should be undertaken with caution.

Drugs Affecting Hepatic Metabolism

The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug-metabolizing enzymes.

Cimetidine - Cimetidine inhibits many cytochrome P_{450} (oxidative) enzymes. In a study where Paxil (30 mg q.d.) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during co-administration with oral cimetidine (300 mg t.i.d.) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of Paxil after the 20 mg starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

Phenobarbital - Phenobarbital induces many cytochrome P_{450} (oxidative) enzymes. When a single oral 30 mg dose of Paxil was

administered at phenobarbital steady state (100 mg q.d. for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since Paxil exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed. No initial Paxil dosage adjustment is considered necessary when co-administered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

[The following paragraph has been modified on the basis of findings communicated to you in our February 23, 1995 letter.]

Phenytoin - When a single oral 30 mg dose of Paxil w administered at phenytoin steady state (300 mg q.d. for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 50% and 35%, respectively) compared to Paxil administered alone. In a separate study, when a single oral 300 mg dose of phenytoin was administered at paroxetine steady state (30 mg q.d. for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the 2 drugs are both being chronically dosed. However, there is a case report of an elevated phenytoin level after four weeks of PAXIL and phenytoin co-administration. While no initial dosage adjustments are considered necessary, the concurrent use of these two drugs may require a decrease in phenytoin dose, which should be guided by phenytoin blood level monitoring.

Drugs Metabolized by Cytochrome $P_{450}IID_6$

[The following section has been modified on the basis of findings communicated to you in our February 23, 1995 letter.]

Many drugs, including most antidepressants (paroxetine, other SSRI's, and many tricyclics) are metabolized by the cytochrome P450 isozyme 2D6. Like other agents that are metabolized by P450IID6, paroxetine is significantly inhibit

either PAXIL or the other drugs.

Therefore, co-administration of Paxil with other drugs that are metabolized by this isozyme, including certain antidepressants (e.g., nortriptyline, amitriptyline, imipramine, desipramine and fluoxetine), phenothiazines (e.g., thioridazine) and Type 1C anti-arrhythmics (e.g., propafenone, flecainide and encainide), or that

inhibit this enzyme (e.g., quinidine), should be approached with caution.

At steady state, when the $P_{450}IID_6$ pathway is essentially saturated, paroxetine clearance is governed by alternative P_{450} isozymes which, unlike $P_{450}IID_6$, show no evidence of saturation.

[The following paragraph has been added on the basis of findings communicated to you in our August 30, 1995 letter.]

Drugs Metabolized by Cytochrome P450IIIA4

Concomitant use of PAXIL with drugs metabolized by cytochrome P450IIIA4 has not been formally studied. Based on limited in vitro data, it appears that paroxetine does inhibit this isozyme and, thus, may produce elevated plasma levels of drugs metabolized by IIIA4. Since increased levels of terfenadine, astemizole, and cisapride have been associated with serious cardiovascular events, the concomitant use of PAXIL with these drugs is not recommended. (see CONTRAINDICATIONS and WARNINGS).

Drugs Highly Bound to Plasma Protein

Because paroxetine is highly bound to plasma protein, administration of *Paxil* to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

Alcohol

Although Paxil does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking Paxil (paroxetine hydrochloride).

Lithium

A multiple-dose study has shown that there is no pharmacokinetic interaction between Paxil and lithium carbonate. However, since there is little clinical experience, the concurrent administration of paroxetine and lithium should be undertaken with caution.

Digoxin

The steady-state pharmacokinetics of paroxetine was not altered when administered with digoxin at steady state. Mean digoxin AUC at steady state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of paroxetine and digoxin should be undertaken with caution.

Diazepam

Under steady-state conditions, diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

Procyclidine

Daily oral dosing of *Paxil* (30 mg q.d.) increased steady-state AUC_{0-24}, C_{max} and C_{min} values of procyclidine (5 mg oral q.d.) by 35%, 37% and 67%, respectively, compared to procyclidine alone at steady state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

[The following paragraph has been modified on the basis of findings communicated to you in our February 23, 1995.]

~~Propranolol~~Beta-Blockers

In a study where propranolol (80 mg b.i.d.) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during co-administration with Paxil (30 mg q.d.) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated. Although the co-administration of PAXIL with other beta-blockers has not been formally studied, there has been a case report of severe hypotension when PAXIL was added to chronic metoprolol treatment. This combination should be used with caution.

Electroconvulsive Therapy (ECT)

There are no clinical studies of the combined use of ECT and Paxil.

Carcinogenesis, Mutagenesis, Impairment of Fertility

[Changes have been made in the values for multiples of the maximum human daily dose based on a new CDER policy for computation. The standard weight of patients is considered to be 60 kg instead of 50 kg. The conversion factor used in computing body surface area for the rat is 6 rather than 9. We have also made corrections in the multiples of maximum human dose since the new maximum human dose is now 60 mg.]

Carcinogenesis

Two-year carcinogenicity studies were conducted in mice and rats given paroxetine in the diet at ~~1, 5 and 25 mg/kg/day (mice) and 1, 5 and 20 mg/kg/day (rats). The maximum doses in these studies were approximately 25 (mouse) and 20 (rat) times the maximum dose recommended for human use in the treatment of depression (50 mg/day) and approximately 21 (mouse) and 17 (rat) times the maximum recommended human dose for the treatment of OCD (60 mg/day) on a mg/kg basis. On a mg/m^2 basis, this is 2.5~~ [redacted] (mouse)

and ~~5.8~~ 3.9 (rat) times the maximum recommended human dose (MRHD) for depression, on a mg/m² basis. Because the MRHD for depression is slightly less than that for OCD (50 mg vs. 60 mg), the doses used in these carcinogenicity studies were only ~~and 2.1~~ 2.0 (mouse) and ~~4.8~~ 3.2 (rat) times the MRHD for OCD and Panic Disorder. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50 and 4/50 for control, low-, middle- and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis

Paroxetine produced no genotoxic effects in a battery of 5 *in vitro* and 2 *in vivo* assays that included the following: bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes and in a dominant lethal test in rats.

Impairment of Fertility

~~Serotonergic compounds are known to affect reproductive function in animals. Impaired reproductive function (i.e.,~~ A reduced pregnancy rate~~, increased pre and post implantation losses, decreased viability of pups)~~ was found in reproduction studies in rats at doses of paroxetine which were ~~15 or more times the highest recommended human dose for depression (50 mg/day) or 12.5 or more times the highest recommended dose of OCD (60 mg/day) on a mg/kg basis. These are 4.4~~ 2.9 times~~, 3.7~~ the MRHD for depression ~~times~~ or ~~3.7~~ 2.4 times the ~~maximum recommended human doses for depression and~~ MRHD for OCD, ~~respectively~~ on a mg/m² basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions, which consisted of vacuolation of epididymal tubular epithelium and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis occurred at doses which were ~~25 and 21 times the highest recommended human dose for depression and OCD respectively on a mg/kg basis. These are 7.3~~ 4.9 times the MRHD for depression ~~and 6.1~~ and 4.1 times the ~~maximum recommended doses for depression,~~ MRHD for OCD, ~~respectively~~ on a mg/m² basis.

Pregnancy

[As with other serotonin reuptake inhibitors, we find it necessary to request that the decreased survival of rat pups in reproduction toxicology studies for paroxetine receive more emphasis in labeling. Because it is not clear whether this finding was related to effects of the drug on the developing fetus *in utero* or was secondary to postnatal drug effects on nursing dams and/or pups, we have labeled PAXIL® pregnancy category C.]

Teratogenic Effects - Pregnancy Category ~~B~~ C

Reproduction studies were performed in rats and rabbits at doses up to ~~50 and~~ ~~times the maximum recommended human dose for depression (5,0 mg/day; and up to 42 and 5 times the maximum daily human dose for OCD (60 mg/day), respectively on a mg/kg basis. These are 10~~ 2.7 (rat) and ~~2~~ 2.2 (rabbit) times the maximum recommended human dose (MRHD) for depression (50 mg) and ~~8.3~~ 8.1 (rat) and ~~1.7~~ 1.9 (rabbit) times the ~~maximum recommended human dose~~ MRHD for OCD, on a mg/m² basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at 0.19 times (mg/m²) the MRHD for depression and at 0.16 times (mg/m²) the MRHD for OCD and Panic Disorder. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

The effect of paroxetine on labor and delivery in humans is unknown.

Nursing Mothers

Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when Paxil (paroxetine hydrochloride) is administered to a nursing woman.

Usage in Children

Safety and effectiveness in children have not been established.

Geriatric Use

In worldwide [redacted] Paxil clinical trials, 17% of *Paxil*-treated patients (approximately 700) were 65 years of age or older. Pharmacokinetic studies revealed a decreased clearance in the

elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

[Please modify the table that follows by the addition of the placebo rates for each of depression and OCD.]

Twenty-one percent (881/4,126) of Paxil patients in worldwide clinical trials in depression and 11.8% (64/542) of Paxil patients in worldwide trials in OCD discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for Paxil compared to placebo) included:

	Depression	OCD
CNS		
Somnolence	2.3%	-
Insomnia	1.9%	1.7%
Agitation	1.3%	-
Tremor	1.3%	-
Anxiety	1.1%	-
Dizziness	-	1.5%
Gastrointestinal		
Constipation	-	1.1%
Nausea	3.4%	1.9%
Diarrhea	1.0%	-
Dry mouth	1.0%	-
Vomiting	1.0%	-
Other		
Asthenia	1.7%	1.9%
Abnormal ejaculation[1]	1.6%	2.1%
Sweating	1.1%	-
Impotence[1]	-	1.5%

Where numbers did not provided the incidence for the adverse event on placebo, the placebo incidence was approximately the greatest number equal to two times the incidence on placebo.

1 Incidence corrected for gender.

Commonly Observed Adverse Events

Depression

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo, derived from the table below) were: asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance and other male genital disorders.

Obsessive Compulsive Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of at least 5% for Paxil and for which the incidence was approximately twice or more the incidence among placebo-treated patients, derived from the table below) were: nausea, dry mouth, decreased appetite, constipation, dizziness, somnolence, tremor, sweating, impotence and abnormal ejaculation.

Incidence in Controlled Clinical Trials

[We are concerned about the usability of labeling that becomes excessively long as additional AE tables are added for each new indication. As as alternative, we would like you to consider a table that combines depression and OCD, i.e., side by side. This has the advantage of being one table rather than two, and it also permits the prescriber to directly compare adverse event rates for the 2 indications. Since the conditions of study were different for the two indications, e.g., dose, duration of trial, etc., it will be necessary to include placebo rates for both indications. To further shorten the table, it might be a 2% table for both indications. It, of course, could be organized by declining frequency for only one of the indications, preferably depression. Other changes would be desirable as well, including: round up or down to whole numbers; remove to a footnote any events for which the placebo rate is equal to or greater than the paroxetine rate. We have revised the narrative introduction to such a table, but have not attempted to create a revised table.]

The table that follows enumerates adverse events that occurred at an incidence of 2% or more among paroxetine-treated depressed patients who participated in short-term (6-week) placebo-controlled trials in which patients were dosed in a range of 20 to 50 mg/day and also among paroxetine-treated OCD patients who participated in placebo-controlled trials of 12-week duration in which patients were dosed in a range of 20 to 60 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials.

Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Depression[1]

Body System	Preferred Term	*Paxil* (n=421)	Placebo (n=421)
Body as a Whole	Headache	17.6%	17.3%
	Asthenia	15.0%	5.9%
	Abdominal Pain	3.1%	4.0%
	Fever	1.7%	1.7%
	Chest Pain	1.4%	2.1%
	Trauma	1.4%	0.5%
	Back Pain	1.2%	2.4%
Cardiovascular	Palpitation	2.9%	1.4%
	Vasodilation	2.6%	0.7%
	Postural Hypotension	1.2%	0.5%
Dermatologic	Sweating	11.2%	2.4%
	Rash	1.7%	0.7%
Gastrointestinal	Nausea	25.7%	9.3%
	Dry Mouth	18.1%	12.1%
	Constipation	13.8%	8.6%
	Diarrhea	11.6%	7.6%
	Decreased Appetite	6.4%	1.9%
	Flatulence	4.0%	1.7%
	Vomiting	2.4%	1.7%
	Oropharynx Disorder[2]	2.1%	0.0%
	Dyspepsia	1.9%	1.0%
	Increased Appetite	1.4%	0.5%
Musculoskeletal	Myopathy	2.4%	1.4%
	Myalgia	1.7%	0.7%
	Myasthenia	1.4%	0.2%
Nervous System	Somnolence	23.3%	9.0%
	Dizziness	13.3%	5.5%
	Insomnia	13.3%	6.2%
	Tremor	8.3%	1.9%
	Nervousness	5.2%	2.6%
	Anxiety	5.0%	2.9%
	Paresthesia	3.8%	1.7%
	Libido Decreased	3.3%	0.0%

	Agitation	2.1%	1.9%
	Drugged Feeling	1.7%	0.7%
	Myoclonus	1.4%	0.7%
	CNS Stimulation	1.2%	3.6%
	Confusion	1.2%	0.2%
Respiration	Respiratory Disorder[3]	5.9%	6.4%
	Yawn	3.8%	0.0%
	Pharyngitis	2.1%	2.9%
Special Senses	Blurred Vision	3.6%	1.4%
	Taste Perversion	2.4%	0.2%
Urogenital System	Ejaculatory Disturbance[4,5]	12.9%	0.0%
	Other Male Genital Disorders[4,6]	10.0%	0.0%
	Urinary Frequency	3.1%	0.7%
	Urination Disorder[7]	2.9%	0.2%
	Female Genital Disorders[4,8]	1.8%	0.0%

1. Events reported by at least 1% of patients treated with Paxil (paroxetine hydrochloride) are included.
2. Includes mostly "lump in throat" and "tightness in throat."
3. Includes mostly "cold symptoms" or "URI."
4. *Percentage corrected for gender.*
5. Mostly "ejaculatory delay."
6. Includes "anorgasmia," "erectile difficulties," "delayed ejaculation/orgasm," and "sexual dysfunction," and "impotence."
7. Includes mostly "difficulty with micturition" and "urinary hesitancy."
8. Includes mostly "anorgasmia" and "difficulty reaching climax/orgasm."

Table 2. Treatment- Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Obsessive- Compulsive Disorder[1]

Body System	Preferred Term	Paxil (n=542)	Placebo (n=265)
Body as a Whole	Asthenia	21.8%	13.6%
	Chest Pain	2.8%	1.9%
	Chills	2.0%	0.7%
	Infection	5.3%	4.9%
Cardiovascular	Palpitation	2.0%	0.4%
	Vasodilation	2.9%	1.5%
Dermatologic	Rash	1.3%	1.9%
	Sweating	3.9%	3.0%
Gastrointestinal	Constipation	15.7%	6.4%
	Decreased Appetite	9.0%	3.4%
	Diarrhea	10.3%	9.8%
	Dry Mouth	18.1%	8.7%
	Increased Appetite	4.2%	3.0%
	Nausea	23.3%	9.8%
Nervous System	Abnormal Dreams	3.9%	1.1%
	Amnesia	2.2%	1.1%
	Concentration Impaired	2.8%	1.5%
	Depersonalization	2.6%	0.4%
	Dizziness	12.4%	6.0%
	Hyperkinesia	2.2%	1.5%
	Insomnia	23.8%	13.2%
	Libido Decreased	7.2%	3.8%
	Myoclonus	3.3%	0.4%
	Nervousness	8.5%	8.3%
	Somnolence	24.3%	17.2%
	Tremor	10.5%	1.1%
Special Senses	Abnormal Vision	3.7%	2.3%
	Taste Perversion	2.0%	0.0%
Urogenital System	Abnormal Ejaculation[2]	23.3%	1.3%
	Female Genital Disorder[2]	3.3%	0.0%
	Impotence[2]	8.2%	1.3%
	Urinary Frequency	3.3%	1.1%
	Urination Impaired	3.3%	0.4%

1. Events reported by at least 2% of Paxil-treated patients are included except the following events which had an incidence on placebo [illegible] pain, headache, [illegible] dyspepsia, [illegible] myalgia, [illegible] respiratory disorder, [illegible] pharyngitis.

2. Percentage is gender-corrected.

Dose Dependency of Adverse Events

A comparison of adverse event rates in a fixed-dose study comparing Paxil 10, 20, 30 and 40 mg/day with placebo in the treatment of depression revealed a clear dose dependency for some of the more common adverse events associated with Paxil use, as shown in the following table:

Table 3 Treatment-Emergent Adverse Experience Incidence in a Depression Dose-Comparison Trial*

	Placebo	Paxil			
Body System/ Preferred Term		10 mg	20 mg	30 mg	40 mg
	n=51	n=102	n=104	n=101	n=102
Body as a Whole					
Asthenia	0.0%	2.9%	10.6%	13.9%	12.7%
Dermatology					
Sweating	2.0%	1.0%	6.7%	8.9%	11.8%
Gastrointestinal					
Constipation	5.9%	4.9%	7.7%	9.9%	12.7%
Decreased Appetite	2.0%	2.0%	5.8%	4.0%	4.9%
Diarrhea	7.8%	9.8%	19.2%	7.9%	14.7%
Dry Mouth	2.0%	10.8%	18.3%	15.8%	20.6%
Nausea	13.7%	14.7%	26.9%	34.7%	36.3%
Nervous System					
Anxiety	0.0%	2.0%	5.8%	5.9%	5.9%
Dizziness	3.9%	6.9%	6.7%	8.9%	12.7%
Nervousness	0.0%	5.9%	5.8%	4.0%	2.9%
Paresthesia	0.0%	2.9%	1.0%	5.0%	5.9%
Somnolence	7.8%	12.7%	18.3%	20.8%	21.6%
Tremor	0.0%	0.0%	7.7%	7.9%	14.7%
Special Senses					
Blurred Vision	2.0%	2.9%	2.9%	2.0%	7.8%
Urogenital System					
Abnormal Ejaculation	0.0%	5.8%	6.5%	10.6%	13.0%
Impotence	0.0%	1.9%	4.3%	6.4%	1.9%
Male Genital Disorders	0.0%	3.8%	8.7%	6.4%	3.7%

*Rule for including adverse events in table: incidence at least 5% for one of paroxetine groups and ≥ twice the placebo incidence for at least one paroxetine group.

In a fixed-dose study comparing placebo and Paxil 20, 40 and 50 mg in the treatment of OCD, there was no clear relationship between adverse events and the dose of Paxil to which patients were randomized. The most frequent events observed in the Paxil 60 mg dose group were similar to those in other treatment groups.

Adaptation to Certain Adverse Events

Over a 4- to 6-week period, there was evidence of adaptation to some adverse events with continued therapy (e.g., nausea and dizziness), but less to other effects (e.g., dry mouth, somnolence and asthenia).

Weight and Vital Sign Changes

Significant weight loss may be an undesirable result of treatment with *Paxil* for some patients but, on average, patients in controlled trials had minimal (about 1 pound) weight loss vs. smaller changes on placebo and active control. No significant changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were observed in patients treated with *Paxil* in controlled clinical trials.

ECG Changes

In an analysis of ECGs obtained in 682 patients treated with *Paxil* and 415 patients treated with placebo in controlled clinical trials in depression, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests

In placebo-controlled clinical trials, patients treated with Paxil exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients. In particular, the *Paxil*-vs.-placebo comparison in depression and OCD respectively for alkaline phosphatase was 0% vs. 0% and 0% vs 0%, SGOT 0.3% vs. 0.3% and 1.1% vs 1.1%, SGPT 1% vs. 0.3% and 1.1% vs 0% and bilirubin 0% vs. 0.8% and 0% vs 1.1%.

Other Events Observed During the Premarketing Evaluation of Paxil (paroxetine hydrochloride)

[The following adverse events were reported at least once in the pool of 542 patients with OCD who were treated with paroxetine, and these need to be added to the table that follows: CPK increased; myasthenia; aphasia; confusion; hemoptysis; seborrhea; vesiculobullous rash; blepharitis; mydriasis; uterine spasm.]

During its premarketing assessment in depression, multiple doses of *Paxil* were administered to 4,126 patients in phase 2 and 3 studies. The conditions and duration of exposure to *Paxil* varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. During premarketing clinical trials in OCD, 542 patients received multiple doses of Paxil. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 4,126 patients exposed to multiple doses of Paxil (paroxetine hydrochloride) who experienced an event of the type cited on at least one occasion while receiving *Paxil*. All reported events are included except those already listed in Table 1, those reported in terms so general as to be

uninformative and those events where a drug cause was remote. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

Body as a Whole - *frequent:* chills, malaise; *infrequent:* allergic reaction, carcinoma, face edema, moniliasis, neck pain; *rare:* abscess, adrenergic syndrome, cellulitis, neck rigidity, pelvic pain, peritonitis, ulcer.

Cardiovascular System - *frequent:* hypertension, syncope, tachycardia; *infrequent:* bradycardia, conduction abnormalities, electrocardiogram abnormal, hypotension, migraine, peripheral vascular disorder; *rare:* angina pectoris, arrhythmia, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

Digestive System -*infrequent:* bruxism, dysphagia, eructation, glossitis, increased salivation, liver function tests abnormal, mouth ulceration, rectal hemorrhage; *rare:* aphthous stomatitis, bloody diarrhea, bulimia, colitis, duodenitis, esophagitis, fecal impactions, fecal incontinence, gastritis, gastroenteritis, gingivitis, hematemesis, hepatitis, ileus, jaundice, melena, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue edema, tooth caries.

Endocrine System -*rare:* diabetes mellitus, hyperthyroidism, hypothyroidism, thyroiditis.

Hemic and Lymphatic Systems -*infrequent:* anemia, leukopenia, lymphadenopathy, purpura; *rare:* abnormal erythrocytes, eosinophilia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia.

Metabolic and Nutritional -*frequent:* edema, weight gain, weight loss; *infrequent:* hyperglycemia, peripheral edema, thirst; *rare:* alkaline phosphatase increased, bilirubinemia, dehydration, gout, hypercholesteremia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, SGOT increased, SGPT increased.

Musculoskeletal System- *infrequent:* arthralgia, arthritis; *rare:* arthrosis, bursitis, myositis, osteoporosis, tetany.

Nervous System- *frequent:* amnesia, CNS stimulation, concentration

impaired, depression, emotional lability, vertigo; *infrequent:* abnormal thinking, akinesia, alcohol abuse, ataxia, convulsion, depersonalization, hallucinations, hyperkinesia, hypertonia, incoordination, lack of emotion, manic reaction, paranoid reaction, hypesthesia; *rare:* abnormal electroencephalogram, abnormal gait, antisocial reaction, choreoathetosis, delirium, delusions, diplopia, drug dependence, dysarthria, dyskinesia, dystonia, euphoria, fasciculations, grand mal convulsion, hostility, hyperalgesia, hypokinesia, hysteria, libido increased, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, paralysis, psychosis, psychotic depression, reflexes increased, stupor, withdrawal syndrome.

Respiratory System-*frequent:* cough increased, rhinitis; *infrequent:* asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu, sinusitis; *rare:* carcinoma of lung, hiccups, lung fibrosis, sputum increased.

Skin and Appendages- *frequent:* pruritus; *infrequent:* acne, alopecia, dry skin, ecchymosis, eczema, furunculosis, urticaria; *rare:* angioedema, contact dermatitis, erythema nodosum, maculopapular rash, photosensitivity, skin discoloration, skin melanoma, skin hypertrophy.

Special Senses-*infrequent:* abnormality of accommodation, ear pain, eye pain, mydriasis, otitis media, taste loss, tinnitus; *rare:* amblyopia, cataract, conjunctivitis, corneal ulcer, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, otitis externa, photophobia, anisocoria, deafness, keratoconjunctivitis.

Urogenital System-*infrequent:* abortion, amenorrhea, breast pain, cystitis, dysmenorrhea, dysuria, menorrhagia, nocturia, polyuria, urethritis, urinary incontinence, urinary retention, urinary urgency, vaginitis; *rare:* breast atrophy, breast carcinoma, breast neoplasm, female lactation, hematuria, kidney calculus, kidney function abnormal, kidney pain, mastitis, nephritis, oliguria, prostatic carcinoma, vaginal moniliasis.

Postmarketing Reports

[The following section has been modified based on findings communicated to you in our February 23, 1995 letter.]

Voluntary reports of adverse events in patients taking *Paxil* that have been received since market introduction and not listed above that may have no causal relationship with the drug include [redacted] liver function tests (the most severe [redacted] was fatal, and one other case involving grossly elevated transaminases associated with severe liver dysfunction), [redacted] toxic epidermal necrolysis, priapism, thrombocytopenia, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events; extrapyramidal symptoms which have included dystonia, akathisia, bradykinesia, cogwheel rigidity, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and trismus; and serotonin syndrome, associated in some cases with concomitant use of serotonergic drugs and

with drugs which may have impaired *Paxil* metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor). There have been spontaneous reports that abrupt discontinuation may lead to symptoms such as dizziness, sensory disturbances, agitation or anxiety, nausea and sweating; these events are generally self-limiting.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Paxil (paroxetine hydrochloride) is not a controlled substance.

Physical and Psychologic Dependence

Paxil has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of *Paxil* misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

No deaths were reported following acute overdose with *Paxil* alone or in combination with other drugs and/or alcohol (18 cases, with doses up to 850 mg) during premarketing clinical trials in depression and OCD. Signs and symptoms of overdose with *Paxil* included: nausea, vomiting, drowsiness, sinus tachycardia and dilated pupils. There were no reports of ECG abnormalities, coma or convulsions following overdosage with *Paxil* alone.

Overdosage Management

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. There are no specific antidotes for *Paxil*. Establish and maintain an airway; ensure adequate oxygenation and ventilation. Gastric evacuation either by the induction of emesis or lavage or both should be performed. In most cases, following evacuation, 20 to 30 grams of activated charcoal may be administered every 4 to 6 hours during the first 24 to 48 hours after ingestion. An ECG should be taken and monitoring of cardiac function instituted if there is any evidence of abnormality. Supportive care with frequent monitoring of vital signs and careful observation is indicated. Due to the large volume of distribution of *Paxil*, forced diuresis, dialysis, hemoperfusion and

exchange transfusion are unlikely to be of benefit.

A specific caution involves patients taking or recently having taken paroxetine who might ingest by accident or intent excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and its active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation.

In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Depression

Usual Initial Dosage

Paxil (paroxetine hydrochloride) should be administered as a single daily dose, usually in the morning. The recommended initial dose is 20 mg/day. Patients were dosed in a range of 20 to 50 mg/day in the clinical trials demonstrating the antidepressant effectiveness of Paxil. As with all antidepressants, the full antidepressant effect may be delayed. Some patients not responding to a 20 mg dose may benefit from dose increases, in 10 mg/day increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least 1 week.

Maintenance Therapy

There is no body of evidence available to answer the question of how long the patient treated with Paxil should remain on it. It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Obsessive Compulsive Disorder

[The following section has been slightly modified.]

Usual Initial Dosage

Paxil should be administered as a single daily dose, usually in the morning. The recommended dose of Paxil in the treatment of OCD is 40 mg daily. Patients should be started on 20 mg/day and the dose can be increased in 10 mg/day increments at [illegible] intervals. Patients were dosed in a range of 20 to 60 mg/day in the clinical trials demonstrating the effectiveness of Paxil in the treatment of OCD, and the maximum dosage should not exceed 60 mg/day.

Maintenance Therapy

Although the efficacy of Paxil beyond 12 weeks of dosing for OCD has not been documented in controlled trials, OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Dosage for Elderly or Debilitated, and Patients with Severe Renal or Hepatic Impairment

The recommended initial dose is 10 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 40 mg/day.

Systematic evaluation of the efficacy of Paxil (paroxetine hydrochloride) has shown that efficacy is maintained for periods of up to 1 year with doses that averaged about 30 mg.

Switching Patients to or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of a MAOI and initiation of Paxil therapy. Similarly, at least 14 days should be allowed after stopping Paxil before starting a MAOI.

HOW SUPPLIED

Paxil is supplied as film-coated, modified-oval tablets as follows:
20 mg pink, scored tablets engraved on the front with PAXIL and on the back with 20.
NDC 0029-3211-13 Bottles of 30
NDC 0029-3211-20 Bottles of 100
NDC 0029-3211-21 SUP 100's (intended for institutional use only)
30 mg blue tablets engraved on the front with PAXIL and on the back with 30.
NDC 0029-3212-13 Bottles of 30
Store at controlled room temperature (15° to 30°C; 59° to 86°F).
DATE OF ISSUANCE MONTH YEAR

SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101
Printed in U.S.A.

Doc #DAVID\LABPXOCD.AE1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-031/S-009

SmithKline Beecham Pharmaceuticals
ATTENTION: Michael J. Brennan, Ph.D.
Four Falls Corporate Center
Route 23 & Woodmont Avenue
P.O. Box 1510
King of Prussia, PA 19406

MAR 15 1996

Dear Dr. Brennan:

Please refer to your March 29, 1995 supplemental new drug application, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the use of Paxil (paroxetine hydrochloride) 20 and 30 mg tablets in panic disorder (PD).

We acknowledge receipt of the following amendments and correspondence dated April 13, 1995, July 5, 1995, July 7, 1995, August 1, 1995, August 4, 1995, August 7, 1995, and February 27, 1996.

We have completed our review of supplemental application S-009 and it is approvable. Before the application may be approved, however, it will be necessary for you to submit the following information and respond to the following issues:

CLINICAL

1. Labeling

Accompanying this letter (See Attachment) is the Agency's proposal for the labeling of Paxil. Our proposal is based on the labeling proposal submitted in your original supplement.

We have proposed a number of changes to your draft labeling and explanations for these changes are provided in the bracketed comments embedded within the proposed text. In certain instances, we have asked you to further modify labeling. Some of the modifications in this labeling proposal are pertinent to the pending Obsessive Compulsive Disorder (OCD) claim which we expect to have finalized at the time the PD claim achieves an approval status. Division staff would be happy to meet with you to discuss any diagreements you might have with any part of the proposed labeling format or content.

2. Safety Update

Our review of the safety of paroxetine in the treatment of panic disorder was based on data accumulated through 5-1-94 for the integrated database and through 12-31-94 for serious events. You will need to submit a final safety update including safety data accumulated since these cutoff dates.

3. World Literature Update

Prior to the approval of Paxil for panic disorder, we require an updated report on the world's archival literature pertaining to the safety of Paxil in this population. This report should cover all relevant published papers, including clinical or preclinical data, that were not submitted with the original NDA or in subsequent amendments.

We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversly affect conditionsl about the safety of paroxetine in this population. The report should also detal how the literature search was conducted, by whom, (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clincal data, but new findings in preclnical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

4. Foreign Regulatory Update/Labeling

We require a review of the status of all actions with regard to paroxetine in the treatment of panic disorder, either taken or pending before foreign regulatory authroities. Approval actions can be noted, but we ask that you desribe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution ofthe matter. If paroxetine is approved for use in panic disorder in any countries, we ask that you providie us current labeling for paroxetine in those countries, along with English translations when needed.

Please submit fifteen copies of the printed labels and other labeling, ten of which are individually mounted on heavy weight paper or similar paper.

In addition, please submit three copies of the introductory promotional and/or advertising campaign that you propose to use for this new indication. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert, directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications
HFD-040, Room 17B-17
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

In accordance with the policy described in Section 314.102(d) of the new drug regulations and in the Center for Drug Evaluation and Research Staff Staff Manual Guide CDB 4820.6, you may request an informal conference with the division to discuss what further steps you need to secure approval. The meeting is to be requested at least 15 days in advance. Alternatively, you may choose to receive such a report via a telephone call. Should you wish this conference or a telephone report, please call Mr. Merril Mille, Senior Regulatory Management Officer, at (301) 594-5528.

Sincerely yours,

3/16/96

Paul D. Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ATTACHMENT

mlle

ATTACHMENT

DRAFT LABELING PROPOSAL

Note: Brackets [] embedded within the text that follows include comments and explanations concerning the proposed draft labeling. For some sections, few changes were proposed, while others required more extensive modification. New language and modifications to currently approved labeling are shaded (redline font) to facilitate supervisory review of this document. This revision is based on the version of labeling submitted in the 3-29-95 original submission. Some of the modifications included in this labeling proposal are pertinent to the OCD claim which we expect to have finalized at the time the PD claim achieves an approval status. If you feel that further revisions are necessary to this draft, please use this exact document as the starting document. Please use the 'strikeout' font to indicate the material you wish to delete and the 'redline' font to indicate the material you wish to add. A copy of this document can be provided to you in electronic format if requested.

PRESCRIBING INFORMATION

PAXIL®
brand of
paroxetine hydrochloride tablets

DESCRIPTION

Paxil (paroxetine hydrochloride) is an orally administered antidepressant with a chemical structure unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic or other available antidepressant agents. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-trans-4R-(4'-fluorophenyl)-3S-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3HCl$ $1/2H_2O$. The molecular weight is 374.8 (329.4 as free base). The structural formula is:

[Insert structural formula here]

Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of 120° to 138°C and a solubility of 5.4 mg/mL in water.

Each film-coated tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: 20 mg pink (scored); 30 mg blue. Inactive ingredients consist of dibasic calcium phosphate dihydrate, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide and one or more of the following: D&C Red No. 30, FD&C Blue No. 2.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The antidepressant action of paroxetine and its efficacy in the treatment of Obsessive Compulsive Disorder (OCD) and Panic Disorder (PD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* radioligand binding studies indicate that paroxetine has little affinity for muscarinic, $alpha_1$-, $alpha_2$-, beta-adrenergic-, dopamine (D_2)-, $5\text{-}HT_1$-, 5-HT - and histamine (H)-receptors; antagonism of muscarinic, histaminergic and $alpha_1$-adrenergic receptors has been associated with various anticholinergic, sedative and cardiovascular effects for other psychotropic drugs.

Because the relative potencies of paroxetine's major metabolites are at most 1/50 of the parent compound, they are essentially inactive.

Pharmacokinetics

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male subjects (n=15) received 30 mg tablets daily for 30 days, steady-state paroxetine concentrations were achieved by approximately 10 days for most subjects, although it may take substantially longer in an occasional patient. At steady state, mean values of C_{max}, T_{max}, C_{min} and $T_{1/2}$ were 61.7 ng/mL (CV 45%), 5.2 hr. (CV 10%), 30.7 ng/mL (CV 67%) and 21.0 hr. (CV 32%), respectively. The steady-state C_{max} and C_{min} values were about 6 and 14 times what would be predicted from single-dose studies. Steady-state drug exposure based on AUC_{0-24} was about 8 times greater than would have been predicted from single-dose data in these subjects. The excess accumulation is a consequence of the fact that one of the enzymes that metabolizes paroxetine is readily saturable.

In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of 20 to 40 mg daily for the elderly and 20 to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{min} values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than doubled.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by cytochrome $P_{450}IID_6$. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see PRECAUTIONS).

Approximately 64% of a 30 mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as

metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.

Distribution

Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.

Protein Binding

Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/mL. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.

Renal and Liver Disease

Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below 30 mL/min was approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30 to 60 mL/min and patients with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, C_{max}).

The initial dosage should therefore be reduced in patients with severe renal or hepatic impairment, and upward titration, if necessary, should be at increased intervals (see DOSAGE AND ADMINISTRATION).

Elderly Patients

In a multiple-dose study in the elderly at daily paroxetine doses of 20, 30 and 40 mg, C_{min} concentrations were about 70% to 80% greater than the respective C_{min} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced. (See DOSAGE AND ADMINISTRATION.)

Clinical Trials

Depression

The efficacy of Paxil as a treatment for depression has been established in 6 placebo-controlled studies of patients with depression (ages 18 to 73). In these studies Paxil was shown to be significantly more effective than placebo in treating depression by at least 2 of the following measures: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI) Severity of Illness. Paxil was significantly better than placebo in improvement of the HDRS sub-factor scores, including the depressed mood item, sleep disturbance factor and anxiety factor.

A study of depressed outpatients who had responded to Paxil (HDRS total score <8) during an initial 8-week open-treatment phase and were then randomized to continuation on Paxil or placebo for 1 year demonstrated a significantly lower relapse rate for patients taking Paxil (15%) compared to those on placebo (39%). Effectiveness was similar for male and female patients.

Obsessive Compulsive Disorder

[The following language is pertinent to the OCD claim but included here since we expect these changes to be finalized at the time the PD claim achieves an approval status.]

The effectiveness of Paxil in the treatment of obsessive compulsive disorder (OCD) was demonstrated in two 12-week multicenter placebo-controlled studies of adult outpatients (Studies 1 and 2). Patients in all studies had moderate to severe OCD (DSM-IIIR) with mean baseline ratings on the Yale Brown Obsessive Compulsive Scale (YBOCS) total score ranging from 23 to 26. Study 1, a dose-range finding study where patients were treated with fixed doses of 20, 40 or 60 mg/day demonstrated that daily doses of paroxetine 40 and 60 mg are effective in the treatment of OCD. Patients receiving doses of 40 and 60 mg paroxetine experienced a mean reduction of approximately 6 and 7 points respectively on the YBOCS total score which was significantly greater than the approximate 4 point reduction at 20 mg and a 3 point reduction in the placebo-treated

patients. Study 2 was a flexible dose study comparing paroxetine (20 to 60 mg daily) with clomipramine (25 to 250 mg daily). In this study, patients receiving paroxetine experienced a mean reduction of approximately 7 points on the YBOCS total score which was significantly greater than the mean reduction of approximately 4 points in placebo-treated patients.

The following table provides the outcome classification by treatment group on Global Improvement items of the Clinical Global Impressions (CGI) scale for study 1.

Outcome Classification (%) on CGI-Global Improvement Item for Completers in Study 1				
Outcome Classification	Placebo (N=74)	Paxil 20mg (N=75)	Paxil 40mg (N=66)	Paxil 60mg (N=66)
Worse	14%	7%	7%	3%
No Change	44%	35%	22%	19%
Minimally Improved	24%	33%	29%	34%
Much Improved	11%	18%	22%	24%
Very Much Improved	7%	7%	20%	20%

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

The long-term maintenance effects of Paxil in OCD were demonstrated in a long-term extension to Study 1. Patients who were responders on paroxetine during the 3-month double-blind phase and a 6-month extension on open-label paroxetine (20-60 mg/day) were randomized to either paroxetine or placebo in a 6-month double-blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Panic Disorder

[We have modified this subsection by revising the language describing the 3 positive studies and deleting the description of study 228, since we view that study as having a design flaw that would preclude any definitive conclusions about long-term efficacy. However, we have included a brief description of study 222, since we believe that the design of that study was adequate to address the question of long-term efficacy, even though it was a preliminary trial without a clear, prospectively defined analysis plan.]

The effectiveness of Paxil in the treatment of Panic Disorder was demonstrated in three 10-12 week multicenter, placebo-controlled studies of adult outpatients (Studies 1-3). Patients in all studies had Panic Disoder (DSM-IIIR), with or without agoraphobia. In these studies, Paxil was shown to be significantly more effective than placebo in treating panic disorder by at least 2 out of 3 measures of panic attack frequency and on the Clinical Global Impression Severity of Illness score.

Study 1 was a 10-week dose-range finding study involving fixed paroxetine doses of 10, 20, or 40 mg/day and placebo. A significant difference from placebo was observed only for the 40 mg/day group. At endpoint, 76% of patients receiving paroxetine 40 mg/day were free of panic attacks, compared to 32% of placebo patients.

Study 2 was a 12-week flexible-dose study comparing paroxetine (10 to 60 mg daily) and placebo. At endpoint, 51% of paroxetine patients were free of panic attacks compared to 32% of placebo-treated patients.

Study 3 was a 12-week flexible-dose study comparing paroxetine (10 to 60 mg daily) given concurrently with standardized cognitive behavioral therapy to placebo. At endpoint, 33% of the paroxetine-treated patients showed a reduction to 0 or 1 panic attacks compared to 14% of placebo patients.

In both studies 2 and 3, the mean paroxetine dose for completers at endpoint was approximately 40 mg/day.

Longer-term maintenance effects of Paxil in panic disorder were demonstrated in an extension to Study 1. Patients who were responders during the 10-week double-blind phase and during a 3-month double-blind extension phase were randomized to either paroxetine (10, 20, or 40 mg/day) or placebo in a 3-month double blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

INDICATIONS AND USAGE

Depression

Paxil (paroxetine hydrochloride) is indicated for the treatment of depression.

The efficacy of Paxil in the treatment of a major depressive episode was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see CLINICAL PHARMACOLOGY). A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant action of Paxil in hospitalized depressed patients has not been adequately studied.

The efficacy of Paxil in maintaining an antidepressant response for up to 1 year was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use Paxil for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Obsessive Compulsive Disorder

[The following language is pertinent to the OCD claim but included here since we expect these changes to be finalized at the time the PD claim achieves an approval status.]

Paxil is indicated for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD) as defined in the DSM-IV. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of Paxil was established in two 12-week trials with obsessive compulsive outpatients whose diagnoses corresponded most closely to the DSM-IIIR category of obsessive compulsive disorder (see Clinical Trials under CLINICAL PHARMACOLOGY).

Obsessive compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

A 6-month relapse prevention trial demonstrated a lower relapse rate in patients assigned to paroxetine compared to those on placebo (see Clinical Pharmacology). Nevertheless, the physician who elects to use Paxil for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Panic Disorder

[We have substantially modified the panic disorder statement by (1) including more details of the definition of the disorder, and (2) modifiying the statement regarding long-term efficacy data; as noted above, we believe that only study 222 provides adequate data to address this issue.]

Paxil is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and

associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of Paxil was established in three 10 to 12 week trials in anxious patients whose diagnoses corresponded to the DSM-IIIR category of panic disorder (see Clinical Trials under Clinical Pharmacology).

Panic disorder (DSMIV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes [(1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.]

A 3-month relapse prevention trial in patients with panic disorder demonstrated a lower relapse rate in patients assigned to paroxetine compared to those on placebo (see Clinical Pharmacology). Nevertheless, the physician who prescribes Paxil for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS and PRECAUTIONS).

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving another serotonin reuptake inhibitor drug in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with *Paxil*, limited animal data on the effects of combined use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Paxil (paroxetine hydrochloride) not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. At least 2 weeks should be allowed after stopping *Paxil* before starting a MAOI.

Potential Astemizole, Cisapride, and Triazolam Interactions

> [As discussed in our 3-4-96 teleconference with you, the potential for an interaction of paroxetine with astemizole, cisapride, and triazolam will need to be included as a warning until you have obtained in vitro data to address this concern.]

Ketoconazole, a potent inhibitor of cytochrome P450IIIA4, blocks the metabolism of terfenadine, astemizole and cisapride, all of which are metabolized by this system, and the resulting increases in plasma concentrations of these drugs have been associated with QT prolongation and torsades de pointes-type ventricular tachycardia, sometimes fatal. Ketoconazole also blocks the metabolism of triazolam, resulting in increases in plasma concentration of this drug and enhanced pharmacological effects. In vitro studies have shown Paxil to have only a modest inhibitory effect on the metabolism of terfenadine and alprazolam, another substrate for the P450IIIA4 isozyme, compared to a much more potent

inhibitory effect of ketoconazole. Furthermore, an in vivo interaction study involving co-administration of paroxetine and terfenadine under steady-state conditions revealed no effect of paroxetine on QTc or on terfenadine kinetics. Thus, concurrent administration of Paxil with terfenadine would not be expected to pose a hazard. It is unknown at this time whether or not the concurrent administration of Paxil with astemizole, cisapride, or triazolam would pose a hazard, and until in vivo or in vitro data are available to address these potential interactions, the administration of Paxil with astemizole, cisapride, and triazolam should be undertaken with caution (see PRECAUTIONS).

PRECAUTIONS

General

Activation of Mania/Hypomania

During premarketing testing, hypomania or mania occurred in approximately 1.0% of Paxil-treated unipolar patients compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for Paxil and 11.6% for the combined active-control groups. As with all antidepressants, Paxil should be used cautiously in patients with a history of mania.

Seizures

During premarketing testing, seizures occurred in 0.1% of Paxil-treated patients, a rate similar to that associated with other antidepressants. Paxil should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Suicide

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Paxil should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Hyponatremia

Several cases of hyponatremia have been reported. The hyponatremia appeared to be reversible when Paxil was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Abnormal Bleeding

There have been several reports of abnormal bleeding (mostly ecchymosis and purpura) associated with paroxetine treatment, including a report of impaired platelet aggregation. While a causal relationship to paroxetine is unclear, impaired platelet aggregation may result from platelet serotonin depletion and contribute to such occurrences.

Use in Patients with Concomitant Illness

Clinical experience with Paxil in patients with certain concomitant systemic illness is limited. Caution is advisable in using Paxil in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Paxil has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. Evaluation of electrocardiograms of 682 depressed patients who received Paxil in double-blind, placebo-controlled trials, however, did not indicate that Paxil is associated with the development of significant ECG abnormalities. Similarly, Paxil (paroxetine hydrochloride) does not cause any clinically important changes in heart rate or blood pressure.

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance <30 mL/min.) or severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Paxil:

Interference with Cognitive and Motor Performance

Any psychoactive drug may impair judgment, thinking or motor skills. Although in controlled studies Paxil has not been shown to impair psychomotor performance, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Paxil therapy does not affect their ability to engage in such activities.

Completing Course of Therapy

While patients may notice improvement with Paxil therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant Medication

Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Although Paxil has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking Paxil.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing

Patients should be advised to notify their physician if they are breast-feeding an infant. (See PRECAUTIONS Nursing Mothers.)

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

Tryptophan

As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are co-administered. Adverse experiences, consisting primarily of headache, nausea, sweating and dizziness, have been reported when tryptophan was administered to patients taking Paxil (paroxetine hydrochloride). Consequently, concomitant use of Paxil with tryptophan is not recommended.

Monoamine Oxidase Inhibitors

See CONTRAINDICATIONS and WARNINGS.

Warfarin

Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the face of unaltered prothrombin time) between paroxetine and warfarin. Since there is little clinical experience, the concomitant administration of Paxil and warfarin should be undertaken with caution.

Drugs Affecting Hepatic Metabolism

The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug-metabolizing enzymes.

Cimetidine - Cimetidine inhibits many cytochrome P_{450} (oxidative) enzymes. In a study where Paxil (30 mg q.d.) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during co-administration with oral cimetidine (300 mg t.i.d.) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of Paxil after the 20 mg starting dose should be guided by clinical

effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

Phenobarbital - Phenobarbital induces many cytochrome P_{450} (oxidative) enzymes. When a single oral 30 mg dose of Paxil was administered at phenobarbital steady state (100 mg q.d. for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since Paxil exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed. No initial Paxil dosage adjustment is considered necessary when co-administered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

Phenytoin - When a single oral 30 mg dose of Paxil was administered at phenytoin steady state (300 mg q.d. for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 50% and 35%, respectively) compared to Paxil administered alone. In a separate study, when a single oral 300 mg dose of phenytoin was administered at paroxetine steady state (30 mg q.d. for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when these drugs are co-administered; any subsequent adjustments should be guided by clinical effect. (see **Postmarketing Reports** under ADVERSE REACTIONS).

Drugs Metabolized by Cytochrome $P_{450}IID_6$

Many drugs, including most antidepressants (paroxetine, other SSRIs, and many tricyclics), are metabolized by the cytochrome P450 isozyme P450IID6. Like other agents that are metabolized by P450IID6, paroxetine may significantly inhibit the activity of this isozyme. In most patients (>90%), the P450IID6 isozyme is saturated early during PAXIL dosing. In one study, daily dosing of PAXIL (20 mg q.d.) under steady-state conditions increased single dose desipramine (100 mg) Cmax, AUC, and $T_{1/2}$ by an average of approximately two-, five-, and three-fold. Concomitant use of

PAXIL with other drugs metabolized by cytochrome P450IID6 has not been formally studied but may require lower doses than usually prescribed for either PAXIL or the other drug.

Therefore, co-administration of Paxil with other drugs that are metabolized by this isozyme, including certain antidepressants (e.g., nortriptyline, amitriptyline, imipramine, desipramine and fluoxetine), phenothiazines (e.g., thioridazine) and Type 1C anti-arrhythmics (e.g., propafenone, flecainide and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

At steady state, when the $P_{450}IID_6$ pathway is essentially saturated, paroxetine clearance is governed by alternative P_{450} isozymes which, unlike $P_{450}IID_6$, show no evidence of saturation. (See Tricyclic Antidepressants under PRECAUTIONS).

Drugs Metabolized by Cytochrome P450IIIA4

[As noted under Warnings, the reference to any potential 3A4 interactions may be modified and placed in this subsection if additional reassuring in vitro data can be obtained to address this concern.]

Paroxetine has been shown in vitro to be a modest inhibitor of cytochrome P450IIIA4. Both in vitro data and an in vivo terfenadine/paroxetine interaction study suggest that there may be no clinically important interaction for terfenadine and paroxetine. It is unknown whether or not the concurrent administration of Paxil with astemizole, cisapride, or triazolam would pose a hazard, and caution is indicated with such use (see WARNINGS).

Tricyclic Antidepressants (TCA)

Caution is indicated in the co-administration of tricyclic antidepressants (TCAs) with PAXIL, because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is co-administered with PAXIL (see Drugs Metabolized by Cytochrome $P_{450}IID_6$ under PRECAUTIONS).

Drugs Highly Bound to Plasma Protein

Because paroxetine is highly bound to plasma protein, administration of *Paxil* to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

Alcohol

Although Paxil does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking Paxil (paroxetine hydrochloride).

Lithium

A multiple-dose study has shown that there is no pharmacokinetic interaction between Paxil and lithium carbonate. However, since there is little clinical experience, the concurrent administration of paroxetine and lithium should be undertaken with caution.

Digoxin

The steady-state pharmacokinetics of paroxetine was not altered when administered with digoxin at steady state. Mean digoxin AUC at steady state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of paroxetine and digoxin should be undertaken with caution.

Diazepam

Under steady-state conditions, diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

Procyclidine

Daily oral dosing of *Paxil* (30 mg q.d.) increased steady-state AUC_{0-24}, C_{max} and C_{min} values of procyclidine (5 mg oral q.d.) by 35%, 37%

and 67%, respectively, compared to procyclidine alone at steady state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

Beta-Blockers

In a study where propranolol (80 mg b.i.d.) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during co-administration with Paxil (30 mg q.d.) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated. **(see Postmarketing Reports under ADVERSE REACTIONS).**

Theophylline

Reports of elevated theophylline levels associated with Paxil treatment have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

Electroconvulsive Therapy (ECT)

There are no clinical studies of the combined use of ECT and Paxil.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

> [Please note that the penultimate sentence of this subsection has been deleted from the paragraph below. Although this sentence was part of the original labeling, we see no rationale for maintaining this text in labeling at this time.]

Two-year carcinogenicity studies were conducted in mice and rats given paroxetine in the diet at doses up to 2.4 (mouse) and 3.9 (rat) times the maximum recommended human dose (MRHD) for depression on a mg/m^2 basis. Because the MRHD for depression is slightly less than that for OCD (50 mg vs. 60 mg), the doses used in these carcinogenicity studies were only 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD and Panic Disorder. There was a significantly greater number of male rats in the high-dose group

with reticulum cell sarcomas (1/100, 0/50. 0/50 and 4/50 for control, low-, middle- and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis

Paroxetine produced no genotoxic effects in a battery of 5 *in vitro* and 2 *in vivo* assays that included the following: bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes and in a dominant lethal test in rats.

Impairment of Fertility

A reduced pregnancy rate was found in reproduction studies in rats at doses of paroxetine which were 2.9 times the MRHD for depression or 2.4 times the MRHD for OCD on a mg/m^2 basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions, which consisted of vacuolation of epididymal tubular epithelium and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis occurred at doses which were 4.9 times the MRHD for depression and 4.1 times the MRHD for OCD on a mg/m^2 basis.

Pregnancy

Teratogenic Effects - Pregnancy Category C

Reproduction studies were performed in rats and rabbits at doses up to 9.7 (rat) and 2.2 (rabbit) times the maximum recommended human dose (MRHD) for depression (50 mg) and 8.1 (rat) and 1.9 (rabbit) times the MRHD for OCD, on a mg/m^2 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of

lactation when dosing occurred during the last [redacted] of gestation and continued throughout lactation. This [redacted] occurred at 0.19 times (mg/m^2) the MRHD for depression and [redacted] (mg/m^2) the MRHD for OCD. The no-effect dose for [redacted] was not determined. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

The effect of paroxetine on labor and delivery in humans is unknown.

Nursing Mothers

Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when Paxil (paroxetine hydrochloride) is administered to a nursing woman.

Usage in Children

Safety and effectiveness in children have not been established.

Geriatric Use

In worldwide premarketing Paxil clinical trials, 17% of *Paxil*-treated patients (approximately 700) were 65 years of age or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

[Please add 2 additional columns to this table including the Paxil and placebo data for the Panic disorder studies.]

Twenty-one percent (881/4,126) of Paxil patients in worldwide clinical trials in depression and 11.8% (64/542) and 9.4% (44/469) of Paxil patients in worldwide trials in OCD and Panic Disorder, respectively, discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for Paxil compared to placebo) included the following:

	Depression		OCD	
	Paxil	Placebo	Paxil	Placebo
CNS				
Somnolence	2.3%	0.6%	-	
Insomnia	1.9%	0.6%	1.7%	0%
Agitation	1.3%	0.6%	-	
Tremor	1.3%	0.3%	-	
Anxiety	1.1%	0.3%	-	
Dizziness	1.4%	0.3%	1.5%	0%
Gastrointestinal				
Constipation	-		1.1%	0%
Nausea	3.4%	1.1%	1.9%	0%
Diarrhea	1.0%	0.3%	-	
Dry mouth	1.0%	0.3%	-	
Vomiting	1.0%	0.3%	-	
Other				
Asthenia	1.7%	0.5%	1.9%	0.4%
Abnormal ejaculation[1]	1.6%	0%	2.1%	0%
Sweating	1.1%	0.3%	-	
Impotence[1]	-		1.5%	0%

Where numbers are not provided the incidence of the adverse events in PAXIL patients was not >1% and was greater than or equal to two times the incidence of placebo.

1. Incidence corrected for gender.

Commonly Observed Adverse Events

Depression

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo, derived from the table below) were: asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance and other male genital disorders.

Obsessive Compulsive Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of at least 5% for Paxil and for which the incidence was approximately twice or more the incidence among placebo-treated patients, derived from the table below) were: nausea, dry mouth, decreased appetite, constipation, dizziness, somnolence, tremor, sweating, impotence and abnormal ejaculation.

Panic Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of at least 5% for Paxil and for which the incidence was approximately twice or more the incidence among placebo-treated patients) were: asthenia, sweating, decreased appetite, libido decreased, tremor, abnormal ejaculation, female genital disorders and impotence.

Incidence in Controlled Clinical Trials

Depression

Table 1 enumerates adverse events that occurred at an incidence of 1% or more among paroxetine-treated patients who participated in short term (6-week) placebo-controlled trials in which patients were dosed in a range of 20 to 50 mg/day.

Reported adverse events were classified using a standard COSTART-based Dictionary terminology. The prescriber should be aware that these figures cannot be used to predict the incidence of side

effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Depression[1]

Body System	Preferred Term	*Paxil* (n=421)	Placebo (n=421)
Body as a Whole	Headache	18%	17%
	Asthenia	15%	6%
Cardiovascular	Palpitation	3%	1%
	Vasodilation	3%	1%
Dermatologic	Sweating	11%	2%
	Rash	2%	1%
Gastrointestinal	Nausea	26%	9%
	Dry Mouth	18%	12%
	Constipation	14%	7%
	Diarrhea	12%	8%
	Decreased Appetite	6%	2%
	Flatulence	4%	2%
	Oropharynx Disorder[2]	2%	0%
	Dyspepsia	2%	1%
Musculoskeletal	Myopathy	2%	1%
	Myalgia	2%	1%
	Myasthenia	1%	0%
Nervous System	Somnolence	23%	9%
	Dizziness	13%	6%
	Insomnia	13%	6%
	Tremor	8%	2%
	Nervousness	5%	3%
	Anxiety	5%	3%
	Paresthesia	4%	2%
	Libido Decreased	3%	0%
	Drugged Feeling	2%	1%
	Confusion	1%	0%
Respiration	Yawn	4%	0%
Special Senses	Blurred Vision	4%	1%
	Taste Perversion	2%	0%

Urogenital System	Ejaculatory Disturbance[3,4]	13%	0%
	Other Male Genital Disorders[3,5]	10%	0%
	Urinary Frequency	3%	1%
	Urination Disorder[6]	3%	0%
	Female Genital Disorders[3,7]	2%	0%

1. Events reported by at least 1% of *Paxil*-treated patients are included, except the following; events which had an incidence on placebo ≥ *Paxil*: abdominal pain, agitation, back pain, chest pain; CNS stimulation, fever, increased appetite, myoclonus, pharyngitis, postural hypotension, respiratory disorder (includes mostly "cold symptoms" or "URI"), trauma and vomiting.
2. Includes mostly "lump in throat" and "tightness in throat."
3. Incidence is gender-corrected.
4. Mostly "ejaculatory delay."
5. Includes "anorgasmia", "erectile difficulties", "delayed ejaculation/orgasm", and "sexual dysfunction," and "impotence."
6. Includes mostly "difficulty with micturition" and "urinary hesitancy."
7. Includes mostly "anorgasmia" and "difficulty reaching climax/orgasm."

Obsessive-Compulsive Disorder and Panic Disorder

Table 2 enumerates adverse events that occurred at a frequency of 2% or more among OCD treated patients on Paxil who participated in placebo-controlled trials of 12-week duration in which patients were dosed in a range of 20 to 60 mg/day or among Panic Disorder patients on Paxil who participated in placebo controlled trials of 10-12 weeks duration in which patients were dosed in a range of 10-60 mg/day.

Table 2
Treatment Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Obsessive Compulsive Disorder and Panic Disorder[1]

		Obsessive Compulsive Disorder		Panic Disorder	
Body System	Preferred Term	Paxil (n=542)	Placebo (n=265)	Paxil (n=469)	Placebo (n=324)
Body as a Whole	Asthenia	22%	14%	14%	5%
	Abdominal Pain	-	-	4%	3%
	Chest Pain	3%	2%	-	-
	Back Pain	-	-	3%	2%
	Chills	2%	1%	2%	1%
Cardiovascular	Vasodilation	4%	1%	-	-
	Palpitation	2%	0%	-	-
Dermatologic	Sweating	9%	3%	14%	6%
	Rash	3%	2%	-	-
Gastrointestinal	Nausea	23%	10%	23%	17%
	Dry Mouth	18%	9%	18%	11%

	Constipation	16%	6%	8%	5%
	Diarrhea	10%	10%	12%	7%
	Decreased Appetite	9%	3%	7%	3%
	Increased Appetite	4%	3%	2%	1%
Nervous System	Insomnia	24%	13%	18%	10%
	Somnolence	24%	17%	19%	11%
	Dizziness	12%	6%	14%	10%
	Tremor	11%	1%	9%	1%
	Nervousness	9%	8%	-	-
	Libido Decreased	7%	4%	9%	1%
	Agitation	-	-	5%	4%
	Anxiety	-	-	5%	4%
	Abnormal Dreams	4%	1%	-	-
	Concentration Impaired	3%	2%	-	-
	Depersonalization	3%	0%	-	-
	Myoclonus	3%	0%	3%	2%
	Amnesia	2%	1%	-	-
Respiratory System	Rhinitis	-	-	3%	0%
Special Senses	Abnormal Vision	4%	2%	-	-
	Taste Perversion	2%	0%	-	-
Urogenital System	Abnormal Ejaculation[2]	23%	1%	21%	1%
	Female Genital Disorder[2]	3%	0%	9%	1%
	Impotence[2]	8%	1%	5%	0%
	Urinary Frequency	3%	1%	2%	0%
	Urination Impaired	3%	0%	-	-
	Urinary Tract Infection	2%	1%	2%	1%

1. Events reported by at least 2% of OCD or Panic Disorder Paxil-treated patients are included, except the following events which had an incidence on placebo≥Paxil: [OCD]: abdominal pain, agitation, anxiety, back pain, cough increased, depression, headache, hyperkinesia, infection, paresthesia, pharyngitis, respiratory disorder, rhinitis and sinusitis. [Panic Disorder]: abnormal dreams, abnormal vision, chest pain, cough increased, depersonalization, depressions, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, myalgia, nervousness, palpitation, paresthesia, pharyngitis, rash, respiratory disorder, sinusitis, taste perversion, trauma, urination impaired and vasodilation.

2. Incidence is gender-corrected.

Dose Dependency of Adverse Events

A comparison of adverse event rates in a fixed-dose study comparing Paxil 10, 20, 30 and 40 mg/day with placebo in the treatment of depression revealed a clear dose dependency for some of the more common adverse events associated with Paxil use, as shown in the following table:

Table 3 Treatment-Emergent Adverse Experience Incidence in a Depression Dose-Comparison Trial*

	Placebo	Paxil			
Body System/ Preferred Term		**10 mg**	**20 mg**	**30 mg**	**40 mg**
	n=51	**n=102**	**n=104**	**n=101**	**n=102**
Body as a Whole					
Asthenia	0.0%	2.9%	10.6%	13.9%	12.7%
Dermatology					
Sweating	2.0%	1.0%	6.7%	8.9%	11.8%
Gastrointestinal					
Constipation	5.9%	4.9%	7.7%	9.9%	12.7%
Decreased Appetite	2.0%	2.0%	5.8%	4.0%	4.9%
Diarrhea	7.8%	9.8%	19.2%	7.9%	14.7%
Dry Mouth	2.0%	10.8%	18.3%	15.8%	20.6%
Nausea	13.7%	14.7%	26.9%	34.7%	36.3%
Nervous System					
Anxiety	0.0%	2.0%	5.8%	5.9%	5.9%
Dizziness	3.9%	6.9%	6.7%	8.9%	12.7%
Nervousness	0.0%	5.9%	5.8%	4.0%	2.9%
Paresthesia	0.0%	2.9%	1.0%	5.0%	5.9%
Somnolence	7.8%	12.7%	18.3%	20.8%	21.6%
Tremor	0.0%	0.0%	7.7%	7.9%	14.7%
Special Senses					
Blurred Vision	2.0%	2.9%	2.9%	2.0%	7.8%
Urogenital System					
Abnormal Ejaculation	0.0%	5.8%	6.5%	10.6%	13.0%
Impotence	0.0%	1.9%	4.3%	6.4%	1.9%
Male Genital Disorders	0.0%	3.8%	8.7%	6.4%	3.7%

*Rule for including adverse events in table: incidence at least 5% for one of paroxetine groups and ≥ twice the placebo incidence for at least one paroxetine group.

In a fixed-dose study comparing placebo and Paxil 20, 40 and 60 mg in the treatment of OCD, there was no clear relationship between adverse events and the dose of Paxil to which patients were assigned. No new adverse events were observed in the Paxil 60 mg dose group compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and *Paxil* 10, 20 and 40 mg in the treatment of Panic Disorder, there was no clear relationship between adverse events and the dose of *Paxil* to which patients were assigned, except for asthenia, dry mouth, anxiety, libido decreased, tremor and abnormal ejaculation. In flexible dose studies, no new adverse

events were observed in patients receiving *Paxil* 60 mg compared to any of the other treatment groups.

Adaptation to Certain Adverse Events

Over a 4- to 6-week period, there was evidence of adaptation to some adverse events with continued therapy (e.g., nausea and dizziness), but less to other effects (e.g., dry mouth, somnolence and asthenia).

Weight and Vital Sign Changes

Significant weight loss may be an undesirable result of treatment with *Paxil* for some patients but, on average, patients in controlled trials had minimal (about 1 pound) weight loss vs. smaller changes on placebo and active control. No significant changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were observed in patients treated with *Paxil* in controlled clinical trials.

ECG Changes

In an analysis of ECGs obtained in 682 patients treated with *Paxil* and 415 patients treated with placebo in controlled clinical trials in depression, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests

In placebo-controlled clinical trials, patients treated with *Paxil* exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients. In particular, the *Paxil*-vs.-placebo comparisons in depression, OCD and Panic Disorder for alkaline phosphatase, SGOT, SGPT and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

Other Events Observed During the Premarketing Evaluation of Paxil (paroxetine hydrochloride)

[The following is the most recent version of this section proposed for the OCD labeling, and we assume it is also correct regarding PD data. Please verify.]

During its premarketing assessment in depression, multiple doses of *Paxil* were administered to 6,145 patients in phase 2 and 3 studies. The conditions and duration of exposure to *Paxil* varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. During premarketing clinical trials in OCD and Panic Disorder, 542 and 469 patients, respectively, received multiple doses of Paxil. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 7,156 patients exposed to multiple doses of Paxil (paroxetine hydrochloride) who experienced an event of the type cited on at least one occasion while receiving *Paxil*. All reported events are included except those already listed in Tables 1 and 2, those reported in terms so general as to be uninformative and those events where a drug cause was remote. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

Body as a Whole - *frequent:* chills, malaise; *infrequent:* allergic reaction, carcinoma, face edema, moniliasis, neck pain; *rare:* abscess, adrenergic syndrome, cellulitis, neck rigidity, pelvic pain, peritonitis, ulcer.

Cardiovascular System - *frequent:* hypertension, syncope, tachycardia; *infrequent:* bradycardia, conduction abnormalities, electrocardiogram abnormal, hypotension, migraine, peripheral vascular disorder; *rare:* angina pectoris, arrhythmia, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombosis, thrombophlebitis, varicose vein, vascular headache, ventricular extrasystoles.

Digestive System -*infrequent:* bruxism, colitis, dysphagia, eructation, gastroenteris, gingivitis, glossitis, increased salivation, liver function tests abnormal, mouth ulceration, rectal hemorrhage, ulcerative stomatitis; *rare:* aphthous stomatitis, bloody diarrhea, bulimia, choleithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gastritis, gastroenteritis, gum hemorrhage, hematemesis, hepatitis, ileus, intestinal obstruction, jaundice, melena, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue edema, tooth caries, tongue discoloration, tooth malformation.

Endocrine System -*rare:* diabetes mellitus, hyperthyroidism, hypothyroidism, thyroiditis.

Hemic and Lymphatic Systems- *infrequent:* anemia, leukopenia, lymphadenopathy, purpura; *rare:* abnormal erythrocytes, basophilia, eosinophilia, iron deficiency anemia, hypochromic anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

Metabolic and Nutritional- *frequent:* edema, weight gain, weight loss; *infrequent:* hyperglycemia, peripheral edema, SGOT increased, SGPT increased, thirst; *rare:* alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma

globulins increased, gout, **hypercholesteremia, hypercalcemia,** hypocalcemia, hypoglycemia, **hyperkalemia,** hypokalemia, hyponatremia, **hyperphosphatemia, ketosis, lactic dehydrogenase increased.**

Musculoskeletal System- *frequent:* **arthralgia;** *infrequent:* arthritis; *rare:* arthrosis, bursitis, myositis, osteoporosis, **generalized spasm, tenosynovitis,** tetany.

Nervous System- *frequent:* amnesia, CNS stimulation, concentration impaired, depression, emotional lability, vertigo; *infrequent:* abnormal thinking, akinesia, alcohol abuse, ataxia, convulsion, depersonalization, **dystonia,** hallucinations, hostility, hyperkinesia, hypertonia, incoordination, lack of emotion, manic reaction, **neurosis, paralysis,** paranoid reaction, hypesthesia; *rare:* abnormal electroencephalogram, abnormal gait, antisocial reaction, aphasia, choreoathetosis, **circumoral parasthesis,** delirium, delusions, diplopia, drug dependence, dysarthria, dyskinesia, euphoria, extrapyramidal **syndrome,** fasciculations, grand mal convulsion, hyperalgesia, hypokinesia, hysteria, libido increased, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychosis, psychotic depression, reflexes increased, reflexes decreased, stupor, trismus, withdrawal syndrome.

Respiratory System-*frequent:* cough increased, rhinitis; *infrequent:* asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu, sinusitis, voice alteration; *rare:* carcinoma of larynx, carcinoma of lung, emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased.

Skin and Appendages- *frequent:* pruritus; *infrequent:* acne, alopecia, dry skin, ecchymosis, eczema, furunculosis, urticaria; *rare:* angioedema, contact dermatitis, erythema nodosum, erythema multiforme, fungal dermatitis, herpes simplex, herpes zoster, hirsutism, maculopapular rash, photosensitivity, skin discoloration, skin melanoma, skin hypertrophy, seborrhea, skin ulcer, vesiculobullous rash.

Special Senses- *frequent:* tinnitus; *infrequent:* abnormality of accommodation, conjunctivitis, ear pain, eye pain,

mydriasis, otitis media, taste loss, visual field defect; *rare:* amblyopia, anisocroia, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, otitis externa, keratoconjunctivitis, night blindness, parosmia, photophobia, ptosis, retinal hemorrhage.

Urogenital System-*infrequent:* abortion, amenorrhea, breast pain, cystitis, dysmenorrhea, dysuria, hematuria, menorrhagia, nocturia, polyuria, urethritis, urinary incontinence, urinary retention, urinary urgency, vaginitis; *rare:* breast atrophy, breast carcinoma, breast enlargement, breast neoplasm, epididymitis, female lactation, fibrocystic breast, kidney calculus, kidney function abnormal, kidney pain, leukorrhea, mastitis, nephritis, oliguria, metrorrhagia, prostatic carcinoma, pyuria, urethritis, uterine spasm, urolith, vaginal moniliasis, vaginal hemorrhage.

Postmarketing Reports

Voluntary reports of adverse events in patients taking *Paxil* that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barre syndrome, toxic epidermal necrolysis, priapism, thrombocytopenia, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events; extrapyramidal symptoms which have included dystonia, akathisia, bradykinesia, cogwheel rigidity, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and trismus; and serotonin syndrome, associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired *Paxil* metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor). There have been spontaneous reports that abrupt discontinuation may lead to symptoms such as dizziness, sensory disturbances, agitation or anxiety, nausea and sweating; these events are generally self-limiting. There

has been a case report of an elevated phenytoin level after four weeks of Paxil and Phenytoin co-administration. There has been a case report of severe hypotension when Paxil was added to chronic metoprolol treatment. This combination should be used with caution.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Paxil (paroxetine hydrochloride) is not a controlled substance.

Physical and Psychologic Dependence

Paxil has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of *Paxil* misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

No deaths were reported following acute overdose with *Paxil* alone or in combination with other drugs and/or alcohol (18 cases, with doses up to 850 mg) during premarketing clinical trials in depression, OCD, and Panic Disorder. Signs and symptoms of overdose with *Paxil* included: nausea, vomiting, drowsiness, sinus tachycardia and dilated pupils. There were no reports of ECG abnormalities, coma or convulsions following overdosage with *Paxil* alone.

Overdosage Management

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. There are no specific antidotes for *Paxil*. Establish and maintain an airway; ensure adequate oxygenation and ventilation. Gastric evacuation either by the induction of emesis or lavage or both should be performed. In most cases, following evacuation, 20 to 30 grams of activated charcoal may be administered every 4 to 6 hours during the first 24 to 48 hours after ingestion. An ECG should be taken and monitoring of cardiac function instituted if there is any evidence of abnormality. Supportive care with frequent monitoring of vital signs and careful observation is indicated. Due to the large volume of distribution of *Paxil*, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

A specific caution involves patients taking or recently having taken paroxetine who might ingest by accident or intent excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and its active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation.

In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Depression

Usual Initial Dosage

Paxil (paroxetine hydrochloride) should be administered as a single daily dose, usually in the morning. The recommended initial dose is 20 mg/day. Patients were dosed in a range of 20 to 50 mg/day in the clinical trials demonstrating the

antidepressant effectiveness of Paxil. As with all antidepressants, the full antidepressant effect may be delayed. Some patients not responding to a 20 mg dose may benefit from dose increases, in 10 mg/day increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least 1 week.

Maintenance Therapy

There is no body of evidence available to answer the question of how long the patient treated with Paxil should remain on it. It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Obsessive Compulsive Disorder

[The following language is pertinent to the OCD claim but included here since we expect these changes to be finalized at the time the PD claim achieves an approval status.]

Usual Initial Dosage

Paxil should be administered as a single daily dose, usually in the morning. The recommended dose of Paxil in the treatment of OCD is 40 mg daily. Patients should be started on 20 mg/day and the dose can be increased in 10 mg/day increments. Dose changes should occur at intervals of at least one week. Patients were dosed in a range of 20 to 60 mg/day in the clinical trials demonstrating the effectiveness of Paxil in the treatment of OCD, and the maximum dosage should not exceed 60 mg/day.

Maintenance Therapy

A 6-month relapse prevention trial demonstrated a lower relapse rate in patients assigned to paroxetine compared to those on placebo (see Clinical Pharmacology). OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest

effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Panic Disorder

[We have modified this subsection by focusing on 40 mg/day as the dose we believe should be the target dose. We have also modified the statement summarizing long-term experience for reasons given earlier.]

Usual Initial Dosage

Paxil should be administered as a single daily dose, usually in the morning. The recommended target dose of Paxil in the treatment of panic disorder is 40 mg/day. Patients should be started on 10 mg/day. Dose changes should occur in 10 mg/week increments, at intervals of at least 1 week. Patients were dosed in a range of 10 to 60 mg/day in the clinical trials demonstrating the anti-panic effectiveness of Paxil, and the maximum dosage should not exceed 60 mg/day.

Maintenance Therapy

A 3-month relapse prevention trial demonstrated a lower relapse rate in patients assigned to paroxetine compared to those on placebo (see Clinical Pharmacology). Panic disorder is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Dosage for Elderly or Debilitated, and Patients with Severe Renal or Hepatic Impairment

The recommended initial dose is 10 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 40 mg/day.

Switching Patients to or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of a MAOI and initiation of Paxil therapy. Similarly, at least 14 days should be allowed after stopping Paxil before starting a MAOI.

HOW SUPPLIED

Paxil is supplied as film-coated, modified-oval tablets as follows:

20 mg pink, scored tablets engraved on the front with PAXIL and on the back with 20.

NDC 0029-3211-13 Bottles of 30
NDC 0029-3211-20 Bottles of 100
NDC 0029-3211-21 SUP 100's (intended for institutional use only)

30 mg blue tablets engraved on the front with PAXIL and on the back with 30.

NDC 0029-3212-13 Bottles of 30

Store at controlled room temperature (15° to 30 C; 59 to 86°F).

DATE OF ISSUANCE MONTH YEAR

SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101
Printed in U.S.A.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 1, 1996

FROM: Thomas P. Laughren, M.D.
Group Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for Paxil (paroxetine) for Obsessive Compulsive Disorder (OCD) and Panic Disorder (PD)

TO: File NDA 20-031/S-007 & S-009
[**Note:** This memo should be filed with both the 1-18-96 response to the OCD approvable letter and with the 4-5-96 response to the PD approvable letter.

1.0 BACKGROUND

An approvable letter for the Paxil/OCD supplement (S-007) was issued 10-12-95 and a letter for the Paxil/PD supplement (S-009) was issued 3-15-96. The sponsor has now fully responded to both approvable actions, all remaining issues have been resolved, and we are ready to take approval actions on both supplements. The clinical reviews for these responses were done by Paul Andreason, M.D. (for OCD) and James Knudsen, M.D. (for PD).

2.0 CHEMISTRY

One chemistry issue needed resolution, i.e., the sponsor has decided to now market two strengths previously approved but never marketed, i.e., the 10 and 40 mg strengths. The labeling has been modified to provide for these new strengths.

3.0 PHARMACOLOGY

Several very minor changes have been made to the Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy sections of labeling.

4.0 BIOPHARMACEUTICS

A major issue to resolve prior to the approval action on these supplements was where in labeling to address concerns about potential 3A4 inhibition by paroxetine. At the time of the approvable letter for the PD supplement (3-15-96), we were aware of the results from the in vivo terfenadine study suggesting no interaction with paroxetine. On the basis of that study, we had removed the issue from Contraindications and proposed in labeling a Warnings statement to alert clinicians to the possibility of interactions with other 3A4 substrates. In the 4-5-96 amendment, the sponsor included results from in vitro studies involving other 3A4 substrates of concern, and these data revealed paroxetine IC_{50} values for these substrates (astemizole, triazolam, cisapride, dextromethorphan, and cyclosporin) that were at least 2 orders of magnitude less potent than the values for ketoconazole. We had previously agreed that if these values were reassuring, we would move the 3A4 inhibition to the Drug Interactions section of Precautions. The sponsor proposed language consistent with this approach and we agreed with a modification of their proposal.

5.0 CLINICAL DATA

5.1 Safety Update

The sponsor's 1-18-96 amendment for the OCD supplement included a safety update with a cutoff date of 9-30-95. Dr. Andreason reviewed these data and discovered no important new adverse events that would preclude approval of these supplements or that would necessitate additional changes in labeling. The 4-5-96 amendment to the PD supplement included additional updated safety information for the PD studies. These data were reviewed by Dr. Knudsen and he similarly discovered no important new safety findings.

5.2 Demographic Subgroup Analyses for OCD Efficacy Data

Our request for demographic subgroup analyses for the OCD data had been addressed in the original submission. These analyses did not reveal any interactions and this finding is reflected in labeling.

5.3 Pediatric OCD Study

In the 1-18-96 amendment, SKB indicated that a study of paroxetine in adolescents with OCD would be initiated during the first quarter of 1996.

6.0 WORLD LITERATURE UPDATE

In the 4-5-96 amendment, SKB provided the results of its world literature update, including a statement that "there were no findings that would warrant a change in the safety profile for Paxil." Dr. Knudsen reviewed the abstracts provided in this update and did not discover any previously unrecognized important safety concerns for this drug.

7.0 FOREIGN REGULATORY UPDATE

To my knowledge, Paxil is currently approved for the treatment of OCD in 8 countries and for PD in 10 countries.

8.0 LABELING

We have reached agreement with SKB on the final labeling that accompanies the approval letter.

9.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that SKB has submitted sufficient data to support the conclusion that Paxil is effective and acceptably safe in the treatment of both Obsessive Compulsive Disorder and Panic Disorder. I recommend that we issue the attached approval letter with the labeling for which we have reached agreement with the sponsor.

cc:
Orig NDA
HFD-120
HFD-120/TLaughren/PLeber/GDubitsky/PAndreason/JKnudsen/PDavid
/MMille

DOC: MEMPX7&9.AP1

SB
SmithKline Beecham
Pharmaceuticals

April 30, 1996

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
Woodmont II, 4th Floor
1451 Rockville Pike
Rockville, Maryland 20852

Re: NDA 20-031, Supplement 009
Paxil® (paroxetine hydrochloride) Tablets
Revised Final Labeling

Dear Dr. Leber:

Reference is made to our efficacy supplements to New Drug Application for Paxil® (paroxetine hydrochloride) Tablets and NDA 20-031/S-009, which was submitted on March 29, 1995. Reference is also made to your March 15, 1996 approvable letter and your proposed revisions to labeling that were faxed to us on April 29, 1996.

We have reviewed all your proposed labeling and accept the labeling with the following minor changes:

Page 18 Table: Adverse reactions associated with discontinuation of treatment
Depression: The incidence of anxiety was 1.2% and 1.1% for paroxetine and placebo, respectively. Dashes should replace the percentage figures shown.
Panic Disorder: The incidence of insomnia was 1.3% and 0.3% for paroxetine and placebo, respectively. These incidence rates should be added under Panic Disorder.

Page 22 The first sentence of the first paragraph under "Dose Dependency of Adverse Eevnts" should be amended to read: " A comparison of adverse event rates in a fixed-dose study **in the treatment of depression** comparing Paxil 10, 20, 30 and 40 mg/day with placebo revealed a clear dose dependency for some of the more common

adverse events associated with Paxil use, as shown in the following table: "

Page 29 Dosage and Administration/Depression/Maintenance Therapy
The following paragraph should be added; it was in the original depression labeling: "Systematic evaluation of the efficacy of Paxil (paroxetine hydrochloride) has shown that effiacy is maintained for periods up to 1 year with doses that averaged about 30 mg."

All the above changes will be reflected in the final printed labeling that we will forward to you today.

Please do not hesitate to contact me at (610) 917-6582 should you have any questions regarding this submission.

Sincerely,

Michael J. Brennan, Ph.D.
Director, US Regulatory Affairs

SB
SmithKline Beecham
Pharmaceuticals

April 5, 1996

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
Woodmont II, 4th Floor
1451 Rockville Pike
Rockville, Maryland 20852

Re: NDA 20-031, Supplement 009
Paxil® (paroxetine hydrochloride) Tablets
Response to Approvable Letter

Dear Dr. Leber:

Reference is made to our efficacy supplement to New Drug Application for PAXIL® (paroxetine hydrochloride) Tablets, NDA 20-031/S-009, which was submitted on March 29, 1995. Reference is also made to your March 15, 1996 approvable letter. We have addressed the items that you raised in your letter as follows:

1. Labeling

Revisions to the proposed draft labeling are provided in Attachment 1 and are summarized below.

Description: This section has been revised to include descriptions of the 10 mg and 40 mg tablets. This dosage strengths were included in the original NDA .

Clinical Pharmacology/Panic Disorder: We have revised the last sentence of the paragraph describing Study 1; the percent of placebo patients that were panic free and endpoint should be 44% not 32%.

Indications and Usage/OCD: The first sentence of the paragraph describing the relapse prevention trial has been revised to read: "Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial

000001

1250 S. Collegeville Road, PO Box 5089, Collegeville PA 19426-0989 Telephone (610) 917 7000 Fax (610) 917 7707

The table of adverse events associated with withdrawal has been changed to reflect updated patient numbers (6145 patients) in depression trials and to add the incidence rates for Panic Disorder.

Table 2: The incidence of somnolence for placebo patients in the OCD trials was corrected from 17% to 7%.

Other Events: The content of this section has not changed. In a few cases, word order was change to put events in alphabetical order.

Post Marketing Reports: The final sentence, "This combination should be used with caution." was deleted in light of the fact this was a single case report and interactions with β-blockers is addressed within the precautions section.

Dosage and Administration: Statements regarding the relapse prevention trials in OCD and panic disorder have been modified as shown above in the Indications and Usage section.

How Supplied: As noted, we have included description of the 10 and 40 mg tablets.

2. Safety Update

An updated summary of adverse experiences in Studies 29060/108, 29060/120, 29060/187, and 29060/223 and the relapse prevention and/or long-term maintenance extension to these studies (29060/222, and 29060/228) is provided in Appendix 110.0, Attachment 3 of this submission. In response to your October 12, 1995 approvable letter for OCD, we provided an updated safety report with a clinical cut-off of September 30, 1995. This analysis included separate analyses in depressed patients, patients with Obsessive Compulsive Disorder or Panic Disorder. The updated analysis confirms the safety profile that was reflected in the efficacy supplement. We were advised on March 21, 1996 by Merril Mele that this previously submitted safety update satisfied your request for a safety update.

3. World Literature Review

SmithKline Beecham's process for selection, storage and retrieval of published adverse events is as follows:

Profiles listing all SmithKline Beecham (SB) compounds from Phase II in development up to and including, all marketed products have been established are run against external databases which index biomedical literature. All references retrieved which mention any side effect or toxicity (preclinical as well as clinical) linked to an SB product are included in references input to the central product literature database, SB Line. The main source of references for SB Line is the Excerpta Medica database produced by Elsevier. This database covers approximately 3,500 biomedical journals. This source is supplemented by profiles run against the Medline and Biosis databases, plus manual scanning of major journals. Updates from profiles are received weekly. Additional in-house indexing is added by trained SB information staff working from the full text of the articles. Weekly alerts are issued throughout the company listing papers added within the last week which mention specific SB compounds or adverse events associated with any SB product. All adverse event papers are notified to the Central Safety group through these weekly alerts. The database is also available for retrospective searching.

SBLine was formed by the merger of 4 databases which contained product literature information. The new database has been operational since 1992 and contains records entered from this date as well as records from merged databases. Additional SB indexing concentrates on ensuring that numeric details are included for clinical trials and that all adverse events linked to any SB product are included.

An updated citation list along with article abstracts is provided in Attachment 5, volume 2 of this submission. Copies or images of any of these papers can be made available to the Division as well as searchable abstract database, comparable to that provided in the CANDA for this submission.

By this letter we attest that the literature has been systemically reviewed; there were no findings that would warrant a change in the safety profile for Paxil®.

4. Foreign Regulatory Update/Labeling

As summarized in Table 1 in Attachment 4, dossiers for the use of paroxetine in the treatment of Obsessive Compulsive Disorder and Panic Disorder have been submitted in 20 countries. Marketing approval has been achieved in ten countries

(Austria, Canada, Denmark, Finland, Ireland, Italy, South Africa, Spain, Sweden, and UK) for the use of paroxetine in the treatment of Panic Disorder. Copies of approved labeling in Austria, Canada, Sweden, and UK are available and provided in Attachment 4.

Four copies of the proposed draft labeling are provided in this submission. A copy of the this labeling in a Word-Perfect file will be supplied under separate cover.

Please do not hesitate to contact me at (610) 917-6582 should you have any questions regarding this submission.

Sincerely,

Michael J. Brennan, Ph.D.
Director, US Regulatory Affairs

SB
SmithKline Beecham
Pharmaceuticals

April 12, 1996

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
Woodmont II, 4th Floor
1451 Rockville Pike
Rockville, Maryland 20852

Re: NDA 20-031
Paxil® (paroxetine hydrochloride) Tablets
Final Report Study 29060/486

Dear Dr. Leber:

Reference is made to our efficacy supplement to New Drug Application for Paxil® (paroxetine hydrochloride) tablets, NDA 20-031, which were submitted on December 7, 1994 (Supplement 007) and March 29. 1995 (Supplement 009). Reference is also made to your August 28, 1995 letter in which you requested a change to our labeling to address potential drug-drug interactions of Paxil with astemizole, cisapride, terfenadine and triazolam.

On February 16, 1996, we provided you with a preliminary summary of the clinical and pharmacokinetic results of Study 29060/486. Those indicate that coadminstration of Paxil and terfenadine did not affect QTc or terfenadine pharmacokinetics. The results of this study are reflected in draft labeling for Paxil in OCD and panic disorder. We addressed the potential interaction of Paxil® with astemizole, cisapride and triazolam in a series of in vitro studies. A summary of those results were submitted in our April 5, 1996 response. We are now submitting the final report of this Study 29060/486, complete with supporting documentation. Additional desk copies of the report will be provided under separate cover.

Please do not hesitate to contact me at (610) 917-6582 should you have any questions regarding this submission.

Sincerely,

Michael J. Brennan, Ph.D.
Director, US Regulatory Affairs

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989. Telephone (610) 917 7000. Fax (610) 917 7707.

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April 12, 1996

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
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Food and Drug Administration
Woodmont II, 4th Floor
1451 Rockville Pike
Rockville, Maryland 20852

Re: NDA 20-031, Supplement 009
Paxil® (paroxetine hydrochloride) Tablets
Response to Approvable Letter

Dear Dr. Leber:

Reference is made to our efficacy supplement to New Drug Application for PAXIL® (paroxetine hydrochloride) tablets, NDA 20-031, which was submitted on March 29, 1995. Reference is also made to your March 15, 1996 approvable letter.

We addressed the items that you raised in your letter in our April 5, 1996 response. In this submission we included a WordPerfect version of the labeling on diskette and copies of foreign labeling that were not available on April 5, 1996.

The enclosed diskette contains the original version of the labeling (Label.AE2) supplied to us by Merril Mille and our revised version PXL_L10.WPD. Our intent was to facilitate any electronic version comparison that you might conduct. To this end we have only deleted or added text to be consistent with our April 5, 1996 submission. For ease of comparison we have not made some of the stylistic changes (i.e., sub-heading were italicized) that were shown in the April 5, 1996 submission. For your reference we have supplied the version (Label.AE2) that was provided to us in Attachment 1 and our revised copy (PXL_L10.WPD) in Attachment 2. A diskette containing both versions of the labeling in WordPerfect for Windows, 6.1 is provided in Attachment 4.

Marketing approval has been achieved in 10 countries (Austria, Canada, Denmark, Finland, Ireland, Italy, South Africa, Sweden, and UK) for the use of paroxetine in the treatment of Panic Disorder. Copies of Austrian, Canadian, Swedish and UK labeling were provided in our April 5, 1996 response We are now providing copies of the labeling for Denmark, Finland, Ireland, South Africa and Spain (Spanish and English translation). Although we have been advised that the dossier has been approved in Italy, a copy of the final approved labeling is not available at this time.

1250 S Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989. Telephone (610) 917 7000. Fax (610) 917 7707.

Four desk copies of our April 5, 1996 submission are being provided along with the present submission.

The final report of study 29060/486 is now available and is being submitted to NDA 20-031 under separate cover. We provided a preliminary summary of this study on February 16, 1996 to address the Division's concerns with the potential drug-drug interaction of Paxil and terfenadine.

Promotional materials for the launch of Paxil for the treatment of panic disorder were submitted on April 12, 1996. Copies are being sent to the Division under separate cover.

Please do not hesitate to contact me at (610) 917-6582 should you have any questions regarding this submission.

Sincerely,

Michael J. Brennan, Ph.D.
Director, US Regulatory Affairs

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SmithKline Beecham
Pharmaceuticals

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ORIGINAL

January 18, 1996

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HFD-120
EVALUATION AND RESEARCH

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
Woodmont II, 4th Floor
1451 Rockville Pike
Rockville, Maryland 20852

Re: NDA 20-031, Supplement 007
Paxil® (paroxetine hydrochloride) Tablets
Responses to Statistical Review

Dear Dr. Leber:

Reference is made to our efficacy supplement to New Drug Application for PAXIL® (paroxetine hydrochloride) tablets, NDA 20-031, which was submitted on December 7, 1995. Reference is also made to your October 12, 1995 approvable letter. We have addressed the items that you raised in your letter as follows:

CLINICAL

Labeling

Revisions to the proposed draft labeling are provided in Attachment 1 and are summarized below.

Clinical data

In additions to the changes recommended by the Division, the following statement was added to the clinical data section: "The long-term maintenance effects of Paxil in OCD were demonstrated in a long-term extension to Study 1. Patients who were treated with open-label paroxetine (20-60 mg/day) for si : months and then re-randomized to paroxetine were significantly less lightly to relapse than comparably treated patients who were randomized to placebo."

... Corporate Center, ... Woodmont Avenue, PO Box ... King of Prussia, PA 19406

This statement is a summary of the results of study 29060/126 which was submitted to INL (Serial 199) on July 24, 1995. The long-term maintenance and relapse prevention effects of Paxil® are further supported by the final reports two studies (29060/127 and 29060/241).which are included in this submission. Study 29060/127 was the extension to Study 29060/118 and was similar in design to Study 29060/126. Study 29060/241 was the long-term extension to Study 29060/136. Although these two studies support the results of Study 29060/126, we have elected only to reflect the results of Study 29060/126 in our proposed revisions to the draft labeling. This was done with a view reaching early agreement on the final labeling.

Indications And Usage

In additions to the changes recommended by the Division, we have included the following statement: "The effectiveness of Paxil in long-term use has been shown to be maintained for up to 15 months in a randomized trial (see Clinical Trials under CLINICAL PHARMACOLGY). Nevertheless, the physician who elects to use Paxil for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION)." As noted above, this statement is based on the results of Study 29060/126.

Contraindications

The Division has requested that we included a contraindication for the use of Paxil® concomitantly with drugs metabolized by the P450 IIIA4 isoenzyme such as terfenadine, astemizole, and cisapride. After our review of available in vitro and clinical data, we contend that a contraindication is not warranted and propose to include the statement shown below as a precaution.

As the Division acknowledged in your August 30, 1995 letter, paroxetine does not have a marked inhibitory effect on P450IIIA4. This is supported by the von Moltke et al paper[1] cited by the Division. We have reviewed recent clinical studies with Paxil® to assess whether patients taking terfenadine, astemizole, or cisapride concomitantly evidenced an increased incidence of cardiovascular side effects. A summary table of adverse events for patients taking terfenadine (n=111), astemizole (n=41), and cisapride (n=10) concomitantly is provided in Appendix 103.2, Attachment 2. Review of these data dose not suggest that these subgroups showed an increased incidence of cardiovacular adverse expereinces. A listing of patients who received this drugs concomitantly is provided in Appendix 102.0. A listing of adverse experiences for this subgroup is provided in Appendix 103.0, Attachment 2.

[1] Von Moltke LL, et al. Inhibition of alprazolam and desimpramine hydroxylation in vivo by paroxetine and fluvoxamine: Comparison with other selective serotonin reuptake inhibitor antidepressants. J Clin Psychopharm 1995; 15: 125-131.

Precautions

The following statement has been added to this section:

"Drugs Metabolized by Cytochrome P450IIIA4

Depending on the potency of their inhibitory effect, P450IIIA4 inhibitors may interfere and or block the metabolism of drugs such as terfenadine, astemizole and cisapride, that are metabolized by this system and increase plasma concentrations of these drugs. While Paxil is thought to have only a weak inhibitory effect on the P450IIIA4 isozyme. concomitant use of PAXIL with drugs metabolized by cytochrome P450IIIA4 has not been formally studied. Based on limited in vitro data, it appears that paroxetine does inhibit this isozyme but less so than some other agents within this class, Nevertheless, paroxetine may produce elevated levels of drugs metabolized by IIIA4. Since increased levels of terfenadine, astemizole, and cisapride have been associated with serious cardiovascular events, the administration of PAXIL with these drugs should be undertaken with caution."

The Division has requested that individual cases of a possible phenytoin-Paxil® interaction, metoprolol-Paxil® interaction be included within the Precautions section. It is our view that these individual cases are more appropriately cited as individual cases within the Post-Marketing reports section. The information presently contained within the phenytoin and beta-blocker subsections reflects the results of specific drug-drug interaction studies where the potential for interaction was assessed more systematically.

Adverse Events

The Division has proposed that Tables 1 and 2 be combined. As we indicated in the annotated labeling included with the sNDA, our decision to to have two separate tables of adverse experiences for depression and obsessive compulsive patients was largely governed by the fact that two distinct dictionaries were used for the analysis of adverse experiences for patients in these two clinical programs. Our decision to include two separate tables followed the precedent established with the approved labeling for Prozac®. We do recognize the Division's concerns with the multiplication of adverse experience summary tables as additional indications are added to labeling. For this reason our proposed labeling for Panic Disorder (submitted March 29, 1995) includes a table which summarizes the adverse experiences of obsessive compulsive and panic disorder patient in a side-by-side manner. We felt that this was appropriate in that a common adverse experience dictionary was employed in these two clinical programs.

Pregnanacy warning

We have revised the pregnancy warning as requested by the Division.

Other Events

We have updated this section to reflect data on 7156 patients who received multiple doses of Paxil®. This includes 6,145 patients with depression; 542 patients with obsessive compulsion and 469 patients with panic disorder. Two types of changes were made to this section of the proposed labeling: Events which were previously included within this section but increased in frequency were recategorized as frequent or infrequent. This change affected the following 12 terms:

change from infrequent to frequent:
Special Senses -tinnitus

change from rare to infrequent:
Digestive System-Gingivitis, Colitis, Gastroenteritis;
Metabolic / Nutritional - SGPT increased, SGOT increased;
Musculoskeletal - arthralgia;
Nervous System - dystonia, hostility, paralysis;
Special Senses- conjunctivitis;
Urogenital System- hematuria

However, we did not recategorize experiences which were reported at a lower incidence in the updated sample.

Experiences which were reported for patients in the update sample but not previously included within this section have been included. A total of 64 terms have been added to the various subsections. These terms are double-underscored in the proposed labeling.

Safety Update

An updated summary of adverse experiences in Studies 29060/116, 29060/118, 29060/136 and the relapse prevention and/or long-term maintenance extension to these studies (29060/126, 29060/127 and 29060/241) is provided in Appendix 100.0, Attachment 3. A listing of adverse experiences is provided in Appendix 104, Attachment 3. As discussed in detail in the study report of the extension studies, the safety profile that emerges from long-term exposure to paroxetine in Obsessive Compulsive patients is largely comparable to that summarized in Supplement 007.

The cut-off applied for reporting serious adverse event and spontaneous adverse experience reporting was May 31, 1994 in the efficacy supplement that was

submitted on December 7, 1994. The report provided in Attachment 4 provides and update through September 30, 1995. Where possible, we have provided separate analyses in depressed patients, patients with Obsessive Compulsive disorder or Panic Disorder. The tables included in the body of the report allow for a side-by side comparison of the summaries provided within the efficacy supplement and the updated safety information. The updated analysis confirms the safety profile that was reflected in the efficacy supplement.

World Literature Review

SmithKline Beecham's process for selection, storage and retrieval of published adverse events is as follows:

Profiles listing all SmithKline Beecham (SB) compounds from Phase II in development up to and including, all marketed products have been established are run against external databases which index biomedical literature. All references retrieved which mention any side effect or toxicity (preclinical as well as clinical) linked to an SB product are included in references input to the central product literature database, SB Line. The main source of references for SB Line is the Excerpta Medica database produced by Elsevier. This database covers approximately 3,500 biomedical journals. This source is supplemented by profiles run against the Medline and Biosis databases, plus manual scanning of major journals. Updates from profiles are received weekly. Additional in-house indexing is added by trained SB information staff working from the full text of the articles. Weekly alerts are issued throughout the company listing papers added within the last week which mention specific SB compounds or adverse events associated with any SB product. All adverse event papers are notified to the Central Safety group through these weekly alerts. The database is also available for retrospective searching.

SBLine was formed by the merger of 4 databases existing pre-merger which contained product literature information. The new database has been operational since 1992 and contains records entered from this date as well as records from merged databases. Additional SB indexing concentrates on ensuring that numeric details are included for clinical trials and that all adverse events linked to any SB product are included.

An updated citation list along with article abstracts is provided in Attachment 5. Copies or images of any of these papers can be made available to the Division as well as searchable abstract database, comparable to that provided in the CANDA for this submission.

Foreign Regulatory Update/Labeling

As summarized in Table 5 in Attachment 6, dossiers for the use of paroxetine in the treatment of Obsessive Compulsive Disorder and Panic Disorder have been submitted in 20 countries. Marketing approval has been achieved in eight countries (Austria, Canada, Denmark, Iceland, Italy, Spain, Sweden, and UK) for the use of paroxetine in the treatment of Obsessive Compulsive Disorder and in six countries for the use of paroxetine in the treatment of Panic Disorder (Austria, Canada, Denmark, Italy, Sweden, and UK). Copies of approved labeling in Austria, Canada, Sweden, and UK are available and provided in Attachment 6.

Efficacy Data

In your October 12, 1995 letter, you indicated the need to provide exploratory analyses of efficacy data based on age and gender. As discussed in a phone conference on October 20, 1995, these sub-group analyses were included within the Integrated Summary of Efficacy. Dr. Laughren accepted that these analyses satisfied your request and that no further analyses needed to be done. As noted above, we have reflected the subgroup analyses within the draft labeling.

Pediatric Studies

A protocol to study the efficacy and safety in adolescent with obsessive compulsive disorder in presently under internal review and revision. It is anticipated that this protocol will be initiated under the IND within the first quarter 1996.

PHARMACOLOGY

All the requested changes to the Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis Pregnancy Teratogenic Effects sections have been made in the labeling.

Four desk copies have been included with this submission.

Please do not hesitate to contact me at (610) 917-6582 should you have any questions regarding this submission.

Sincerely,

Michael J. Brennan, Ph.D.
Director, US Regulatory Affairs

027 7

PRESCRIBING INFORMATION

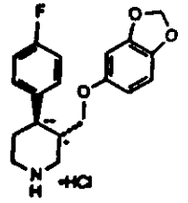
PAXIL®

brand of

paroxetine hydrochloride tablets

DESCRIPTION

Paxil (paroxetine hydrochloride) is an orally administered antidepressant with a chemical structure unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic or other available antidepressant agents. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-trans-4.R-(4'-fluorophenyl)-3.S-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3 \cdot HCl \cdot 1/2H_2O$. The molecular weight is 374.8 (329.4 as free base). The structural formula is:



paroxetine hydrochloride

Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of 128° to 138°C and a solubility of 8.4 mg/mL in water.

Each film-coated tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: 20 mg—pink (scored); 30 mg—blue. Inactive ingredients consist of dibasic calcium phosphate dihydrate, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide and one or more of the following: D&C Red No. 30, FD&C Blue No. 2.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The antidepressant action of paroxetine is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. In vitro studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. In vitro radioligand binding studies indicate that paroxetine has little affinity for muscarinic, alpha1-, alpha2-, beta-adrenergic, dopamine (D_2), 5-HT1, 5-HT2 and histamine (H_1)-receptors; antagonism of muscarinic, histaminergic and alpha1-adrenergic receptors has been associated with various anticholinergic, sedative and cardiovascular effects for other psychotropic drugs.

Because the relative potencies of paroxetine's major metabolites are at most 1/50 of the parent compound, they are essentially inactive.

Pharmacokinetics

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male subjects (n=15) received 30 mg tablets daily for 30 days, steady-state paroxetine concentrations were achieved by approximately 10 days for most subjects, although it may take substantially longer in an occasional patient. At steady state, mean values of C_{max}, T_{max}, C_{min} and $T_{1/2}$ were 61.7 ng/mL (CV 46%), 5.2 hr. (CV 10%), 30.7 ng/mL (CV 67%) and 21.0 hr. (CV 33%), respectively. The steady-state C_{max} and C_{min} values were about 6 and 14 times what would be predicted from single-dose studies. Steady-state drug exposure based on AUC_{24h} was about 8 times greater than would have been predicted from single-dose data in these subjects. The excess accumulation is a consequence of the fact that one of the enzymes that metabolizes paroxetine is readily saturable.

In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of 20 to 40 mg daily for the elderly and 20 to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{max} values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than doubled.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleaved. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by cytochrome $P_{450}IID_6$. Saturation of the enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of the enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see PRECAUTIONS).

Approximately 64% of a 30 mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.

Distribution: Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.

Protein Binding: Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/mL. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.

Renal and Liver Disease: Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below 30 mL/min was approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30 to 60 mL/min and patients with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, C_{max}).

The initial dosage should therefore be reduced in patients with severe renal or hepatic impairment, and upward titration, if necessary, should be at increased intervals. (see DOSAGE AND ADMINISTRATION)

Elderly Patients: In a multiple-dose study in the elderly at daily paroxetine doses of 20, 30 and 40 mg, C_{max} concentrations were about 70% to 80% greater than the respective C_{max} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced. (See DOSAGE AND ADMINISTRATION.)

Clinical Trials

The efficacy of *Paxil* as a treatment for depression has been established in 6 placebo-controlled studies of patients with depression (ages 18 to 73). In these studies *Paxil* was shown to be significantly more effective than placebo in treating depression by at least 2 of the following measures: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)—Severity of Illness. *Paxil* was significantly better than placebo in improvement of the HDRS sub-factor scores, including the depressed mood item, sleep disturbance factor and anxiety factor.

A study of depressed outpatients who had responded to *Paxil* HDRS total score ≤8) during an initial 8-week open-treatment phase and were then randomized to continuation on *Paxil* or placebo for 1 year demonstrated a significantly lower relapse rate for patients taking *Paxil* (15%) compared to those on placebo (38%). Effectiveness was similar for male and female patients.

INDICATIONS AND USAGE

Paxil (paroxetine hydrochloride) is indicated for the treatment of depression.

The efficacy of *Paxil* in the treatment of a major depressive episode was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see CLINICAL PHARMACOLOGY).

A major depressive episode implies a prominent and relatively persistent depressed or dysthonic mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant action of *Paxil* in hospitalized depressed patients has not been adequately studied.

The efficacy of *Paxil* in maintaining an antidepressant response for up to 1 year was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use *Paxil* for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS).

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving another serotonin reuptake inhibitor drug in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with *Paxil*, limited animal data on the effects of combined use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and overall act be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. At least 2 weeks should be allowed after stopping *Paxil* before starting a MAOI.

PRECAUTIONS

General

Activation of Mania/Hypomania: During premarketing testing, hypomania or mania occurred in approximately 1.0% of *Paxil*-treated unipolar patients compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for *Paxil* and 11.8% for the combined active-control groups. As with all antidepressants, *Paxil* should be used cautiously in patients with a history of mania.

Seizures: During premarketing testing, seizures occurred in 0.1% of *Paxil*-treated patients, a rate similar to that associated with other antidepressants. *Paxil* should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for *Paxil* should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Hyponatremia: Several cases of hyponatremia have been reported. The hyponatremia appeared to be reversible when *Paxil* was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Use in Patients with Concomitant Illness: Clinical experience with *Paxil* in patients with certain concomitant systemic diseases is limited. Caution is advisable in using *Paxil* in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Paxil has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. Evaluation of electrocardiograms of 882 patients who received *Paxil* in double-blind, placebo-controlled trials, however, did not indicate that *Paxil* is associated with the development of significant ECG abnormalities. Similarly, Paxil (paroxetine hydrochloride) does not cause any clinically important changes in heart rate or blood pressure.

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance <30 mL/min.) or severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe *Paxil*.

Interference with Cognitive and Motor Performance: Any psychoactive drug may impair judgment, thinking or motor skills. Although in controlled studies *Paxil* has not been shown to impair psychomotor performance, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that *Paxil* therapy does not affect their ability to engage in such activities.

Completing Course of Therapy: While patients may notice improvement with *Paxil* therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant Medication: Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Although *Paxil* has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking *Paxil*.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised to notify their physician if they are breast feeding an infant. (See PRECAUTIONS–Nursing Mothers.)

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

Tryptophan: As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are co-administered. Adverse experiences, consisting primarily of headache, nausea, sweating and dizziness, have been reported when tryptophan was administered to patients taking *Paxil* (paroxetine hydrochloride). Consequently, concomitant use of *Paxil* with tryptophan is not recommended.

Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS and WARNINGS.

Warfarin: Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the face of unaltered prothrombin time) between paroxetine and warfarin. Since there is little clinical experience, the concomitant administration of *Paxil* and warfarin should be undertaken with caution.

Drugs Affecting Hepatic Metabolism. The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug-metabolizing enzymes.

Cimetidine–Cimetidine inhibits multiple cytochrome P_{450} isodistinct enzymes. In a study where *Paxil* (30 mg q.d.) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during co-administration with oral cimetidine (300 mg t.i.d.) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of *Paxil* after the 20 mg starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

Paxil has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. Evaluation of electrocardiograms of 882 patients who received *Paxil* in double-blind, placebo-controlled trials, however, did not indicate that *Paxil* is associated with the development of significant ECG abnormalities. Similarly, Paxil (paroxetine hydrochloride) does not cause any clinically important changes in heart rate or blood pressure.

Phenobarbital–Phenobarbital induces many cytochrome P_{450} isodistinct enzymes. When a single oral 30 mg dose of *Paxil* was administered after phenobarbital steady state (100 mg q.d. for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since *Paxil* exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when co-administered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

Phenytoin–When a single oral 30 mg dose of *Paxil* was administered after phenytoin steady state (300 mg q.d. for 14 days), paroxetine AUC and $T_{1/2}$ were reduced by an average of 50% and 35%, respectively) compared to *Paxil* administered alone. In a separate study, when a single oral 300 mg dose of phenytoin was administered after paroxetine steady state (30 mg q.d. for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when these drugs are co-administered; any subsequent adjustments should be guided by clinical effect.

Drugs Metabolized by Cytochrome $P_{450}IID_6$. Concomitant use of *Paxil* with drugs metabolized by cytochrome $P_{450}IID_6$ has not been formally studied but may require lower doses than usually prescribed for either *Paxil* or the other drug. Many drugs, including most anti-depressants (paroxetine, other SSRIs and many tricyclics) are metabolized by the cytochrome P_{450} isozyme $P_{450}IID_6$. In most patients (>90%), this $P_{450}IID_6$ isozyme is saturated early during *Paxil* dosing. Like other agents that are metabolized by $P_{450}IID_6$, paroxetine may significantly inhibit the activity of this isozyme.

Therefore co-administration of *Paxil* with other drugs that are metabolized by this isozyme, including certain antidepressants (e.g. nortriptyline, amitriptyline, imipramine, desipramine and fluoxetine), phenothiazines (e.g. thioridazine) and Type 1C antiarrhythmics (e.g. propafenone, flecainide and encainide), or that inhibit this enzyme (e.g. quinidine), should be approached with caution.

At steady state, when the $P_{450}IID_6$ pathway is essentially saturated, paroxetine clearance is governed by alternative P_{450} isozymes which, unlike $P_{450}IID_6$, show no evidence of saturation.

Drugs Highly Bound to Plasma Protein. Because paroxetine is highly bound to plasma protein, administration of *Paxil* to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

Alcohol: Although *Paxil* does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking Paxil (paroxetine hydrochloride).

Lithium: A multiple-dose study has shown that there is no pharmacokinetic interaction between *Paxil* and lithium carbonate. However, since there is little clinical experience, the concurrent administration of paroxetine and lithium should be undertaken with caution.

Digoxin: The steady-state pharmacokinetics of paroxetine was not altered when administered with digoxin at steady state. Mean digoxin AUC_{24h} at steady state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of paroxetine and digoxin should be undertaken with caution.

Diazepam: Under steady-state conditions, diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

Procyclidine: Daily oral dosing of *Paxil* (30 mg q.d.) increased steady state AUC_{24h}, C_{max} and C_{min} values of procyclidine (5 mg p.o. q.d.) by 35%, 37% and 67%, respectively, compared to procyclidine alone at steady state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

Propranolol: In a study where propranolol (80 mg b.i.d.) was dosed orally for 18 days (to established steady state) plasma concentrations of propranolol were unaltered during co-administration with *Paxil* (30 mg q.d.) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated.

Electroconvulsive Therapy (ECT): There are no clinical studies of the combined use of ECT and *Paxil*.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Two year carcinogenicity studies were conducted in mice and rats given paroxetine in the diet at 1, 5 and 25 mg/kg/day (mice) and 1, 5 and 20 mg/kg/day (rats). The maximum doses in these studies were approximately 25 (mouse) and 20 (rat) times the maximum dose recommended for human use on a mg/kg basis or 2.5 (mouse) and 5.8 (rat) times the maximum recommended human dose on a mg/m² basis. There was a significant, dose-related number of male rats in the high dose group with reticulum cell sarcomas (1/100, 0/50, 0/50 and 4/50 for control, low, middle and high dose groups, respectively) and a significant, dose-related linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis: Paroxetine and its principal metabolites showed no evidence of genetic toxicity in a battery of 5 *in vitro* and 2 *in vivo* assays that included the following: bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations in mammalian bone marrow and *in vitro* human lymphocytes and mouse germinal cells.

Impairment of Fertility: Serotonergic compounds are known to affect reproductive function in animals. Impaired reproductive function, i.e., reduced pregnancy rate, increased pre- and post-implantation losses, decreased viability of pups, was found in reproduction studies in rats at doses of paroxetine which were 15 or more times the highest recommended human dose on a mg/kg basis or 4 times on a mg/m² basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions, which consisted of vacuolation of epididymal tubular epithelium and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis, occurred at doses which were 25 times the highest recommended human dose on a mg/kg basis or 7.3 times on a mg/m² basis.

Pregnancy

Teratogenic Effects–Pregnancy Category B

Reproduction studies performed in rats and rabbits at doses up to 50 and 6 times the maximum recommended human dose on a mg/kg basis or 10 and 2 times on a mg/m² basis, respectively, have revealed no evidence of teratogenic effects. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

The effect of paroxetine on labor and delivery in humans is unknown.

Nursing Mothers

Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when Paxil (paroxetine hydrochloride) is administered to a nursing woman.

Usage in Children

Safety and effectiveness in children have not been established.

Geriatric Use

In worldwide *Paxil* clinical trials, 17% of *Paxil*-treated patients (approximately 700) were 65 years of age or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended for the elderly; however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Twenty-one percent (688/3276) of *Paxil* patients in worldwide clinical trials discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug-related (i.e., those events associated with dropout at a rate approximately twice or greater for *Paxil* compared to placebo) included:

CNS	
Somnolence	2.3%
Insomnia	1.9%
Agitation	1.3%
Tremor	1.3%
Anxiety	1.1%
Gastrointestinal	
Nausea	3.6%
Diarrhea	1.0%
Dry mouth	1.0%
Vomiting	1.0%
Other	
Asthenia	1.7%
Abnormal ejaculation	1.8%
Sweating	1.1%

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials: The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo, derived from 1% table below) were asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance and other male genital disorders.

Adverse Events Occurring at an Incidence of 1% or More Among Paroxetine-Treated Patients: The table that follows enumerates adverse events that occurred at an incidence of 1% or more among paroxetine-treated patients who participated in short-term (6-week) placebo-controlled trials in which patients were dosed in a range of 20 to 50 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1 Treatment Emergent Adverse Experiences Incidence in Placebo-Controlled Clinical Trials[1]

Body System	Preferred Term	*Paxil* (n=621)	Placebo (n=421)
Body as a Whole	Headache	17.8%	17.3%
	Asthenia	15.0%	9.9%
	Abdominal Pain	3.1%	4.0%
	Fever	1.7%	1.7%
	Chest Pain	1.4%	2.1%
	Trauma	1.4%	0.5%
	Back Pain	1.2%	2.4%
Cardiovascular	Palpitation	2.9%	1.4%
	Vasodilation	2.6%	0.7%
	Postural Hypotension	1.2%	0.5%
Dermatologic	Sweating	11.2%	2.4%
	Rash	1.1%	0.7%
Gastrointestinal	Nausea	25.7%	9.3%
	Dry Mouth	18.1%	12.1%
	Constipation	13.8%	8.8%
	Diarrhea	11.6%	8.8%
	Decreased Appetite	8.4%	1.9%
	Flatulence	4.0%	1.7%
	Vomiting	2.4%	1.7%
	Gastrointestinal Disorder[2]	2.1%	0.0%
	Dyspepsia	1.9%	1.0%
	Increased Appetite	1.4%	0.5%
Musculoskeletal	Myopathy	2.4%	1.4%
	Myalgia	1.7%	0.7%
	Myasthenia	1.4%	0.2%
Nervous System	Somnolence	23.3%	9.0%
	Dizziness	13.3%	5.5%
	Insomnia	13.3%	8.2%
	Tremor	8.3%	1.9%
	Nervousness	5.2%	2.8%
	Anxiety	5.0%	2.9%
	Paresthesia	3.8%	1.7%
	Libido Decreased	3.3%	0.0%
	Agitation	2.1%	1.9%
	Drugged Feeling	1.1%	0.7%
	Hallucinations	1.4%	0.7%
	CNS Stimulation	1.2%	3.8%
	Confusion	1.2%	0.7%
Respiratory	Respiratory Disorder[3]	5.9%	8.4%
	Yawn	3.8%	0.2%
	Pharyngitis	2.1%	2.9%
Special Senses	Blurred Vision	3.8%	1.4%
	Taste Perversion	2.6%	0.7%
Urogenital System	Ejaculatory Disturbance[4]	12.9%	0.0%
	Other Male Genital Disorders[5]	10.0%	0.0%
	Urinary Frequency	3.1%	0.7%
	Urination Disorder[6]	2.9%	0.7%
	Female Genital Disorders[7]	1.8%	0.0%

1 Events reported by at least 1% of patients treated with *Paxil* (paroxetine hydrochloride) are included.
2 Includes mostly "lump in throat" and "tightness in throat."
3 Includes mostly "cold symptoms" or "URI."
4 Percentage corrected for gender.
5 Mostly "ejaculatory delay."
6 Includes "anorgasmia," "erective difficulties," "delayed ejaculation/orgasm" and "sexual dysfunction" and impotence."
7 Includes mostly "difficulty with micturition" and "urinary hesitancy."
8 Includes mostly "anorgasmia" and "difficulty reaching climax/orgasm."

Dose Dependency of Adverse Events: A comparison of adverse event rates in a fixed dose study comparing *Paxil* 10, 20, 30 and 40 mg/day with placebo revealed a clear dose dependency for some of the more common adverse events associated with *Paxil* use as shown in the following table.

Table 2 Treatment Emergent Adverse Experience Incidence in a Dose Comparison Trial[a]

	Placebo	*Paxil*			
Body System/ Preferred Term	0 mg (n=102)	10 mg (n=102)	20 mg (n=104)	30 mg (n=101)	40 mg (n=102)
Body as a Whole					
Asthenia	3.9%	3.9%	10.6%	13.9%	13.1%
Dermatology					
Sweating	2.0%	1.0%	6.7%	8.9%	11.8%
Gastrointestinal					
Constipation	4.9%	4.9%	7.7%	9.9%	12.7%
Decreased Appetite	2.9%	2.0%	5.8%	6.0%	6.9%
Diarrhea	7.8%	9.8%	19.2%	7.9%	14.7%
Dry Mouth	7.8%	9.8%	18.3%	15.8%	20.6%
Nausea	13.7%	14.7%	26.9%	34.7%	36.3%
Nervous System					
Anxiety	0.0%	2.0%	5.8%	5.9%	5.9%
Dizziness	3.9%	6.9%	6.7%	8.9%	12.7%
Nervousness	0.0%	5.9%	5.8%	4.0%	2.9%
Paresthesia	0.0%	2.9%	1.0%	5.0%	5.9%
Somnolence	7.8%	12.7%	18.3%	20.8%	21.6%
Tremor	0.0%	0.0%	7.7%	7.9%	14.7%
Special Senses					
Blurred Vision	2.0%	2.9%	2.9%	2.0%	7.8%
Urogenital Abnormal Ejaculation	0.0%	5.8%	8.5%	10.8%	13.0%
Impotence	0.0%	1.9%	4.3%	6.6%	1.9%
Male Genital Disorders	0.0%	3.8%	8.7%	6.6%	3.7%

[a]Rule for including adverse event in table: incidence at least 5% for one of paroxetine groups and ≥ twice the placebo incidence for at least one paroxetine group.

Adaptation to Certain Adverse Events: Over a 4- to 6-week period, there was evidence of adaptation to some adverse events with continued therapy (e.g., nausea and dizziness) but less to other effects (e.g., dry mouth, somnolence and asthenia).

Weight and Vital Sign Changes: Significant weight loss may be an undesirable result of treatment with *Paxil* for some patients but, on average, patients treated with *Paxil* had minimal (about 1 pound) weight loss. Similar changes on placebo and active control were observed. Significant changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were observed in patients treated with *Paxil* in controlled clinical trials.

ECG Changes: In general, results of ECG obtained in 682 patients treated with *Paxil* and 515 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests: In placebo-controlled clinical trials, patients treated with *Paxil* exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients. In particular, the *Paxil*-placebo comparison for alkaline phosphatase was 0% vs. 0%, SGOT 0.3% vs. 0.3%, SGPT 1% vs. 0.3% and bilirubin 0% vs. 0.8%.

Other Events Observed During the Premarketing Evaluation of *Paxil* (paroxetine hydrochloride)

During its premarketing assessment, multiple doses of *Paxil* were administered to 4,126 patients in phase 2 and 3 studies. The conditions and duration of exposure to *Paxil* varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented therefore represent the proportion of the 4,126 patients exposed to multiple doses of *Paxil* (paroxetine hydrochloride) who experienced an event of the type cited on at least one occasion while receiving *Paxil*. All reported events are included except those already listed in Table 1, those reported in terms so general as to be uninformative and those events where a drug cause was remote. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

Body as a Whole: *frequent:* chills; *malaise; infrequent:* allergic reaction, carcinoma, face edema, moniliasis, neck pain, rare abscess, adrenergic syndrome, cellulitis, neck rigidity, pelvic pain, peritonitis, ulcer.

Cardiovascular System: *frequent:* hypertension, syncope, tachycardia; *infrequent:* bradycardia, conduction abnormalities, electrocardiogram abnormal, hypotension, migraine, peripheral vascular disorder; *rare:* angina pectoris, arrhythmia, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

Digestive System: *infrequent:* bruxism, dysphagia, eructation, glossitis, increased salivation, liver function tests abnormal, mouth ulceration, rectal hemorrhage; *rare:* aphthous stomatitis, bloody diarrhea, bulimia, colitis, duodenitis, esophagitis, fecal impactions, fecal incontinence, gastritis, gastroenteritis, gingivitis, hemorrhoids, hepatitis, ileus, jaundice, melena, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue edema, tooth caries.

Endocrine System: *rare:* diabetes mellitus, hyperthyroidism, hypothyroidism, thyroiditis.

Hemic and Lymphatic Systems: *infrequent:* anemia, leukopenia, lymphadenopathy, purpura; *rare:* abnormal erythrocyte, eosinophilia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia.

Metabolic and Nutritional: *frequent:* edema, weight gain, weight loss; *infrequent:* hyperglycemia, peripheral edema, thirst; *rare:* alkaline phosphatase increased, bilirubinemia, dehydration, gout, hypercholesterolemia, hypocalcemia, hypoglycemia, hyponatremia, hypophosphatemia, SGOT increased, SGPT increased.

Musculoskeletal System: *infrequent:* arthralgia, arthritis; *rare:* arthrosis, bursitis, myositis, osteoporosis, tetany.

Nervous System: *frequent:* amnesia, CNS stimulation, concentration impaired, depression, emotional lability, vertigo; *infrequent:* abnormal thinking, akinesia, alcohol abuse, ataxia, convulsion, depersonalization, hallucinations, hyperkinesia, hypertonia, incoordination, lack of emotion, manic reaction, paranoid reaction; *rare:* abnormal electroencephalogram, abnormal gait, antisocial reaction, choreoathetosis, delirium, delusions, diplopia, drug dependence, dysarthria, dyskinesia, dystonia, euphoria, fasciculations, grand mal convulsion, hostility, hyperalgesia, hypokinesia, hysteria, libido increased, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, paralysis, psychoses, psychotic depression, reflexes increased, stupor, withdrawal syndrome.

Respiratory System: *frequent:* cough increased, rhinitis; *infrequent:* asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu, sinusitis; *rare:* carcinoma of lung, hiccups, lung fibrosis, sputum increased.

Skin and Appendages: *frequent:* pruritus; *infrequent:* acne, alopecia, dry skin, ecchymosis, eczema, furunculosis, urticaria; *rare:* angioedema, contact dermatitis, erythema nodosum, maculopapular rash, photosensitivity, skin discoloration, skin melanoma.

Special Senses: *infrequent:* abnormality of accommodation, ear pain, eye pain, myopathy, otitis media, taste loss, tinnitus; *rare:* amblyopia, cataract, conjunctivitis, corneal ulcer, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, otitis externa, photophobia.

Urogenital System: *infrequent:* abortion, amenorrhea, breast pain, cystitis, dysmenorrhea, dysuria, menorrhagia, nocturia, polyuria, urethritis, urinary incontinence, urinary retention, urinary urgency, vaginitis; *rare:* breast atrophy, breast carcinoma, breast neoplasm, female lactation, hematuria, kidney calculus, kidney function abnormal, kidney pain, mastitis, metrorrhagia, pelvic prostatic carcinoma, vaginal moniliasis.

Postmarketing Reports

Voluntary reports of adverse events in patients taking *Paxil* that have been received since market introduction and not listed above that may have no causal relationship with the drug include: elevated liver function tests (the most severe case was a death due to liver necrosis), and one other case involved grossly elevated transaminases associated with seizure, liver dysfunction, toxic epidermal necrolysis, priapism, thrombocytopenia, syndrome of inappropriate ADH secretion, symptoms suggestive of galactorrhea and galactorrhea, neuroleptic malignant syndrome-like events, extrapyramidal symptoms which have included dystonia, akathisia, bradykinesia, cogwheel rigidity, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and tremus, and serotonin syndrome, associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired *Paxil* metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor). There have been spontaneous reports that abrupt discontinuation may lead to symptoms such as dizziness, sensory disturbances (agitation or anxiety), nausea and sweating; these events are generally self-limiting.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: *Paxil* (paroxetine hydrochloride) is not a controlled substance.

Physical and Psychologic Dependence: *Paxil* has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of *Paxil* misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: No deaths were reported following acute overdose with *Paxil* alone or in combination with other drugs and/or alcohol (18 cases with doses up to 850 mg); during premarketing clinical trials. Signs and symptoms of overdose with *Paxil* included nausea, vomiting, drowsiness, sinus tachycardia, and dilated pupils. There were no reports of ECG abnormalities, coma or convulsions following overdosage with *Paxil* alone.

Overdosage Management: Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. There are no specific antidotes for *Paxil*. Establish and maintain an airway. Ensure adequate oxygenation and ventilation. Gastric evacuation either by the induction of emesis or lavage or both should be performed. In most cases, following evacuation, 20 to 30 grams of activated charcoal may be administered every 4 to 6 hours during the first 24 to 48 hours after ingestion. An ECG should be taken and monitoring of cardiac function instituted if there is any evidence of abnormality. Supportive care with frequent monitoring of vital signs and careful observation is indicated. Due to the large volume of distribution of *Paxil*, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

A specific caution involves patients taking or recently having taken paroxetine who might ingest by accident or intent excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation.

In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Depression

Usual Initial Dosage: *Paxil* (paroxetine hydrochloride) should be administered as a single daily dose, usually in the morning. The recommended initial dose is 20 mg/day. Patients were dosed in a range of 20 to 50 mg/day in the clinical trials demonstrating the antidepressant effectiveness of *Paxil*. As with all antidepressants, the full antidepressant effect may be delayed. Some patients not responding to a 20 mg dose may benefit from dose increases, in 10 mg/day increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least 1 week.

Dosage for Elderly or Debilitated, and Patients with Severe Renal or Hepatic Impairment: The recommended initial dose is 10 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 40 mg/day.

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with *Paxil* should remain on it. It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of *Paxil* (paroxetine hydrochloride) has shown that efficacy is maintained for periods of up to 1 year with doses that averaged about 30 mg.

Switching Patients to or from a Monoamine Oxidase Inhibitor: At least 14 days should elapse between discontinuation of a MAOI and initiation of *Paxil* therapy. Similarly, at least 14 days should be allowed after stopping *Paxil* before starting a MAOI.

HOW SUPPLIED

Paxil is supplied as film-coated, modified-oval tablets as follows:

20 mg pink, scored tablets engraved on the front with PAXIL and on the back with 20

NDC 0029-3211-13 Bottles of 30
NDC 0029-3211-20 Bottles of 100
NDC 0029-3211-21 SUP 100's (intended for institutional use only)

30 mg blue tablets engraved on the front with PAXIL and on the back with 30

NDC 0029-3212-13 Bottles of 30

Store at controlled room temperature 15°-30°C (59°-86°F).

DATE OF ISSUANCE DEC 1994

SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

PX LB

Printed in U.S.A.

ADDENDUM TO:
Review and Evaluation of Clinical Data
NDA #20031-S007

Sponsor:	SmithKline Beecham
Drug:	Paroxetine HCl
Indication:	Obsessive Compulsive Disorder
Material Submitted:	Response to approvable letter; study reports: PAR-127 and PAR-241: Long-term treatment with Paroxetine of Outpatients with Obsessive-Compulsive Disorder: An Extensions of the Fixed Dose Studies PAR-118 and PAR-136.
Correspondence Date:	January 18, 1996
Date Received:	January 22, 1996

I. Background
This is data submitted by the sponsor in response to the Division of Neuropharmacologic Drug Products' (DNDP) approvable letter dated October 12, 1995 and in support of paroxetine as being efficacious in the prevention of relapse of OCD symptoms. This addendum is a review of this response and the data from protocols PAR-127 and PAR-241. PAR-127 and PAR-241 are extended treatment protocols for patients who completed the short-term-treatment protocols PAR-118 and PAR-136. PAR-118 and PAR-136 were 12-week, double-blind, placebo and active treatment controlled, flexible dose studies of the efficacy and safety of paroxetine in the treatment of OCD.

II. Data Reviewed:

A. Clinical

1. Labeling
The sponsor in large part agrees with and will comply with the majority of the requests made by DNDP. The sponsor also has several exceptions and additions to DNDPs labeling suggestions made in the approvable letter.

a. Indications and Usage (Relapse prevention)- The sponsor wishes to add the following statement to the clinical data section, "The long-term maintenance effects of Paxil in OCD were demonstrated in a long-term extension to Study 1 [PAR-116]. Patients who were treated with open-label paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo." This statement is based on the results of study PAR-126 that was reviewed in a previous addendum to NDA 20-031-

S007. The conclusion of this review was that, in this 6-month placebo controlled study of patients who had previously responded to paroxetine, paroxetine was more effective than placebo in the prevention of relapse of OCD symptoms. The sponsor also submitted study reports for PAR-127 and 241.

PAR-127 was designed similarly to PAR-126. This was a multi-center, 12-month extension study of OCD patients who had received paroxetine treatment in protocol PAR-118. The study was divided into a 6-month open label, flexible dose treatment period followed by a 6-month, randomized, double blind, placebo controlled phase in order to assess the prevention of relapse.

At the end of the 6-month open label phase patients were judged to be responders or treatment failures by the following criteria: A therapeutic response was defined as a reduction in the total Y-BOCS score of ≥25% from the baseline level measured at the beginning of study PAR-118 and a decrease in the CGI severity of illness score of two points of more. If patients were judged responders at the end of the open label phase, then they were randomized into placebo or paroxetine groups. Non-responders were not to be entered into the study. The paroxetine treatment group contained 19 patients and the placebo group contained 22 patients.

This study failed to show that paroxetine was statistically significantly better than placebo in the prevention of OCD symptoms as measured by percent relapse (partial relapse-p=0.22; full relapse-p=0.11). The percentages of patients relapsing in each group of study PAR-127 are comparable to the percentages of patients relapsing in the corresponding groups in study PAR-126; however, study PAR-126 has roughly three times the number of patients in each treatment group. It is for this reason that this failure to demonstrate efficacy in relapse prevention is due to an under-powered study. The failure to show results in this study do not detract from the positive outcome of study PAR-126.

PAR-241 is the extension study for PAR-136. This was a prospective double-blind, randomized, parallel-group, comparative multi-center study of patients who had responded (≥ 25% reduction in Y-BOCS score) to 12 weeks of treatment. After completion of the 12 week study, patients were continued in their respective treatment groups for 18 more weeks. Patients in each group who still met criteria for response were re-randomized to either continue the original treatment or placebo (i.e. paroxetine was randomized to paroxetine or placebo; clomipramine was re-randomized to clomipramine or placebo; all patients in the placebo group remained on placebo). Patients re-randomized to placebo had their medications tapered. Patients then entered the trial phase and were treated for a further 8 weeks or until relapse occurred.

Time to relapse in the paroxetine-to-placebo group (n=15) was not significantly shorter than for the paroxetine treatment group (n=13) even though the risk ratio was 3.4. The clomipramine groups were not analyzed. The sponsors state that this was not done because of the small number of patients in the clomipramine/clomipramine and clomipramine/placebo groups (5 and 4 respectively). Patients from the original placebo group were not considered in the analysis.

Study PAR-241 represents a failed study due to lack of power. A comparison with the clomipramine group though planned could not be done. This study neither supports nor detracts from the results of study PAR-126.

The results of study PAR-126 are sufficient evidence to allow the above labeling language given that the other two studies show trends that are similar with study PAR-126.

b. Contraindications-The division requested that the sponsor include a contra-indication for the use of paroxetine concomitantly with other medications that inhibit the cytochrome P450IIIA4 isoenzyme system. The sponsor reviewed their available in vitro and clinical data and contended that a contraindication was not warranted. The sponsor, however, proposed that a similar statement be made in the precaution section. This is ongoing review issue between the sponsor and DNDP and is dealt with in other reviews. The sponsor claims to have a completed human, in vivo, cross-over study of the pharmacokinetic interaction between paroxetine and terfenidine. They have not yet submitted the plasma level interaction data which is the crux of this issue. Moving this information to the precautions section from the contraindication section should wait until this available data can be examined.

The sponsor, in their proposed precautionary note, also states that paroxetine "inhibits this [cytochrome P450IIIA4] isoenzyme but less so than other agents within this class ..". This statement implies that paroxetine is safer than other SSRIs with the same in vitro pharmacokinetic properties and therefore should be deleted.

c. Precautions- DNDP requested that cases of possible phenytoin-paroxetine, metoprolol-paroxetine interaction be included in the precaution section. The sponsor contends that these cases be described in the post-marketing experience section. This is also an ongoing review issue. These possible interactions are represented by one case each. The post-marketing section is devoted to case reports of possibly related adverse events. It is therefore reasonable to make this statement in the post-marketing section; however, if other similar cases emerge a statement should be made in the precautions section.

d. Adverse Events- DNDP proposed that the sponsor combine the 1% Adverse event tables for depression and OCD into one single table. The sponsor decided that two tables were necessary due to the fact that the sponsor had used two different adverse event dictionaries in the development of paroxetine for depression and OCD. Given the difference in the adverse event dictionary terminologies this is not unreasonable. It is recommended that the sponsor round these tables to whole number percent values and order each organ system by frequency of adverse event (highest to lowest) rather than alphabetically as it is now.

e. Pregnancy Warning- The sponsor complied with DNDP's request to change the pregnancy warning to category C.

f. Other Events- This section was updated to reflect the data now gathered on 7156 patients who received multiple doses of paroxetine (including 6145 depression patients, 542 patients with OCD, and 469 patients with panic disorder). Events which were previously included in this section but increased in frequency were moved to the appropriate sections. The following 12 changes were made.

change from infrequent to frequent:
Special Senses-tinnitus

change from rare to infrequent:
Digestive System-gingivitis, colitis, gastroenteritis
Metabolic/Nutritional- SGPT increased, SGOT increased
Musculoskeletal-arthralgia
Nervous System-dystonia, hostility, paralysis
Special Senses-conjunctivitis
Urogenital System-hematuria

The sponsors did not re-categorize experiences which were reported at lower rates in the safety update. Sixty-four new symptoms were added to the various subsections and are outlined in the sponsor's draft labeling.

g. Dosage and Administration
The sponsor states that efficacy was demonstrated for paroxetine in the treatment of OCD for 15 months. The blinded efficacy study phase in the longest extension study was 6 months. Therefore this claim can not be made.

The lowest dose where efficacy was demonstrated in the treatment of OCD was 40 mg/day (study PAR-116). The sponsor gives a therapeutic range of 20-60 mg/day. Labeling should reflect that efficacy was not demonstrated in doses less than 40 mg/day.

2. Safety Update

An updated summary and listing of adverse events for protocols PAR-116, 118, 136, 126, 127, and 241 are provided along with

spontaneous reports for patients taking paroxetine for OCD, panic, depression, and other indications.

a. On going Phase II-IV Clinical Trials
There was only one ongoing clinical trial of paroxetine in OCD patients (n=11; PAR-190) in Denmark. There were no deaths and one serious adverse event (unrelated neoplasm) in patients treated with paroxetine under this protocol.

Serious adverse events and deaths in clinical trials of paroxetine for other indications were reviewed. No serious adverse events were present that have not been addressed in labeling for those indications.

b. Spontaneously reported adverse experiences from worldwide post-marketing experience
Paroxetine was first approved in the United Kingdom as Seroxat in December 1990 and marketed in February 1991. As of September 1995 paroxetine has been approved in 53 and marketed in 34 countries.

There has been one reported death associated with paroxetine use in OCD between February 1991 and September 1995. This was considered unrelated to paroxetine use by this reviewer and the reporting physician. Serious and non-serious spontaneous adverse experiences that were associated with paroxetine use in OCD are representative of the adverse events that are currently reported in the paroxetine draft labeling.

c. Safety data from extension studies PAR-127 and 241
There were no deaths in study 127 and two serious adverse events. The patient 118.009.0226 experienced an infarcted lower bowel in the open label phase; the line listing states that the patient was taking "0 mg/day".[1] The patient's narrative summary states that the patient was discontinued from paroxetine upon admission to the hospital for surgery; this event occurred on day 88 of treatment and states that the patient "resumed taking 60 mg/day" after discharge from the hospital by mistake for 20 days without sequelae. The investigator ruled that this event was unassessable in its relation to paroxetine. Non-serious adverse events experienced in this study were qualitatively and quantitatively representative of adverse events currently reported in draft labeling for the use of paroxetine for OCD.

There were no deaths or drug related serious adverse events in study 241. Adverse events experienced in this protocol were qualitatively and quantitatively representative of adverse events

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[1]Table 40 Summary of serious adverse events; intent to treat population. NDA 20-031 S007 Response to approvable letter Vol. 3 of 68, page 172.

described in the current draft labeling.

d. World literature review
The sponsor provides an update of the world literature in the form of an updated citation list and abstracts. The sponsor did not warrant that they had examined and reported any new safety findings; however, in a recent tele-conference, the sponsor agreed to provide this warranty.

e. Foreign regulatory updating
Applications for marketing paroxetine for the treatment of OCD have been submitted in 20 countries. The sponsor has received marketing approval in 8 countries (Austria, Canada, Denmark, Italy, Iceland, Spain, Sweden, and UK). Copies of labeling from Austria, Canada, Sweden, and UK are provided.

f. Efficacy data
The analyses exploring age and gender were reviewed and appear sufficient for the review and labeling.

g. Pediatric studies
The sponsor agrees to perform efficacy and safety studies in adolescents and anticipates that the protocol will commence within the first quarter of 1996. Currently the agency is asking for a projected study completion date, and the sponsor has agreed to provide such a date.

II Pharmacology
All of the requested labeling changes in the Carcinogenesis, Mutagenesis, and Impairment of Fertility Carcinogenesis Pregnancy Teratogenic Effects sections have been made in labeling.

III Conclusions and Recommendations
In summary, the outstanding issues that must be resolved prior to a recommendation for approval for Paxil in the treatment of OCD are the following:

-The use of terfenidine and paroxetine in concert is an ongoing review issue between the sponsor and DNDP . The sponsor claims to have a completed human, in vivo, cross-over study of the pharmacokinetic interaction between paroxetine and terfenidine. They have not yet submitted the plasma level interaction data which is the crux of this issue. Moving this information to the precautions section from the contraindication section should wait until this available data can be examined.

-The sponsor, in their proposed precautionary note, stated that paroxetine "inhibits this [cytochrome P450IIIA4] isoenzyme but less so than other agents within this class...". This statement implies that paroxetine is safer than other SSRIs with the same in vitro pharmacokinetic properties and therefore should be

deleted.

- The sponsor states that efficacy was demonstrated for paroxetine in the treatment of OCD for 15 months. The blinded efficacy study phase in the longest extension study was 6 months. Therefore this claim can not be made.

- The lowest dose where efficacy was demonstrated in the treatment of OCD was 40 mg/day (study PAR-116). The sponsor gives a therapeutic range of 20-60 mg/day. Labeling should reflect that efficacy was not demonstrated in doses less than 40 mg/day.

- The sponsor must warrant that they have examined the world literature review and update and reported any new safety findings of this review.

- The sponsor agrees to perform efficacy and safety studies in adolescents and anticipates that the protocol will commence within the first quarter of 1996. Currently the agency is asking for a projected study completion date, and the sponsor has agreed to provide such a date.

- It is recommended that the sponsor round the adverse event tables to whole number percent values and order each organ system by frequency of adverse event (highest to lowest) rather than alphabetically as it is now.

The additional relapse prevention studies (PAR-127 and 241) neither support nor detract from the results of study PAR-126 (the one positive relapse prevention study). These studies failed to show efficacy due to their lack of statistical power.

2/12/96

Paul J. Andreason, M.D.
Medical Reviewer

cc: IND
HFD 120
P. David
G. Dubitsky
T. Laughren

4.22-96
This supplement can now be approved once we reach final agreement with the sponsor on labeling. See my memo to the file for more detailed response.
Thomas P. Laughren, MD
GL, PDP

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 20-031/S-009

SPONSOR: SmithKline Beecham Pharmaceuticals

DRUG: Paxil® (paroxetine hydrochloride) Tablets

DRUG CATEGORY: Selective Serotonin Reuptake Inhibitor

MATERIAL REVIEWED: Safety update material specific to panic disorder, as well as the literature update and foreign status update were reviewed.

DATE SUBMITTED: April 5, 1996 and April 12, 1996

DATE RECEIVED: April 16, 1996

I. BACKGROUND

Approval packages for two paroxetine supplements, namely treatment of obsessive compulsive disorder and pa[illegible] disorder, are nearing completion. In response to the 3-14-96 approvable letter, w[illegible]e received two submissions from SmithKline Beecham. These include some labeli[illegible]nges, a reference to a safety update for the paroxetine/panic update, a w[illegible] update and foreign status update.

II. SAFETY UPDATE

An updated summary of adverse experiences in studies 29060/108, 29060/120, 29060/187 and 19060/223 and the relapse prevention and/or long-term maintenance extension to these studies and (29060/222 and 29060/228) was provided by the sponsor in an Appendix 110 (attachment #3 in the Sponsor's submission of April 5, 1996). There were a total of 469 paroxetine-treated patients in these 6 studies. There were no placebo-treated patients. I then looked at treatment-emergent adverse experience, as well as re-examined the treatment-emergent adverse experience incidences in placebo-controlled clinical trials for panic disorder, and found no unusual treatment-emergent adverse experiences or serious adverse experiences. Two treatment-emergent adverse experience terms in the safety update were reported at an incidence of more than two-fold to the placebo-controlled clinical trials. These terms were: weight gain, which was reported as a treatment-emergent adverse experience by

4.3% of the 469 paroxetine-treated patients in the supplement update versus 1% of 469 in the clinical placebo-controlled clinical trials and respiratory disorder, which was reported by 12% of the 469 paroxetine-treated patients in the safety update versus 22% of 469 in the placebo-controlled clinical trials. However, without data for placebo-treated patients in these open-label relapse prevention and long-term maintenance extensions studies submitted in the safety update, data comparisons are somewhat difficult.

III. WORLD-WIDE LITERATURE UPDATE

The Sponsor's process for selection, storage and retrieval of published adverse events was provided on page 4 of the April 5, 1996 submission. In the same submission, abstracts of articles are provided in attachment 5, Volume 2. The Sponsor attested to the fact that literature was systematically reviewed and that there were no new findings that would warrant a change in the existing safety profile for paroxetine. I reviewed the title of each reference for its topical content. I scanned all abstracts for safety data. I did not find any new safety findings which would preclude the approval of paroxetine for the treatment of panic disorder.

IV. FOREIGN REGULATORY UPDATE

Marketing approval has been achieved in ten countries for the use of paroxetine in the treatment of panic disorder. These ten countries are Austria, Canada, Denmark, Finland, Ireland, Italy, South Africa, Spain, Sweden and the U.K.

V. PROPOSED LABELING

On April 20, 1996, the Sponsor submitted a volume that contains the FDA proposed labeling, the SmithKline Beecham proposed labeling, as well as the non-U.S. labeling for the following countries: Denmark, Finland, Ireland, Spain and South Africa, for the use of paroxetine in the treatment of panic disorder. I have looked at the proposed SmithKline Beecham labeling and have no comments.

VI. CONCLUSIONS

There were no new findings submitted that would warrant any change in the safety profile for the use of paroxetine for the treatment of panic disorder.

VII. RECOMMENDATIONS

From a clinical point of view, the supplement is approvable.

James F. Knudsen, M.D., Ph.D.

Review and Evaluation of Clinical Data
NDA # 20,031

Sponsor:	SmithKline Beecham Pharmaceuticals
Drug:	PAXIL (paroxetine HCl) Tablets
Material Submitted:	Study Report: "The Effect of Paroxetine on the Pharmacodynamics and Pharmacokinetics of Terfenadine in Healthy Adult Males"
Correspondence Date:	April 12, 1996
Date Received:	April 15, 1996

I. Background

In vitro data has suggested that paroxetine may be a clinically important inhibitor of cytochrome P450 IIIA based on inhibition of 4-OH alprazolam formation and terfenadine metabolism (see reviews filed to this NDA dated March 22, 1995, and March 30, 1995). Since terfenadine, astemizole, and cisapride are thought to be IIIA substrates and since elevated levels of these three agents have been associated with serious ventricular arrhythmias, such as torsades de pointes, an August 30, 1995, letter to SmithKline Beecham requested that these drugs be contraindicated with PAXIL. It was also suggested that the sponsor conduct an adequately designed in vivo study to further investigate the possibility of a clinically significant interaction between PAXIL and terfenadine. It was also stated that data produced from such a study may be a basis to remove the CONTRAINDICATION for PAXIL and terfenadine co-administration. This submission contains the report of such an interaction study.

II. Summary of Study

A. Methodology

The principal investigator was Daniel E. Everitt, M.D., of the SmithKline Beecham Clinical Pharmacology Unit, Philadelphia, PA.

This was a randomized, open-label, two-period crossover study in which 12 healthy, non-smoking males (age 18-50) received

vomiting, headaches, anorexia, and fatigue) after receiving paroxetine alone for 5 days.

Three subjects each reported one adverse event during paroxetine and terfenadine co-administration (nausea, epistaxis, and sinusitis). All were mild to moderate in severity.

Four subjects had vital sign changes of potential clinical concern[4] during paroxetine and terfendine co-administration. These are summarized in Table 1 below. All occurrences were isolated events unaccompanied by symptoms or significant changes in pulse rate.

Table 1:
Vital Sign Changes of Potential Concern During Paroxetine + Terfenadine Treatment

Subject	Parameter	Time Observed	Baseline Value	Abnormal Value	Change from BL
004	SBP	14 hrs. post-dose, day 12	116	147	+31
004	DBP	4 hrs. post-dose, day 15	66	88	+22
007	SBP	4 hrs. post-dose, day 13	109	142	+33
011	SBP	14 hrs. post-dose, day 13	111	142	+31
012	SBP	pre-dose, day 10	123	156	+33

ECG tracings were reviewed by an independent cardiologist for rhythm, wave morphology, and accuracy of machine-read intervals. No ECG values of potential clinical concern[5] were noted during the course of this study although one subject was noted to have an isolated monomorphic ventricular couplet on day 13 of Treatment B about 2 hours after terfenadine + paroxetine; this event did not reoccur and was not considered

[4]Defined on page 28 of the report.

[5]Defined on page 30 of the report.

terfenadine concentrations over time on Day 8 of Treatment A (steady-state terfenadine) and on Day 15 of Treatment B (steady-state terfenadine + paroxetine) for each subject are provided on pages C-15 to C-25 in the report. Again, to detect any important individual outliers, these plots were examined by the undersigned to detect any major differences between the two treatments for any subject; none were observed.

Table 3:
Terfenadine PK Data (N=11)

	Geometric Mean (range)		Ratio of GM's (B:A) (95% CI)
	Treatment A	Treatment B	
AUC(0→12) (ng-hr/ml)	30.8 (10.8-409)	30.0 (11.0-287)	0.97 (0.87,1.08)
Cmax (ng/ml)	3.64 (0.39-40.3)	3.68 (0.84-27.3)	0.98 (0.80,1.21)

III. Conclusions and Recommendations

Based on the above clinical review, it is concluded that this study demonstrated no convincing evidence that paroxetine and terfenadine co-administration was associated with a significant increase in either QTc or parent terfenadine levels compared to the administration of terfenadine alone. It should be borne in mind that this is a small sample of healthy males and the potential for rare but significant interactions in a larger, less healthy, and more heterogeneous population taking a larger paroxetine dose cannot be defintively ruled out. Nonetheless, it seems reasonable to permit the sponsor to remove the contraindicated use of PAXIL and terfenadine from PAXIL labeling. Retention of a precautionary statement seems prudent, however.

Gregory M. Dubitsky, M.D.
April 18, 1996

cc: NDA# 20,031
HFD-120
HFD-120/GDubitsky
TLaughren
PDavid

4-19-96
I agree with the above assessment
- their data will be summarized by
this biopharm. group as well.

APR 2 9 1996

NDA 20-031 Submission Date: April, 8, 1992

SPONSOR: SmithKline Beecham
Philadelphia PA

DRUG: Paxil (Paroxetine hydrochloride tablets)

CLASSIFICATION: Antidepressant (serotonin reuptake inhibitor)

TYPE OF SUBMISSION: Four interaction studies

REVIEWER: Robert Harris, Ph.D.

SUMMARY

Paroxetine is a serotonin reuptake inhibitor approved for the treatment of depression. The following 4 studies have not yet been reviewed by the Agency. These studies examine the possibility of paroxetine participating in drug-drug interactions. Parts of these studies yield useful information which should be incorporated into the product labeling.

I. A COMPARATIVE STUDY OF THE EFFECTS OF PAROXETINE AND OTHER DRUGS ON CYTOCHROME P450IID6 ACTIVITY IN HUMAN LIVER MICROSOMES (Interim Report)

oxetine is likely a cytochrome P450IID6 (CYPIID6) substrate and thus may also act a petitive inhibitor of this enzyme. Paroxetine hydrochloride and its metabolites M-I curonide, M-I sulfate, M-II, and M-III were tested as inhibitors of human CYPIID6 in vitro. e effect of nineteen other compounds, including other serotonin re-uptake inhibitors such as oxetine, sertraline and fluvoxamine, on CYPIID6 activity were also measured for comparison. CYPIID6 activity was measured via a sparteine oxidase assay.

Paroxetine inhibited sparteine oxidase activity with an inhibitory constant, Ki, of 0.15 uM (Attachment 1). Its major metabolites, M-I glucuronide and M-I sulfate, inhibited enzyme activity to a lesser degree having Ki values of >200 and 120 uM respectively. Paroxetine was the most potent inhibitor of CYPIID6 activity of all serotonin re-uptake inhibitors tested, although fluoxetine and sertraline had Ki values in a similar range (Ki = 0.60 and 0.70 uM respectively). Thus, paroxetine, like other SRIs, interacts with CYPIID6 in vitro. A typical steady state concentration of paroxetine is approximately 0.2 uM which is similar to the Ki value. This suggests that paroxetine could potentially interact with CYPIID6 in vivo. Patients taking this drug with other drugs that are metabolized by CYPIID6 should be monitored for drug interactions.

II. AN OPEN STUDY TO INVESTIGATE THE EFFECTS OF PAROXETINE ON SPARTEINE OXIDASE POLYMORPHISM IN HEALTHY VOLUNTEER SUBJECTS (Study 29060/105/HA/011/SINDRUP)

In vitro studies suggest that paroxetine is metabolized by CYPIID6. Approximately, 7% of the population is deficient in this enzyme, and thus may have an impaired ability to eliminate the drug. To investigate this possibility, the sponsor has compared the metabolism of paroxetine (30

mg/day) in 8 subjects who lacked CYPIID6 (PMs) to the metabolism in 8 subjects who had normal CYPIID6 activity (EMs). In addition, the study examined the effect of chronic dosing of paroxetine on sparteine metabolism (a marker of CYPIID6 activity) in both EM and PM subjects. The protocol is described in Attachment 2.

After single dosing, the Cmax and AUC of paroxetine were, respectively, 2.7 and 3.8 times higher in PM subjects than in EM subjects (Attachment 3). After multiple dosing, the Cmax and AUC were only 1.4 and 1.7 times higher in PMs compared to EMs (Attachment 3). The smaller difference in average Cmax and AUC after multiple dosing compared to single dosing is due to saturation of CYPIID6 in EMs at the higher paroxetine concentrations achieved during multiple dosing. The clearance of paroxetine in EMs at steady state, unlike after a single dose, includes a substantial contribution from enzymes other than CYPIID6--enzymes on which PMs are wholly reliant on for paroxetine metabolism. Thus, the difference in plasma paroxetine levels between EMs and PMs, although still significant, is smaller after multiple dosing compared to single dosing.

This study also illustrated an in vivo interaction between paroxetine and sparteine. Following daily paroxetine administration, there was significant impairment of sparteine oxidation in EM subjects (Attachment 4). After cessation of paroxetine dosing, the metabolism of sparteine increased to approximately normal within about 5 weeks (Attachment 4). These results further support the notion that paroxetine can inhibit CYP2D6 leading to drug interactions. Paroxetine therapy did not affect sparteine metabolism in PMs, further suggesting the involvement of CYP2D6 in the drug interaction.

III. A STUDY TO INVESTIGATE THE EFFECTS OF COADMINISTRATION OF THREE ANTICONVULSANTS (CARBAMAZEPINE, VALPROATE AND PHENYTOIN) AND PAROXETINE IN EPILEPTIC PATIENTS (Study DFG-311b).

Epileptic patients in monotherapy (six carbamazepine, eight valproate and six phenytoin) were given paroxetine (titrated up to 30 mg / day) for sixteen days after a seven day placebo period (study described in Attachment 5). The paroxetine treatment did not have a significant effect on the pharmacokinetics of any of the anticonvulsants (Attachment 6). However, the steady state plasma concentration of paroxetine was significantly higher in patients taking valproate (73 ng/mL) compared to those taking the either carbamazepine (27 ng/mL) or phenytoin (16 ng/mL) (Attachment 7).

IV. AN INTERACTION STUDY OF PAROXETINE ON LITHIUM PLASMA LEVELS IN DEPRESSED PATIENTS STABILIZED ON LITHIUM THERAPY (Study 29060/062/001-010).

Nineteen patients stabilized on chronic lithium therapy were given 20 mg of paroxetine once daily for 3 days followed by 30 mg once daily for 32 days (Attachment 8). Steady state

paroxetine concentrations were usually achieved by day 14. Steady state lithium concentrations were not significantly affected by the presence of paroxetine (Attachment 9). The study did not measure the effect of lithium on paroxetine kinetics.

COMMENTS TO THE MEDICAL OFFICER:

Comment 1. Study I illustrates that paroxetine inhibits CYPIID6 in vitro and can may cause drug interactions with other CYPIID6 substrates in vivo. This possibility is already adequately described in the labeling.

Comment 2. Study II illustrates that people who are deficient in CYPIID6 (PMs) eliminate paroxetine at a slower rate than people who have the enzyme (EMs). After a single dose, Cmax and AUC are approximately 3 fold greater in PMs compared to EMs. After multiple dosing this difference becomes smaller (approximately 1.5 fold) because CYPIID6 becomes saturated at higher plasma paroxetine concentrations and therefore plays a smaller role in paroxetine elimination. Thus, at high plasma concentrations, enzymes other than CYPIID6, (which are present in both PMs and EMs), "take over" in EMs. (In other words, after multiple dosing, the same enzymes are responsible for the majority of paroxetine metabolism in both EMs and PMs). Even if the 1.5 fold difference in AUC between PMs and EMs is not considered clinically significant, it should be described in the labeling. It is important to characterize the effect of the CYPIID6 genetic polymorphism on the metabolism of any drug for which CYPIID6 mediated elimination is suspected.

Comment 3. Study II also illustrates that paroxetine can inhibit CYPIID6 in vivo. This result, which is consistent with the in vitro studies, provides concrete evidence that drug interactions related to CYPIID6 can happen in vivo and should be added to the labeling.

Comment 4. Study III shows that paroxetine does not appear to affect the metabolism of valproate acid, phenytoin, or carbamazepine. However, it appears that valproate may impair paroxetine elimination, leading to unusually high paroxetine concentrations in patients on valproate therapy. These results should be described in the labeling.

Comment 5. Study IV shows that paroxetine does not alter lithium elimination. This result is already reflected in the labeling.

Robert Z. Harris, Ph.D. Robert Harris 4-25-96
Pharmacokinetics Evaluation Branch I

RD/FT initialed by Raman Baweja, Ph.D. R. Baweja 4/29/96

cc: NDA 20-031, HFD-120, HFD-860 (Harris, Baweja, Malinowski), Chron, Drug and Reviewer files
(CLARENCE BOTT, HFD 870, Rm 13B-31 PARKLAWN)

ATTACHMENT 1

Values of inhibition constants (K_i) for the formation of 2-dehydrosparteine in human liver microsomes.

COMPOUND	K_i (μM)
Paroxetine	0.15
M-I glucuronide*	>200
M-I sulphate*	120
M-I	16
M-II	0.50
M-III	>20
Fluoxetine	0.60
Norfluoxetine*	0.43
Sertraline	0.70
Citalopram	5.1
Fluvoxamine	8.2
Thioridazine	0.52
Desipramine	2.3
Clomipramine	2.2
Amitriptyline	4.0
Quinidine	0.03
Metoprolol	37
Lignocaine	200
Antipyrine	>3000

ATTACHMENT 2

SUMMARY

Name of Company:	SmithKline Beecham Pharmaceuticals
Compound:	BRL 29060 - Paroxetine
Study No:	29060/105/HA/001/SINDRUP
Study Title:	An open study to investigate the effects of paroxetine (30 mg od for 14 days) on sparteine oxidase polymorphism in healthy volunteer subjects.
Investigators:	Dr. S.H. Sindrup (Principal), Dr. K. Bresen, Prof. L. Gram
Study Centre:	Dept. of Clinical Pharmacology, Odense University, DK-5000 Odense C, Denmark
SB Responsible Physician:	Dr. C.G.G. Link
Publication:	Draft manuscript submitted to publisher.
Objectives:	1. To determine the extent and duration of the possible in vivo inhibition of P450IID6 by paroxetine, including the time taken for the enzyme to revert back to its original state after cessation of paroxetine treatment. 2. To determine whether the sparteine oxidation phenotype influences the steady state plasma concentration of paroxetine.
Study Period:	18.05.90 to 15.08.90
Study Design/Duration of Treatment:	Open study in 2 groups of subjects, namely extensive (EM) and poor (PM) metabolisers of sparteine. Dosing period was 14 days at a dose level of 30 mg od po paroxetine in all subjects.
Critical Inclusion Criteria:	16 healthy males aged 20 to 40 years, comprising 8 extensive and 8 poor metabolisers of sparteine.
Test Products and Mode of Administration:	Paroxetine tablets (CT no. 28355) containing 10 mg pfb of active ingredient, were supplied. 3 tablets were taken once daily on Study Days 1 to 14 inclusive. Sparteine sulphate tablets, 100 mg, (ex. Giulini Pharma GmbH: Batch No. 7328) were supplied by the investigators and administered as single oral doses on Study Days -1, 1, 8, 14, 16, 21 and 35.
Criteria for Evaluation:	1. <u>Sparteine oxidation</u> Measurement of urinary excretion of unchanged and oxidised sparteine up to 12 hours post-sparteine administration on Days -1, 1, 8, 14, 16, 21 and 35. 2. <u>Pharmacokinetics</u> Plasma concentrations and urinary excretion after the first and last doses, during the approach to steady state and during the run-out phase. 3. <u>Safety monitoring</u> Haematology and clinical chemistry evaluated on Days -1, 16 and 35. Adverse events by standard question on Days -1, 8, 14, 17, 21 and 35.
RESULTS: Demographic:	17 subjects entered, comprising 9 EM and 8 PM. All completed.

SUMMARY

RESULTS: Demographic Cont'd:	Mean (range) age was 24 (20-30) years in the EM group and 27 (22-38) years in the PM group.
Sparteine MR:	Sparteine and its metabolites were assayed by the Odense group, using a gas chromatographic method. Following daily administration of paroxetine, there was significant impairment of sparteine oxidation in the EM subjects. This effect was progressive, but appeared to have stabilised by Day 14, consistent with the time required to reach paroxetine steady state. After cessation of dosing with paroxetine, there was an immediate fall in sparteine MR values, which gradually reverted to near pre-study levels within about a week. This is indicative of a reversible inhibition of cytochrome P450IID6. In PM subjects, dosing with paroxetine had no effect on sparteine MR.
Pharmacokinetics:	Plasma samples were assayed for paroxetine, and urine samples were assayed for paroxetine and, undifferentiated, its major metabolites, using HPLC with fluorescence detection by DMPK, Harlow. The results were subjected to pharmacokinetic analysis and the parameters obtained were compared between the EM and PM groups and between single dose and steady state. Single dose and steady state pharmacokinetic parameters in these groups are listed in the summary table. After the first dose (Day 1), paroxetine plasma levels as described by C_{max}^{1} and AUC_{τ}^{1} were several-fold greater in PMs than EMs with little overlap of the ranges. In all subjects, regardless of phenotype, steady state was achieved by Day 11. At steady state, paroxetine plasma levels remained greater in PMs than in EMs, but the differences had diminished to around two-fold or less for mean C_{max}^{SS}, C_{min}^{SS} and AUC_{τ}^{SS} and the ranges overlapped extensively. Half lives were more than twice as long in PMs than in EMs, as defined by the terminal phase after cessation of chronic dosing. The convergence of plasma levels in the two groups at steady state is the result of pharmacokinetic non-linearity exhibited by EM subjects only. In PM subjects, the relationship between steady state and single dose plasma levels was consistent with linear pharmacokinetic principles. In both EMs and PMs, only a small fraction of the daily dose was excreted as unchanged paroxetine during the dosing intervals on Day 1 and at steady state. Amounts excreted tended to be greater in PMs than in EMs but were always below 2.5% of the daily dose. Correspondingly, a greater percentage of the first dose was excreted as metabolites in EMs than in PMs during the 24 hour collection period, due to enhanced metabolite formation during the first 12 hours. At steady state, however, these differences in metabolite urinary excretion between the two groups disappeared. The observations indicate that the conversion of paroxetine to metabolites is more efficient in EMs than PMs, but the difference is diminished at steady state.

ATTACHMENT 3

SUMMARY TABLE

Pharmacokinetic parameters for paroxetine (mean, range and % CV) in extensive (EM) and poor (PM) metabolisers of sparteine

29060/105/HA/001/SINDRUP

First dose (day 1)		EM	PM	
C_{max} **	Mean Range C.V.	9.4 ng/ml 5.2 - 13.2 31%	25.8 ng/ml 12.3 - 36.4 30%	2.7
AUC_t **	Mean Range C.V.	115 ng.h/ml 45.4 - 211 47%	438 ng.h/ml 221 - 726 39%	3.8
Urinary excretion of paroxetine (% dose in 24 h)	Mean Range C.V.	0.40% 0.08 - 1.41 106%	1.15% 0.68 - 2.14 41%	
Urinary excretion of 'metabolites' (% dose in 24 h)	Mean Range C.V.	28.1% 19.9 - 36.4 29%	7.4% 4.2 - 14.6 41%	
CL_R	Mean Range C.V.	0.92 L/h 0.47 - 2.71 75%	0.90 L/h 0.44 - 1.81 56%	

Steady state (day 14)		EM	PM	
C_{max}^{ss} *	Mean Range C.V.	56.6 ng/ml 41.8 - 75.2 22%	80.0 ng/ml 41.6 - 122 34%	1.4
C_{min}^{ss} *	Mean Range C.V.	26.4 ng/ml 12.2 - 45.2 39%	54.1 ng/ml 24.5 - 103 46%	2.0
AUC_t^{ss} *	Mean Range C.V.	892 ng.h/ml 447 - 1278 31%	1536 ng.h/ml 735 - 2557 40%	1.7
$t_{\frac{1}{2}}$ **	Mean Range C.V.	17.0 hours 12.9 - 20.5 17%	41.1 hours 28.8 - 52.9 20%	
Urinary excretion of paroxetine (% dose in 24 h)	Mean Range C.V.	2.00% 0.92 - 4.17 53%	3.57% 2.05 - 8.44 60%	
Urinary excretion of 'metabolites' (% dose in 24 h)	Mean Range C.V.	25.0% 14.8 - 36.3 32%	22.3% 16.5 - 26.6 17%	
CL_R^{ss}	Mean Range C.V.	0.77 L/h 0.21 - 1.97 72%	0.80 L/h 0.26 - 1.78 62%	

Statistical analysis of plasma pharmacokinetic data (EM vs PM): *$p<0.05$

In each group, the subjects are arranged in order of increasing sparteine MR.

Subjects 14,8,13 and 7 are fast EMs (MR < 0.4)

Subjects 1,11,10,15 and 9 are slow EMs (MR > 0.4)

11. Areas under the plasma concentration versus time curves of paroxetine (ng.h/ml) in EM and PM subjects after the first and 1t dose of paroxetine (30 mg) administered daily for 14 days.

29060/105/HA/001/SINDRUP

Extensive metabolisers			Poor metabolisers		
Subject No.	AUC_τ^1	AUC_τ^{ss}	Subject No.	AUC_τ^1	AUC_τ^{ss}
14					
8					
13					
7					
1					
11					
10					
15					
9					
Mean (SD, CV%)	115 (53.8, 47%)	892 (272, 31%)	Mean (SD, CV%)	438 (173, 39%)	1536 (615, 40%)

group, the subjects are arranged in order of increasing sparteine MR.

14,8,13 and 7 are fast EMs (MR < 0.4)

1,11,10,15 and 9 are slow EMs (MR > 0.4)

able 13 Terminal phase half-lives of paroxetine (hour) in EM and PM subjects after last dose of paroxetine (30 mg) administered daily for 14 days.

29060/105/HA/001/SINDRUP

Extensive metabolisers		Poor metabolisers	
Subject No.	$t_{½}$	Subject No.	$t_{½}$
14		2	
8		17	
13		5	
7		12	
1		6	
11		4	
10		16	
15		3	
9			
Mean (SD,CV%)	17.0 (2.8,17%)	Mean (SD,CV%)	41.1 (8.2,20%)

each group, the subjects are arranged in order of increasing sparteine MR.

bjects 14,8,13 and 7 are fast EMs (MR < 0.4)

bjects 1,11,10,15 and 9 are slow EMs (MR > 0.4)

ATTACHMENT 4

ble 21 Metabolic ratios of sparteine before, during and after 14 days of once daily administration of paroxetine (30 mg) to EM and PM subjects

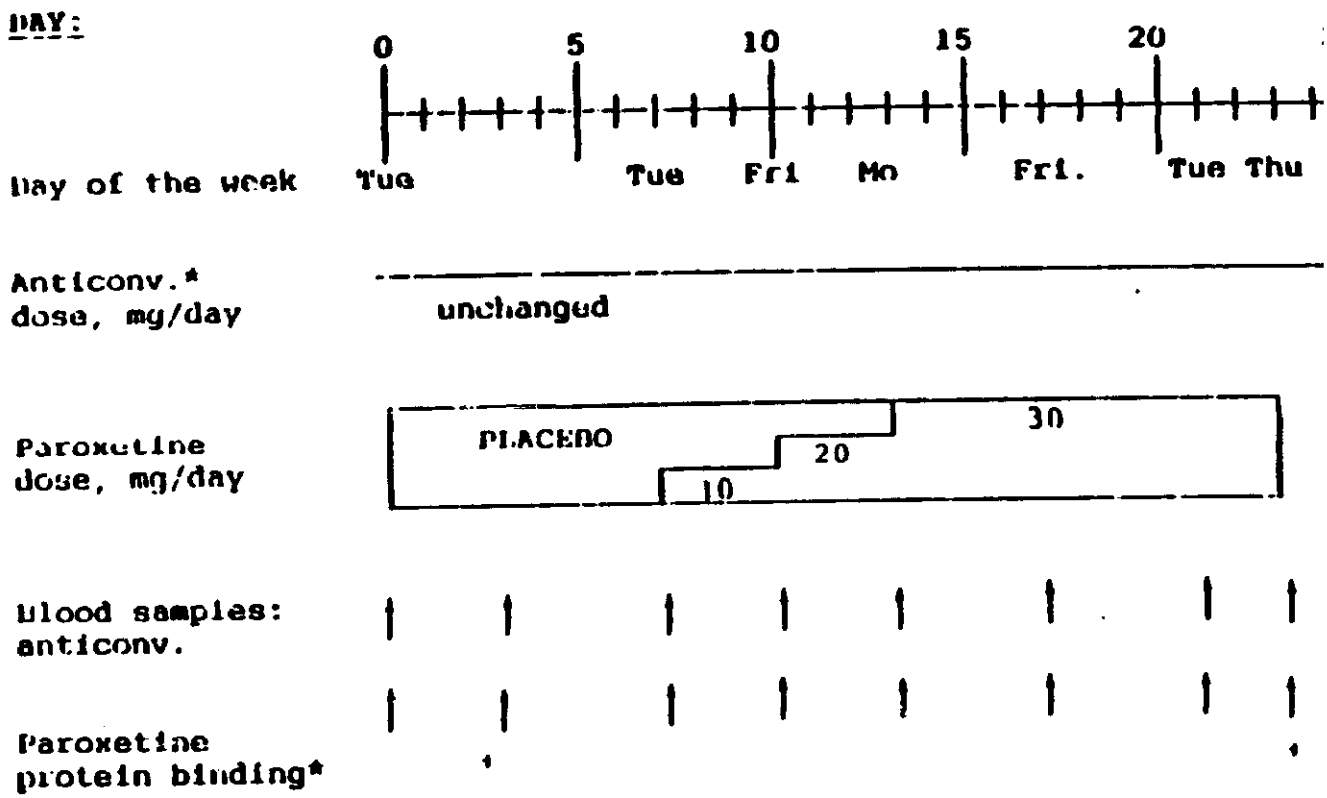
29060/105/HA/001/SINDRUP

Phenotype	Subject No.	Pre-study	During Paroxetine			After Paroxetine		
			Day 1	Day 8*	Day 14	Day 16	Day 21	Day 35
Fast EM	14							
	8							
	13							
	7							
	Mean							
Slow EM	1							
	11							
	10							
	15							
	Mean							
PM	2							
	17							
	5							
	12							
	6							
	4							
	16							
	3							
	Mean	166	157	152	135	166	123	186

* All tests carried out overnight except day 8 (daytime test)

ATTACHMENT 5

Fig. 1. Flow-sheet for the interaction study DFG-



*Dose: unchanged for at least 3 months before

for anticonv. and paroxetine.

The purpose of the present study was to investigate the effects of co-administration of paroxetine to epileptic patients in monotherapy with one of the three anticonvulsants: carbamazepine, valproate and phenytoin. It also was intended to investigate a possible phenobarbitone/paroxetine interaction, but it has not been possible to find patients in monotherapy with phenobarbitone. This part of the study was therefore cancelled.

Before the present study seven epileptic patients (3 valproate and 4 carbamazepine) in stable treatment were given paroxetine 20 mg/d for 4 days and 30 mg/d for 10 days. Three of these patients did not complete the schedule due to nausea, headache, and tiredness. The reason for the severity and the high frequency of adverse reactions could not be accounted for. Neither the plasma concentrations of carbamazepine/valproate or paroxetine nor the clinico-chemical parameters offered any explanation. The study has been reported earlier (JL/LEJ 10.01.1989).

It was therefore decided to further investigate the co-administration of paroxetine to stabilised epileptic patients using a modification of the previous protocol. A 7 day placebo period preceded paroxetine treatment and the dosage of paroxetine was to increase at a slower rate (JL/HM/EKK 02.05.1989). Assessments of the protein binding of paroxetine, carbamazepine, valproate, and phenytoin were also included.

MATERIALS AND METHODS

Patients and drugs

Twenty non-elderly epileptic patients in stable treatment (same dose of drug and less than one fit per year) with carbamazepine (6), valproate (8) or phenytoin (6) were given paroxetine. The scheme was 0 mg/day (placebo) for seven days, 10 mg/day for three days, 20 mg/day for three days and 30 mg/day for ten days.

A flow-sheet for the study is given in Fig. 1.

Only one patient (JUS-12), a phenytoin patient, did not fulfill the paroxetine treatment. The patient stopped six days earlier than planned due to private problems.

The dosage was blind to the patients (single blind); they took 3 apparently identical tablets every morning in the dosing period.

The paroxetine dose was given as 10 mg white, pentagonal and filmcoated tablets (Batch no CT 17830); the anticonvulsant treatment continued unchanged.

The study was carried out at two centers: University Clinic of Neurology, Hvidovre Hospital, Copenhagen (BJ-1, JH-2, HG-3, AM-9, LV-10, KEN-14, SH-4, EP-5, EB-6, BG-7, BG-8, HC-13,

Ethics

The study was performed in accordance with the II Helsinki Declaration adopted June 1964 by the 18th World Medical Assembly, Helsinki, Finland and revised October 1975 and 1983 respectively by the 29th World Medical Assembly, Tokyo, Japan and the 35th World Medical Assembly, Italy.

Consent to participation was obtained from patients on the basis of written and verbal information on the nature and scope of the study.

The study was submitted to the Ethical Committees for review.

Plasma concentrations

Plasma concentrations of paroxetine and valproate, carbamazepine or phenytoin were determined before paroxetine, during the placebo period, during the paroxetine intake and after the paroxetine period. The plasma sampling is shown in Fig. 1. Blood samples were drawn in the morning before administration of drug. Plasma samples were kept frozen until analysis.

Free concentrations of the three anticonvulsants were determined on day 3 (in the placebo period) and day 23 (at the end of the paroxetine period). The free concentration of paroxetine was determined on day 23. The free concentration of paroxetine in plasma from the placebo period was also to have been determined after addition of paroxetine to obtain the in vitro protein binding of paroxetine.

Valproate, phenytoin, and carbamazepine were determined by fluorexcence polarization immunoassay (TD_x) at Bispebjerg Hospital (Popelka et al. 1981).

Paroxetine was determined by a specific HPLC-method (Sratt et al., 1987).

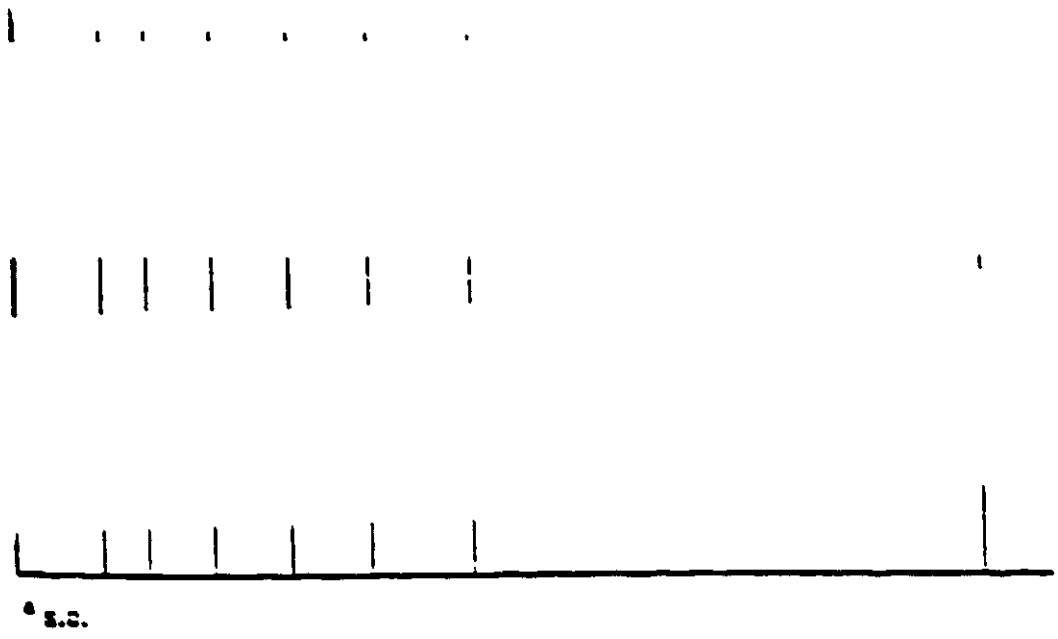
The protein binding of paroxetine (free concentration) was determined as described earlier (D 87046/29060/100, Beecham Internal Report).

Clinical and clinico-chemical parameters were determined at the hospitals by routine methods, no sooner than two weeks before and no later than one week after the paroxetine period.

RESULTS

Demographic data, doses of anticonvulsants, plasma concentrations of anticonvulsants and paroxetine, as well as other

ATTACHMENT 6



[a] s.c.

[b] Drop-out after 10 mg/d for 3 days, 20 mg/d for 3 days and 30 mg/d for four days.

ATTACHMENT 7

b) Valproate values are significantly higher than carbamazepine and phenytoin values ($p = 0.05$). Paroxetine levels in carbamazepine and phenytoin patients are not significantly different ($p = 0.05$).

ATTACHMENT 8

2. METHODS

2.1 Design of study

Nineteen non-elderly male or female patients (18-65 years) previously stabilised on chronic lithium therapy participated in this open, multicentre study in Belgium. Throughout the five-week study period, patients continued to receive their normal lithium therapy. Each patient received 20 mg paroxetine (blue pentagonal tablet formulation) once daily on days 1-3, followed by 30 mg paroxetine once daily on days 4-35. All doses were administered in the morning.

2.2 Sample collection

The sampling schedule for measurement of paroxetine plasma concentrations required blood samples (5 ml into EDTA tubes) to be collected before the first dose and before dosing on days 7, 14, 21, 28 and 35.

In addition, blood samples were collected on the same occasions for lithium plasma concentration measurement, about 12 hours after the previous evening's lithium administration. The lithium measurements were carried out locally using the hospitals' standard flame photometric method.

Plasma for paroxetine measurement was separated by centrifugation, removed and stored at -20°C until being transferred (in dry-ice) to the Pharmacokinetics Unit, DMPD, Harlow, for assay. While awaiting assay, samples were again stored at -20°C.

ATTACHMENT 9

Table 2: Plasma concentrations of lithium (mMol/L) before and during five weeks of daily dosing with paroxetine, in depressed patients receiving lithium therapy.

29060/062/001-01C

Patient No.	Lithium concentration (mMol/L)					
	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35
1000						
1001						
1002						
1006						
1008						
1010						
1011						
1012						
1013						
1014						
1015						
1016						
1017						
1019						
1020						
1021						
1022						
1023						
1024						

N.D. = no data

1008 1010 1011 1012 1013 1014 1015 1016 1017 1019 1020 1021 1022 1023 1024			
Mean (SD,CV%)	73.4 (52.2, 71%)	0.83 (0.36, 43%)	0.76 (0.18, 24%)

(a) only day 14 and day 21 values available.

(b) day 28 data not available.

(c) day 35 data not available.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-031 Submission Dates: Feb 16, 1996
SPONSOR: SmithKline Beecham April 5, 1996
Philadelphia PA April 12, 1996
DRUG: Paxil (20 mg Paroxetine hydrochloride tablets)
CLASSIFICATION: Antidepressant (serotonin reuptake inhibitor)
TYPE OF SUBMISSION: Terfenadine interaction study
REVIEWER: Robert Harris, Ph.D.

SUMMARY

The sponsor has submitted the results of a well designed clinical study that investigated the possibility of a paroxetine-terfenadine interaction (Attachment 1). The study showed that paroxetine, 20 mg qd, does not inhibit terfenadine elimination (Attachment 2).

Based on the fact that terfenadine is metabolized specifically by CYP3A4, the sponsor wanted to conclude that paroxetine would not inhibit other CYP3A4 mediated reactions. Specifically, the sponsor suggested that the results of terfenadine study could be extrapolated to astemizole, triazolam and cisapride. Under certain circumstances, however, it may be difficult to extrapolate the results obtained with one CYP3A4 substrate (in this case terfenadine) to other CYP3A4 substrates. A discussion about these difficulties was sent via email to Dr. Thomas Laughren (Attachment 3). The Agency decided that although further clinical interaction studies may not be necessary, it would be prudent to have the sponsor perform in vitro interaction studies that specifically examine the potential of paroxetine to inhibit the metabolism of cisapride, triazolam and astemizole. The results of these in vitro studies would help determine whether further clinical study are necessary.

The sponsor performed the in vitro studies described above (Attachment 4). The Ki values determined were comparable to the Ki value for the inhibition of terfenadine metabolism by paroxetine (146 μM and 19 μM for terfenadine hydroxylation and dealkylation respectively). Because paroxetine does not inhibit terfenadine metabolism in vivo, it is very reasonable to conclude that paroxetine will not inhibit the metabolism of the other CYP3A4 substrates in vivo.

Labeling Comment: The labeling proposed by the sponsor (Drugs Metabolized by Cytochrome P450IIIA4, Attachment 5) is supported by the data. However, it would be appropriate to change 'Paroxetine is a weak inhibitor...' to 'Paroxetine is a moderate inhibitor...' The Ki for paroxetine against CYP3A4 is about 50 μM. There are no set rules as to what defines a potent, moderate, or weak inhibitor of an enzyme, and it is reasonable to call paroxetine either a weak or a moderate inhibitor--although moderate seems to be most appropriate. What ever word or phrase the Agency chooses, it is important to remain consistent for all drugs with similar inhibitory potential.

Comment to Medical Officer: Please verify the conclusion that there was no PD interaction as measured by prolongation of the QTc intervals.

Recommendation: The sponsor has provided the Agency with all of the information that has been requested. A clinical study has been performed with terfenadine, and in vitro work has been performed with cisapride, astemizole, cyclosporin and triazolam. All of the data obtained suggest that paroxetine will not interact with these drugs. Short of further clinical interaction studies, the sponsor has done everything possible to show that paroxetine should not interact with the narrow therapeutic range CYP3A4 substrates in vivo. Please see Labeling Comment.

Robert Z. Harris, Ph.D.
Pharmaceutical Evaluation I

Robert Harris 4-26-96

FT initialed by Raman Baweja, Ph.D.

R. Baweja 4/29/96.

cc: NDA 20-031, HFD-120, HFD-860 (Harris, Baweja, Mehta, Malinowski), Chron, Reviewer, and Drug (Clarence Bott HFD-870, PKLN RM. 13B-31).

Clinical Study Synopsis

(Page 1 of 5)

STUDY TITLE
The Effect of Paroxetine on the Pharmacodynamics and Pharmacokinetics of Terfenadine in Healthy Adult Males

INVESTIGATOR(S) AND CENTER(S)
Daniel E. Everitt, M.D.
SmithKline Beecham Clinical Pharmacology Unit
Presbyterian Medical Center of the University of Pennsylvania Health System
Philadelphia, Pennsylvania
USA

PUBLICATIONS
None as of March, 1996

STUDY DATES
22 November 1995 to 6 February 1996

OBJECTIVES
The objectives of this study were to establish the lack of effect of paroxetine on the pharmacodynamics (as assessed by QTc intervals of resting 12-lead ECG) of terfenadine; to assess the safety and tolerability of the co-administration of paroxetine with terfenadine; and to investigate the effects of paroxetine on the pharmacokinetics of terfenadine and terfenadine carboxylate.

STUDY DESIGN
This was a randomized, open-label, two-period, period-balanced, cross over study. During two study sessions, healthy adult male volunteers received terfenadine alone or terfenadine concomitantly with paroxetine following a 7 day paroxetine run-in period. The treatment regimens were separated by a minimum of 14 days.

STUDY POPULATION
Up to 24 healthy non-smoking adult men between the ages of 18 and 50 years and body weight ≥ 50 kg and within 15 % of ideal were to be enrolled. A total of twelve (12) subjects were randomized to treatment and eleven (11) completed the study.

TREATMENT AND ADMINISTRATION
BRL 29060/ Paxil®, oral tablets, 20 mg (Paroxetine; SmithKline Beecham Pharmaceuticals, Lot number X94077) and Seldane®, 60 mg (Terfenadine; Marion Merrell Dow Inc, Lot number X95247) were used in this study. The treatment regimens were: A) Terfenadine 60 mg BID for 7 days with terfenadine 60 mg x 1 on day 8; B) Paroxetine 20 mg once daily for 15 days + Terfenadine 60 mg BID on study days 8 through day 14 and once on day 15.

Clinical Study Synopsis
(Page 2 of 5)

EVALUATION CRITERIA

Safety Parameters

Adverse events, blood pressure, pulse rate, ECG (including ECG intervals and disclosures), and clinical laboratory data were reviewed to evaluate the safety of subjects. All subjects were on continuous dual-lead telemetry monitoring during terfenadine dosing during both treatment regimens. Any clinically relevant abnormalities or values of potential clinical concern were described.

Pharmacokinetic Parameters

Serial plasma samples (0-12 hours) were collected after the final dose of terfenadine on the mornings of Day 8 (regimen A: terfenadine alone) and Day 15 (regimen B: terfenadine with paroxetine). Predose samples were also collected on the mornings of Days 1 (session #1 only), 2, 4, 6 and 7 (regimen A) and Days 9, 11, 13 and 14 (regimen B). These samples were analyzed for terfenadine and its active metabolite carboxyterfenadine using methods based on LC/MS/MS and HPLC with fluorescence detection, respectively. The lower limits of quantification (LLQ) for these methods were 0.050 ng/mL (using a 1.0 mL aliquot) and 10.05 ng/mL (using a 0.5 mL aliquot), respectively. In addition, the plasma samples collected on the mornings of Days 1, 13, 14 and 15 (regimen B) were analyzed for paroxetine using a method based on LC/MS/MS (LLQ 0.10 ng/mL using a 0.5 mL aliquot). Pharmacokinetic parameters for terfenadine and carboxyterfenadine were derived using non-compartmental analysis.

STATISTICAL METHODS

The focus of the statistical evaluation was to establish lack of effect of paroxetine on the pharmacodynamics (as assessed by QTc intervals) of terfenadine, using an equivalence approach; two one-sided T-tests expressed as 90% confidence intervals (CI). Equivalence was statistically demonstrated when the 90% confidence interval for the difference between paroxetine + terfenadine minus terfenadine alone (B-A) was contained within the range of -40 msec to +40 msec. Exceeding this range was only of clinical concern if it was on the upper end of the equivalence range. Maximum QTc post dose and mean QTc post dose measures were analyzed separately by analysis of variance (ANOVA) appropriate to the study design with terms for sequence, subject nested within sequence, period and regimen (A or B). The point estimates and corresponding 90% percent confidence interval for the differences of B-A were computed using the residual variance.

For the pharmacokinetic analyses, Ln-transformed AUC(0-12) and Cmax values for each compound were analyzed separately by analysis of variance (ANOVA). The point estimates and corresponding 95% confidence interval for the difference B-A were computed using the residual variance.

SUBJECT DISPOSITION AND KEY DEMOGRAPHIC DATA

A total of twelve (12) subjects were randomized to treatment and all twelve (12) of these subjects received at least one dose of study medication. Eleven (11) subjects completed the study. The following table summarizes the demographics of the study population:

Clinical Study Synopsis
(Page 4 of 5)

Parameter	Estimate	PE	90% C.I.
maxqtc	B - A	-2.07	(-12.54, 8.41)
meanqtc	B - A	-1.07	(-4.14, 1.99)

Regimen:

A. Terfenadine 60 mg BID for 7 days with Terfenadine 60 mg x 1 on day 8;

B. Paroxetine 20 mg once daily for 15 days + Terfenadine 60 mg BID on study days 8 through day 14 and once on day 15.

PHARMACOKINETIC

RESULTS

Predose plasma concentrations of paroxetine on the last three days of coadministration with terfenadine indicate that paroxetine steady state had been reached by this time. Plasma concentrations of carboxyterfenadine were, as expected, much higher than those of terfenadine itself. For both compounds, steady state was generally reached by the fourth day of terfenadine dosing either alone (Regimen A) or with paroxetine (Regimen B). Complete steady state pharmacokinetic parameters could be derived for all except subject 001, in whom plasma concentrations of terfenadine mostly remained below the LLQ (both regimens); only Cmax and Tmax values could be derived for this subject. The statistical analysis of terfenadine and carboxyterfenadine AUC(0-12) and Cmax data is summarized in the following Teble:

Pharmacokinetic parameter (n=11)	Geometric mean (range)		Point estimate (B:A) [95% CI]
	Regimen A (alone)	Regimen B (+paroxetine)	
Terfenadine			
AUC(0-12)* [ng.h/mL]	30.8 (16.8-409)	30.0 (11.0-287)	0.97 [0.87, 1.08]
Cmax [ng/mL]	3.64 (0.39-40.3)	3.68 (0.84-27.3)	0.98 [0.80, 1.21]
Carboxyterfenadine			
AUC(0-12) [ng.h/mL]	1648 (839-2081)	1351 (956-1900)	0.83 [0.74, 0.92]
Cmax [ng/mL]	248 (111-353)	197 (138-246)	0.80 [0.67, 0.95]

* n=10 (subject 001 not evaluable)

Coadministration of terfenadine with paroxetine resulted in average decreases in terfenadine AUC(0-12) and Cmax of only 3% and 2%, respectively, compared to administration alone. The true ratios are likely to lie between a 13% decrease and an 8% increase for terfenadine AUC(0-12) and between a 20% decrease and a 21% increase for terfenadine Cmax. The within-subject variability in terfenadine AUC(0-12) and Cmax values was 10.6% and 22.1%, respectively. Coadministration of terfenadine with paroxetine resulted in average decreases in carboxyterfenadine AUC(0-12) and Cmax of 17% and 20%, respectively, compared to administration alone. The true ratios are likely to lie between an 8% and a 26% decrease for carboxyterfenadine AUC(0-12) and between a 5% and a 33% decrease for carboxyterfenadine Cmax. The within-subject variability in carboxyterfenadine AUC(0-12) and Cmax values was 11.6% and 18.3%, respectively.

Table A

Study Medication Used

Study Drug	Appearance	Formulation	Dose Unit	Lot Number of Packaged Drug	
				SB	Commercial
BRL 29060/ Paroxetine*	pink, scored, oval, film-coated	Tablet	20 mg	X94077	156-4B11
Terfenadine**	round, white	Tablet	60 mg	X95247	P51956

* Paxil®

** Seldane®, Marion Merrell Dow Inc., Kansas City, MO.

Data Source: Appendix A, page 86.

Study medication administered at the CPU was stored at approximately room temperature in a locked area.

3.5.2 Dosage and Administration

The treatment regimens were:

A) Terfenadine, 60 mg, twice a day (BID) for 7 days with a single dose of terfenadine, 60 mg, on Day 8;

B) Paroxetine, 20 mg, once daily for 15 days + Terfenadine, 60 mg, BID on Days 8 through 14 and once on Day 15.

Paroxetine was administered in the CPU on Day 1. Paroxetine was self-administered by subjects as outpatients on Days 2-7 of Regimen B. Subject were instructed to take 1 tablet every morning at approximately 08:00. On Days 1-8 of Regimen A and on Days 1 and 8-15 of Regimen B, study medication was administered in the CPU. Paroxetine, 20 mg, and terfenadine, 60 mg, were administered orally with 240 mL of tepid water at approximately 08:00. The evening dose of terfenadine was administered at approximately 20:00; except on the evening of Day 8 of Regimen A and Day 15 of Regimen B when no evening dose of terfenadine was administered.

3.5.3 Methods of Blinding

This was an open-label study.

Physical examination findings, laboratory data, and ECG tracings obtained during the treatment phase were compared to the corresponding results prior to dosing. Specific values of potential clinical concern were defined in the protocol; any laboratory, vital sign or ECG values exceeding these pre-defined thresholds were identified and tabulated (see Sections 5.5, 5.6, and 5.7 below). Any such changes considered clinically significant were recorded as adverse experiences in the case report form.

3.10 Pharmacokinetic Assessments

3.10.1 Sampling Times

On the final day of terfenadine dosing in each treatment period, i.e., Day 8 of Regimen A (terfenadine alone) and Day 15 of Regimen B (terfenadine dosed with paroxetine), serial blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours post-dose. Pre-dose samples were also collected on the mornings of Days 1, 2, 4, 6 and 7 (Regimen A) and Days 9, 11, 13 and 14 (Regimen B).

Separate pre-dose blood samples (approx. 5 mL in EDTA) were collected on the mornings of Day 1 (Regimen A) and Days 13, 14 and 15 (Regimen B).

3.10.2 Specimen Preparation

Samples for terfenadine and carboxyterfenadine assays (approximately 10 mL in tubes containing EDTA) were centrifuged at approximately 4°C and the resultant plasma was transferred to plain polypropylene tubes and frozen at approximately –20°C. These plasma samples were transported frozen to Phoenix International Life Sciences (Quebec, Canada), where they were stored at approximately –20°C while awaiting assay.

Plasma obtained from the samples for paroxetine assay by centrifugation at approximately 4°C was transferred to plain polypropylene tubes, frozen at approximately –20°C, and transported to the Drug Analysis Department, SmithKline Beecham Pharmaceuticals, Welwyn, UK.

Statistical results

The statistical analysis of terfenadine and carboxyterfenadine AUC(0-12) and Cmax data is presented in full in Appendix E, and summarized in Table 11.18, page 196, and in the Table J, below.

Table J

Summary of Terfenadine and Carboxyterfenadine AUC(0-12) and Cmax Data

Pharmacokinetic parameter (n=11)	Geometric mean (range)		Point estimate (B:A) [95% CI]
	Regimen A (alone)	Regimen B (+paroxetine)	
Terfenadine			
AUC(0-12)* [ng.h/mL]	30.8 (10.8-409)	30.0 (11.0-287)	0.97 [0.87, 1.08]
Cmax [ng/mL]	3.64 (0.39-40.3)	3.68 (0.84-27.3)	0.98 [0.80, 1.21]
Carboxyterfenadine			
AUC(0-12) [ng.h/mL]	1648 (839-2081)	1351 (956-1900)	0.83 [0.74, 0.92]
Cmax [ng/mL]	248 (111-353)	197 (138-246)	0.80 [0.67, 0.95]

* n=10 (subject 001 not evaluable).

Source: Tables 11.10 to 10.11, pages 188 to 189, Tables 11.14 to 11.15, pages 192 to 193 and Appendix E, Tables E-3 to E-6, pages E-4 to E-11.

Coadministration of terfenadine with paroxetine resulted in average decreases in terfenadine AUC(0-12) and Cmax of only 3% and 2%, respectively, compared to terfenadine administration alone. The true ratios are likely to lie between a 13% decrease and an 8% increase for terfenadine AUC(0-12) and between a 20% decrease and a 21% increase for terfenadine Cmax. The within-subject variability in terfenadine AUC(0-12) and Cmax values was 10.6% and 22.1%, respectively. Significant period effects were observed for both parameters (p=0.0001 and p=0.0122, respectively), indicating systematic differences in average response between the two dosing periods. However, no significant sequence effects were observed.

Coadministration of terfenadine with paroxetine resulted in average decreases in carboxyterfenadine AUC(0-12) and Cmax of 17% and 20%, respectively, compared to administration alone. The true ratios are likely to lie between an 8%

Table 11.10

AUC(0-12) [ng.h/mL] for terfenadine following repeated oral administration of terfenadine (60 mg bid) alone and with paroxetine at steady state (20 mg once daily) to healthy subjects

Subject No.	Regimen A (Alone)	Regimen B (+ paroxetine)	Ratio (B:A)
1			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
N	10	10	
Arith. Mean	63.18	51.10	
SD	121.81	83.31	
Median	24.37	27.15	
Minimum	10.76	10.95	
Maximum	409.00	287.00	
Geom. Mean	30.83	29.95	
CVb%	128.1	108.2	

ND - Not Determined (insufficient data above LLQ, both regimens)

Regimen A: Terfenadine 60 mg bid for 7 days and once on day 8
Regimen B: Paroxetine 20 mg once daily for 15 days, with terfenadine 60 mg bid on days 8-14 and once on day 15

Table 11.11

Cmax [ng/mL] for terfenadine following repeated oral administration of terfenadine (60 mg bid) alone and with paroxetine at steady state (20 mg once daily) to healthy subjects

Subject No.	Regimen A (Alone)	Regimen B (+ paroxetine)	Ratio (B:A)
1			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
N	11	11	
Arith. Mean	6.84	5.46	
SD	11.22	7.32	
Median	4.35	3.84	
Minimum	0.39	0.84	
Maximum	40.29	27.28	
Geom. Mean	3.64	3.68	
CVb%	154.2	97.3	

Regimen A: Terfenadine 60 mg bid for 7 days and once on day 8
Regimen B: Paroxetine 20 mg once daily for 15 days, with terfenadine 60 mg bid on days 8-14 and once on day 15

Table 11.13

Cmin [ng/mL] for terfenadine following repeated oral administration of terfenadine (60 mg bid) alone and with paroxetine at steady state (20 mg once daily) to healthy subjects

Subject No.	Regimen A (Alone)	Regimen B (+ paroxetine)	Ratio (B:A)
1			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
N	10	10	
Arith. Mean	3.64	3.17	
SD	6.68	6.04	
Median	1.53	1.23	
Minimum	0.52	0.76	
Maximum	22.58	20.32	

ND - Not Determined (insufficient data above LLQ, both regimens)

Regimen A: Terfenadine 60 mg bid for 7 days and once on day 8
Regimen B: Paroxetine 20 mg once daily for 15 days, with terfenadine 60 mg bid on days 8-14 and once on day 15

Table 11.14

AUC(0-12) [ng.h/mL] for carboxyterfenadine following repeated oral administration of terfenadine (60 mg bid) alone and with paroxetine at steady state (20 mg once daily) to healthy subjects

Subject No.	Regimen A (Alone)	Regimen B (+ paroxetine)	Ratio (B:A)
1			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
N	11	11	
Arith. Mean	1688	1380	
SD	334	299	
Median	1825	1307	
Minimum	839	956	
Maximum	2081	1900	
Geom. Mean	1648	1351	
CVb%	25.1	21.6	

Regimen A: Terfenadine 60 mg bid for 7 days and once on day 8
Regimen B: Paroxetine 20 mg once daily for 15 days, with terfenadine 60 mg bid on days 8-14 and once on day 15

Table 11.15

Cmax [ng/mL] for carboxyterfenadine following repeated oral administration of terfenadine (60 mg bid) alone and with paroxetine at steady state (20 mg once daily) to healthy subjects

Subject No.	Regimen A (Alone)	Regimen B (+ paroxetine)	Ratio (B:A)
1			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
N	11	11	
Arith. Mean	259	201	
SD	68	40	
Median	278	206	
Minimum	111	138	
Maximum	353	246	
Geom. Mean	248	197	
CVb%	32.9	21.0	

Regimen A: Terfenadine 60 mg bid for 7 days and once on day 8
Regimen B: Paroxetine 20 mg once daily for 15 days, with terfenadine 60 mg bid on days 8-14 and once on day 15

Table 11.17

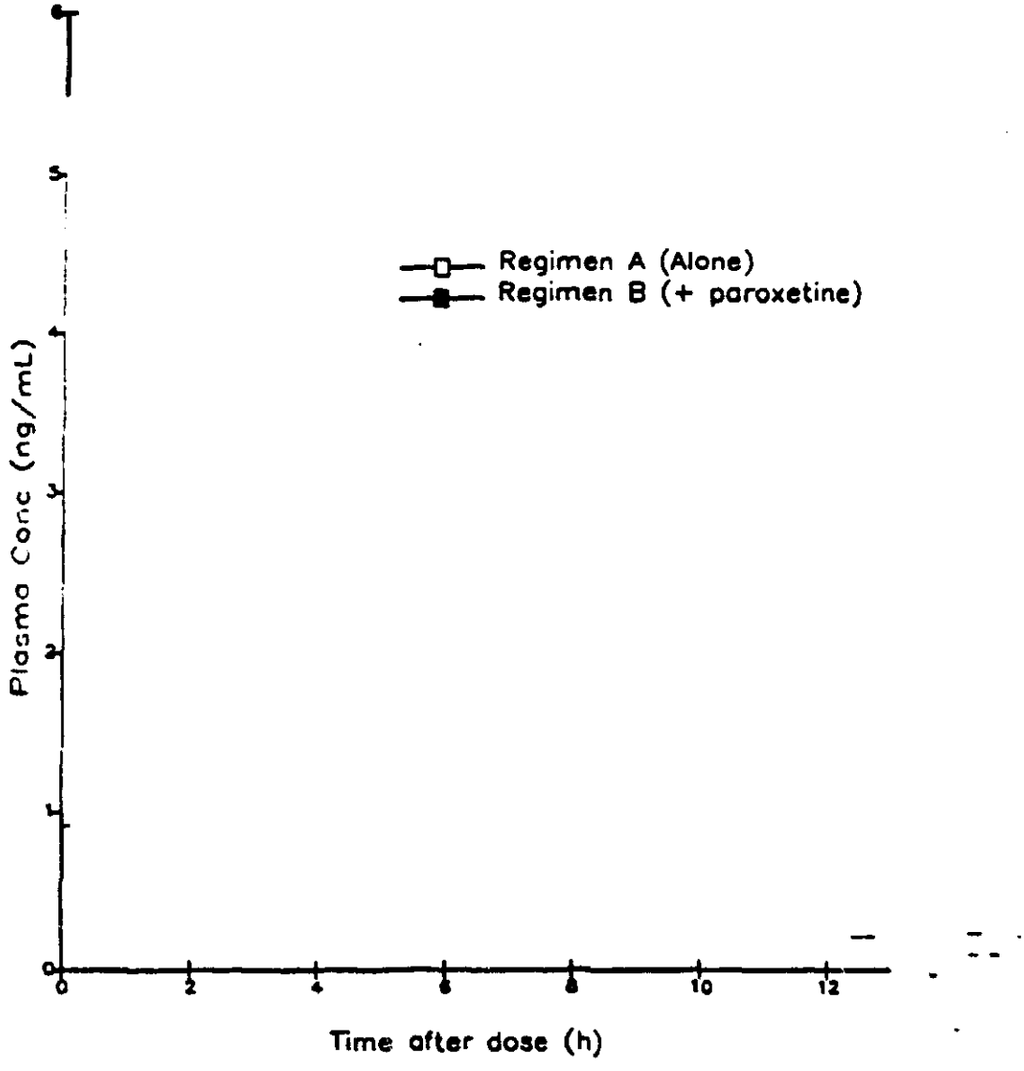
Cmin [ng/mL] for carboxyterfenadine following repeated oral administration of terfenadine (60 mg bid) alone and with paroxetine at steady state (20 mg once daily) to healthy subjects

Subject No.	Regimen A (alone)	Regimen B (+ paroxetine)	Ratio (B:A)
1			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
N	11	11	
Arith. Mean	68.6	62.0	
SD	15.1	21.0	
Median	60.5	59.3	
Minimum	44.2	33.0	
Maximum	92.5	113.6	

Regimen A: Terfenadine 60 mg bid for 7 days and once on day 8
Regimen B: Paroxetine 20 mg once daily for 15 days, with terfenadine 60 mg bid on days 8-14 and once on day 15

Figure 12.1

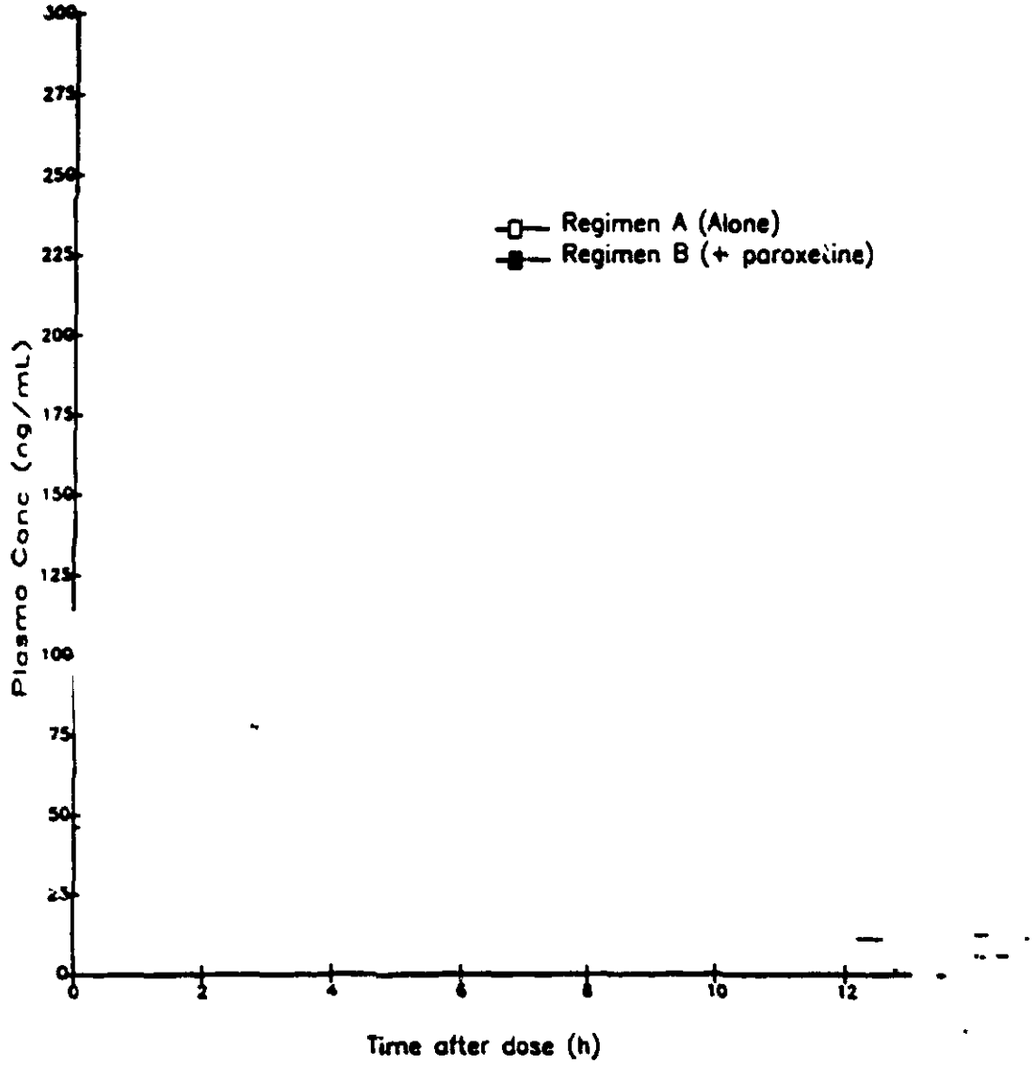
Mean (±SD) plasma concentration versus time curves for terfenadine following repeated oral administration of terfenadine (60 mg bid) alone and with paroxetine at steady state (20 mg once daily) to healthy subjects [n=10*]



* - Excludes Subject 10 (both regimens)

Figure 12.2

Mean (±SD) plasma concentration versus time curves for carboxyterfenadine following repeated oral administration of terfenadine (60 mg bid) alone and with paroxetine at steady state (20 mg once daily) to healthy subjects [n=11]



ATTACHMENT 3

ELECTRONIC MAIL MESSAGE

Date: 20-Feb-1996 04:17pm EST
From: Robert Harris
HARRISR
Dept: HFD-860 MOC2 4058
Tel No: 301-594-5513 FAX t-

TO: Thomas Laughren (LAUGHREN)

CC: Paul Leber (LEBER)
CC: Paul David (DAVID)
CC: Andrew Mosholder (MOSHOLDERA)
CC: Raman Baweja (BAWEJA)

Subject: Drug Interactions

Tom:

From what I have been told, the Agency has been presented conclusive evidence that Paxil does not significantly inhibit terfenadine metabolism in vivo. Based on this finding, the conclusion was reached that Paxil will not inhibit the metabolism of any other drug metabolized by CYP3A4 (e.g. cyclosporine, tacrolimus, astemizole, and cisapride). Although classical enzyme kinetics would support this type of conclusion, CYP3A4 does not follow classical kinetics. Thus, when CYP3A4 is involved, it may not be prudent to make generalized predictions about the possibility of drug interactions based upon the results of a single drug interaction study.

For classical competitive inhibitors, the inhibition constant, Ki, is simply equal to the inhibitor's binding constant to the enzyme. Thus, the inhibitor should inhibit the metabolism of all substrates with the same Ki value. In this case, if it is found that a molecule does not inhibit the metabolism of a drug by an enzyme, it is perfectly reasonable to make the conclusion that the molecule will not inhibit any reaction that the enzyme catalyzes. From what I have seen, most CYPs seem to demonstrate classical enzyme kinetics.

CYP3A, however, appears to be very nonclassical. There is a fair amount of literature evidence that suggests that this enzyme has at least two substrate/inhibitor binding sites (e.g Biochemistry 33:6450-6455, 1994; 1995 Intl. ISSX meeting, poster abstract #314). Assuming that this literature is correct, it is very likely that an inhibitor could bind to one site much more tightly than to the other site. Thus, it is possible that an inhibitor could weakly inhibit the elimination of one CYP3A4 substrate, yet potently inhibit the elimination of a different CYP3A4 substrate. Consistent with this prediction, it has been shown that ketoconazole is a much better inhibitor of terfenadine hydroxylation than of terfenadine N-dealkylation even though both reactions are catalyzed specifically by CYP3A4 (J. Clin. Pharmacol. 34:1222-7, 1994-Greenblatt's work). Recent kinetic studies utilizing midazolam support the conclusion that CYP3A4 has multiple substrate/inhibitor binding sites (Kent Kuntze, University

of Washington, personal communication). It has also been shown that CYP3A4 can adopt a number of different conformations, and that the different conformations have distinct substrate specificities (J. Biol. Chem. 270:5014-8, 1995). Again, this result demonstrates that a CYP3A4 inhibitor may inhibit the oxidation of one CYP3A substrate while not inhibiting the oxidation of a different substrate. (Finally, in my graduate work I showed that horseradish peroxidase (HRP) has multiple substrate binding sites. HRP is a hemoprotein enzyme that, like CYP3A4, is very "promiscuous" or able to oxidize a wide variety of molecules having different shapes and sizes. I found that certain inhibitors could completely abolished HRP's ability to metabolize some substrates whereas the same inhibitors did not in the least bit affect the metabolism of other substrates. The same situation, I believe, may hold for CYP3A4).

A second relevant issue is that the small intestine contains lots of CYP3A4, and it is very difficult to predict how an inhibitor will affect presystemic drug metabolism in the gut. For example, going back to the terfenadine/Paxil situation, it is possible that terfenadine and Paxil are absorbed in different parts of the GI tract so that Paxil has no effect on terfenadine metabolism in the gut (assuming that terfenadine is even metabolized in the gut). However, Paxil and cisapride (or some other CYP3A substrate) may be absorbed in the same region of the gut, and the local gut concentrations of Paxil may be very high in this region. Thus, Paxil may be able to significantly inhibit the presystemic metabolism of cisapride and other drugs even though it did not have a significant effect on terfenadine metabolism.

I should stress that everything that I have written is simply a possibility. I certainly have not seen all of the data, so I am in no position to make a recommendation. The bottom line, in my opinion, is simply that it is much more difficult to make extrapolations regarding CYP3A4 than other CYPs, so caution should be exercised.

Bob Harris

ATTACHMENT 4

Memorandum of Preliminary Data

An *in vitro* investigation into the inhibition of the metabolism of CYP3A substrates by paroxetine and ketoconazole

H.G. Oldham and S.E Clarke

Objectives:

Comparison of the *in vitro* inhibition caused by ketoconazole and paroxetine against astemizole, triazolam and cisapride metabolism

Methods:

- Microsomal elimination of astemizole was measured by a specific LC/MS/MS assay.
- Triazolam 4-hydroxy and α-hydroxy product formation from triazolam and norcisapride formation from cisapride was measured by a specific LC/MS/MS assay. Calibration was performed based upon relative response to cisapride and triazolam, as reference calibration standards were not available. Triazolam and cisapride disappearance kinetics were unsuitable for inhibition experiments.
- Demethylation of [N-^{14}C-methyl]dextromethorphan was determined by quantitation of [^{14}C]formaldehyde and [^{14}C]formic acid production. Cyclosporine oxidation was determined by HPLC with radiochemical detection.
- Each experiment was performed in human hepatic microsomes from a single donor characterised for 1A2, 2A6, 2C9/8, 2C19, 2D6, 2E1, 3A and 4A.

Results:

Table 1 IC_{50} values for astemizole clearance, triazolam hydroxylation, cisapride N-dealkylation, dextromethorphan N-demethylation and cyclosporin oxidase

Activity	IC_{50} (uM)	
	Ketoconazole	Paroxetine
astemizole intrinsic clearance	0.49	48
triazolam 4-hydroxylation	0.14	43
triazolam α-hydroxylation	0.08	32
cisapride N-dealkylation	0.60	>>100
dextromethorphan N-demethylation	0.43	50
cyclosporin oxidation	0.21	120

TABLE 2 (amended): INHIBITION OF TERFENADINE METABOLISM		
Inhibitor	Mean Ki (±S.E.) in μM (n=5-6)	
	Hydroxylation	N-Dealkylation
SSRI's		
Desmethylsertraline	6.7 (±2.0)	1.2*
Norfluoxetine	10.7 (±3.3)	1.9 (±0.24)
Sertraline	24.5 (±4.4)	3.9 (±0.64)
Fluvoxamine	90.4 (±36.6)	11.3 (±0.7)
Paroxetine	146 (±4.0)	18.6 (±5.3)
Fluoxetine	186 (±94)	21.3 (±3.2)
Test Comparators		
Ketoconazole	0.24 (±0.04)	0.024 (±0.003)
Itraconazole	2.4	0.27
Fluconazole	>100	>100

* Harmonic mean.

III. Updated Source of In Vitro Data

The pharmacokinetic study of fluvoxamine and paroxetine inhibition of alprazolam metabolism, summarized in Table 1, page 3, of the original review, has just recently been published: von Moltke LL, et al. Inhibition of Alprazolam and Desipramine Hydroxylation In Vitro by Paroxetine and Fluvoxamine: Comparison With Other Selective Serotonin Reuptake Inhibitor Antidepressants. J Clin Psychopharmacol 1995;15: 125-131.

Thus, this information is no longer considered confidential and may be referenced in correspondence with sponsors.

ATTACHMENT 5

patients assigned to paroxetine showed a lower relapse rate compared to patients on placebo (see Clinical Pharmacology)."

Indications and Usage/Panic Disorder: A similar change was made to the first sentence of the paragraph describing the relapse prevention trial to read: "Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In this trial patients assigned to paroxetine showed a lower relapse rate compared to patients on placebo (see Clinical Pharmacology)."

Warnings: As agreed in our March 4, 1995 phone conference, the warning statement regarding potential astemizole, cisapride, and triazolam interactions could be removed if we had in-vitro data which indicated that paroxetine only had a weak inhibitory effect on the metabolism of these drugs. We have provided in Attachment 2 a report of our in-vitro studies which have demonstrated that ketoconazole was at least two orders of magnitude more potent than paroxetine.

Precautions/Drugs Metabolized by Cytochrome $P_{450}IIA_4$: In light of our in-vitro studies, we have revised this section as follows:

> ***Drugs Metabolized by Cytochrome P450IIIA4*** : Paroxetine is a weak inhibitor of cytochrome $P_{450}IIIA_4$, which is involved in the metabolism of drugs such as alprazolam, terfenadine, astemizole, triazolam, cisapride and cyclosporin. In *in vitro* studies, ketoconazole, a potent inhibitor of P450IIIA4 activity in human liver, was at least 100 times more potent than paroxetine as an inhibitor of $P_{450}IIIA_4$ activity for these substrates. In a clinical study involving coadministration of paroxetine and terfenadine at steady state conditions, paroxetine had no effect on terfenadine pharmacokinetics, and there was no alteration of QTc. Based on these data, concurrent administration of Paxil with $P_{450}IIIA_4$ substrates would be not be expected to pose a hazard.

Pregnancy: We have revised the last sentence to be in keeping with a Class C warning. It now reads: " . . . this drug should be used during pregnancy only if the potential benefit justifies the risk."

Adverse Reactions
Associated with Discontinuation of Treatment: The incidence of withdrawals in clinical trials in depression was changed to reflect updated numbers. The incidence of withdrawals was changed to 20% (1,199/6,145).

Millo

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: March 15, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Paxil Panic Approvable Action: NDA 20-031 S-009

TO: File NDA 20-031 s-009

This memorandum explicates the basis for my decision to issue an approvable action letter for S-009 tc NDA 20-031; approval of the supplement will allow Paxil™ [paroxetine] to be marketed as a treatment for Panic disorder.

Paxil: current regulatory status

Paxil™ [paroxetine] is an SSRI currently marketed for the treatment of depression at maximum daily doses of 50 mg. A Supplement (007) for Paxil's use (@ 40-60 mg/d) in the management of Obsessive Compulsive Disorder [OCD] was declared approvable in October of 1995; the sponsor's response to that action is currently under review by the Division.

Panic Disorder Supplement[submitted 3/29/95]

Effectiveness

The review team, headed by Dr. Laughren, finds the reports submitted to supplement S-009 sufficient to support the claim that Paxil, administered at a daily dose of 40 to 60 mg, will be effective for use in the "treatment of panic attacks in patients with Panic Disorder, with or without agoraphobia, as defined in DSM-IV."

Although I do not have anything of substantive importance to add to Dr. Laughren's analysis and summary of these 3 positive trials, I prefer that a different claimed indication be granted (see discussion below). Before dealing with the matter of the wording of the claim, I will summarize my understanding of the review team's findings.

In his memorandum of January 31, 1996, Dr. Laughren identifies 3 adequate and well controlled clinical investigations as sources of the substantial evidence supporting the sponsor's claims: 1) **Study 120**[1], a 10 week long, parallel, multiclinic (20 centers) fixed dose comparison of 10, 20 and 40 mg a day of Paxil with placebo, 2) **Study 108**, a 12 week long, parallel, placebo controlled investigation, conducted at 7 centers in Denmark, in which Paxil was titrated from a daily minimum dose of 20 mg to a maximum daily dose of 60 mg, and 3) **Study 187**[2], a 12 week long, parallel, multiclinic (39 centers, mostly in Europe) investigation that compared paroxetine (range of 20 to 60 mg/day) to both clomipramine (range of 50 -150 mg a day) and placebo.

A fourth RCT, **Study 223**, comparing flexible doses of paroxetine (10 to 60 mg a day) with both placebo and alprazolam (1 to 6 mg a day on a bid schedule) failed to discriminate either drug[3] from placebo. Because alprazolam (Xanax™) is approved for the use in the management of Panic Disorder, this trial is consider 'failed,' rather than negative.

The patients enrolled in each positive study appear reasonably representative of at least some patients in the population of patients with Panic Disorder that will be treated with Paxil if it is approved for this indication.

The set of outcome assessment methods[4] employed in these studies also seems appropriate. The decision to rely on a single, primary, outcome measure as the basis for the regulatory assessment of the effectiveness of Paxil is somewhat controversial, however.

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[1] This study had a double blind extension phase, "extension 222."

[2] This study had a double blind extension phase, 228

[3] There is some indication that alprazolam randomized patients do better than those assigned to placebo, however, the effect is small and detected on only some of the many outcomes measured.

[4] Response to treatment in each of the 3 studies was evaluated with assessments that, on face, are capable of measuring the intensity of the symptoms that are considered by most experts to be core manifestations of Panic Disorder (e.g., discrete panic attacks, anticipatory anxiety, phobic avoidance).

Some experts, especially those who believe that the disabling features of the syndrome are tied more closely to anticipatory anxiety, phobic avoidance, (in the extreme, agoraphobia) and "secondary" depression, than to the frequency of Panic attacks, may find the Division's reliance on panic attack frequency alone as an ill-informed choice. Clearly, the agency could demand that a sponsor show an effect both on panic attack frequency and the disabling phenomena that comprise the complete set of clinical manifestations that characterize the full blown Panic Disorder syndrome. While such a requirement may on first impression seem attractive, it would make it more difficult, if not impossible, for sponsors to gain approval of drugs with the ability to suppress the frequency of panic attacks.

In my judgment, therefore, the imposition of the more demanding requirement could not be justified from a regulatory perspective because it would preclude a sponsor from gaining approval of a drug with a demonstrable clinical benefit of unarguable value. Panic attacks, it should be emphasized, are not meaningless epiphenomena or surrogates, but dysphoric events. Accordingly, from a regulatory perspective, a drug with a demonstrated capacity to reduce panic attack frequency alone must be deemed effective in use.

The discussion of this matter brings up yet another controversial issue that, although not directly relevant to this decision on Paxil, is important vis a vis claims that sponsors might make for effects on phenomena seen in patients with Panic Disorder. What claim or claims should be granted to the sponsor of a drug, for example, that has no demonstrable effect on the frequency of panic attacks, but does ameliorate other manifestations of the syndrome (e.g., phobic avoidance, depression, etc.)?

A treatment with the capacity to reduce anxiety, depression, or phobic avoidance would, despite a lack of an effect on panic attack frequency, be quite beneficial. The regulatory problem presented by such a treatment is that the effects enumerated are not unambiguously anti-panic effects. Accordingly, any agreement to label a product with such actions as an anti-Panic agent, would open the door to any number of 'pseudospecific' anti-panic claims being made by sponsors of products already marketed as anxiolytics or antidepressants[5].

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[5] The issue turns on the distinction between a drug that has an effect on a specific disorder, or manifestations unique to that disorder, and one that has an effect on phenomena common to many disorders. Morphine, for

Fortunately, in my view at least, the controversy surrounding an action on Paxil can be largely avoided.

First, we can grant the sponsor a general claim for effectiveness in the management of Panic Disorder, relying, as we do in antidepressant drug labeling, on the remainder of the Indications section to describe the basis of the outcome relied upon in clinical trials to justify this claim. I discussed this alternative with Dr. Laughren and he agrees that it is preferable.

Second, the evidence adduced in the 3 positive trials also documents, albeit less robustly, that Paxil has statistically significant effects on measures of both fear and avoidance. Indeed, relative to those assigned to placebo, Paxil randomized subjects even exhibit improvements on assessments believed to measure social, work and family adjustment (i.e., Study 120 @ 40 mg/d and Study 187[6]).

It is worthy of note that short term randomized controlled trials of the kind employed by the sponsor are often faulted because they evaluate the effectiveness of a drug intended for chronic use (i.e., years) over a relatively brief interval of time (i.e., weeks). The problem, of course, is hardly unique to treatments for Panic Disorder. In any case, in recent years, attempts to develop evidence of efficacy in sustained use have become more common, in part due to our demands, in part as a result of pressure from those in the ranks of academe.

As noted above, two of the trials submitted in this supplement had double blind extensions.

Study 228, an extension of 187 was basically a continuation design that relied on comparisons made among groups not created through randomization; accordingly, it has no clear cut interpretation vis a vis effectiveness in extended use.

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example, may reduce the pain of metastatic carcinoma, but it is an analgesic, not a treatment for metastatic carcinoma.

[6] In fact, the effects on family, work and social adjustment are more robust and consistent over time in Study 187 than are the effects on panic attack, a somewhat surprising finding.

Study 222, an extension of Study 120, however, provided for re-randomization of subjects who had not relapsed after 3 months of extended treatment to either their randomized treatment or placebo. Among the 37 paroxetine patients in the extended phase who met criteria and had been re-randomized to placebo, 11 (30%) suffered a relapse. Among the 43 paroxetine patients re-randomized to continue their paroxetine dose, 2 or 43 relapsed (5%). (N.B. placebo responders were not re-randomized). These results, although not as robust as we might prefer, are evidence that paroxetine treatment continues to benefit some Panic Disorder patients in extended use. Accordingly, I found the last paragraph of the review team's proposed indications section too severe when it asserted that " the effectiveness of Paxil in long-term use...has not been systematically evaluated in controlled trials." I discussed this with Dr. Laughren and we agreed that it would be more accurate to say that the effectiveness of Paxil in long-term use has not been definitively documented (or words to that effect.)

Safety in use

Paxil is a marketed drug product and the question of its safety in use is, therefore, largely settled. Admittedly, a drug might be deemed reasonably safe for use in one condition and not another, either because of fundamental differences in the intrinsic nature of the patients treated or the severity of the illness being treated. For the record, it is important to note that the risks of Paxil are unlikely to differ as a function of the disease treated (i.e., I expect OCD and Panic patients to be at equivalent risk biologically). More critically, the benefits of Paxil in the management of Panic Disorder seem as likely to outweigh its risks as when the product is used to treat OCD.

Labeling

Again, because Paxil is a marketed product, its labeling is largely acceptable from a regulatory standpoint as is. Ordinarily, we would only have to modify it to the extent required to address Panic Disorder specific issues.

I have already discussed my views on the wording of the Claimed Indication (see effectiveness section.)

Our action on this Panic supplement (S-009) is complicated, however, by the fact that paroxetine is an inhibitor (in vitro) of CYP 450 3A4 and we are currently in the midst of an effort aimed at producing uniformity of labeling

among SSRI and related serotonergic drug products[7] vis a vis the potential consequences of their capacity to inhibit this critical isozyme.

We are in possession of preliminary report of the results of a bio study that indicate that paroxetine, despite its in vitro capacity to inhibit 3A4, has no effect on terfenidine clearance in vivo when it is at steady state and administered at 20 mg a day (a low dose). While some deem it possible to extrapolate from paroxetine's lack of effect on terfenidine to a conclusion that it will not reduce the clearance of other 3A4 substrates (astemizole, cisapride, triazolam), one cannot be certain. Accordingly, we are striking a compromise. Rather than contraindicating Paxil's use with the enumerated products (as we have previously proposed), we will have its labeling provide a Warning which describes the problem, gives the results of the terfenidine bio study and explains why there are persisting residual concerns about the remaining products.

Conclusion:

Our review of Supplement 009 documents that SmithKline Beecham has provided reports of tests that show that Paxil is safe for use and effective in use as for the management of Panic Disorder. Accordingly, I am issuing an approvable action letter.

Paul Leber, M.D.
3/15/96

[7] The sponsors of Prozac [fluoxetine], Zoloft[sertraline], and Paxil [paroxetine], have been asked to contraindicate the use of these drugs with terefenidine, astemizole, and cisapride. More recently, concerns have arisen about triazolam as well. Luvox [fluvoxamine] and Serzone [nefazodone] already carry these contraindications. The need for a contraindication arises because the first 3 drugs identified are potentially cardiotoxic and are eliminated metabolically primarily via a 3A4 enzymatic pathway. Although less likely to be fatal, the presumed narrowness of triazolam's therapeutic ratio makes its administration with a 3A4 inhibitor imprudent.

Cc: NDA 20-031; S-009

HFD-100
Temple
HFD-120
Katz
Laughren
Fitzgerald
Andreason
Dubitsky
David
HFD-713
Nevius
Hoberman

Mille

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 31, 1996

FROM: Thomas P. Laughren, M.D. TPL
Group Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for
Paxil (paroxetine) for Panic Disorder (PD)

TO: File NDA 20-031/S-009
[Note: This overview should be filed with the 3-29-95 original submission.]

1.0 BACKGROUND

Paxil (paroxetine) is a selective serotonin reuptake inhibitor (SSRI) that was approved for the treatment of depression in December, 1992 (NDA 20-031). Supplement S-009 includes data from clinical trials supporting the use of paroxetine in the treatment of panic disorder (PD), in a dose range of 40-60 mg/day [Note: The maximum recommended dose in currently approved labeling is 50 mg/day.].

Since the proposal is to use the currently marketed paroxetine formulations for this new indication, there was no need for substantial chemistry, pharmacology, or biopharmaceutics reviews of this supplement. Consequently, the focus was on clinical data. The safety and efficacy data were reviewed by James Knudsen, M.D. The efficacy data were also examined by Japo Choudhury, Ph.D. from the Division of Biometrics.

The original supplement for PD was submitted 3-29-95. The review was based on the original submission plus amendments containing responses to requests for additional information, including a 7-7-95 amendment providing data for extension study 222.

At the present time, Xanax (alprazolam), a triazolobenzodiazepine, is the only drug approved for the panic disorder indication in the US. However, a number of other drugs are believed to be effective and are widely used for the treatment of this indication, including other benzodiazepines, the tricyclic antidepressants, MAOIs phenelzine in particular), and other SSRIs.

All p-value data presented refer to 2-sided p-values. Alpha was set at 0.05, except for study 120, where Dunnet's test was used, and the criterion p-value was set at p , 0.019.

5.1.1.1 Study 120

This was a randomized, 20-center (US and Canada), double-blind, parallel group, 10-week, fixed-dose study comparing paroxetine at 3 fixed doses [10, 20, and 40 mg/day; titration up to the two higher dose groups by adding 10 mg/day at week 2 (for the 20 mg and 40 mg groups) and 20 mg/day at week 3 (for the 40 mg group); qd schedule] and placebo for the treatment of PD in adult outpatients meeting DSMIIIR criteria for PD. Patients were required to have at least 2 full panic attacks (i.e., ≥4 of the DSMIIIR criteria for a panic attack) in the 2 week period between screening and baseline. Patients could have sufficient depressive symptoms to meet criteria for major depressive disorder, providing the panic disorder symptoms were considered primary.

Patients completed a Panic Diary and an Anticipatory Anxiety Assessment (AAA) daily. Patients were rated at baseline and the ends of weeks 1, 2, 3, 4, 6, 8, and 10 on the following: Panic Diary and AAA (investigator summarized the information from these instruments); and CGI [range 1-7, for both improvement (I) and severity (S) scales]. Patients were rated at baseline and the ends of weeks 4 and 10 on the following: Marks-Sheehan Phobia Scale (MSPS); Sheehan Disability Scale (SDS).

Reduction in the number of full panic attacks was identified as the primary efficacy variable, using 3 approaches (all with reference to an interval of the previous 2 weeks): (1) proportion of patients having zero full panic attacks, (2) proportion of patients having ≥ 50% reduction from baseline in the mean number of full panic attacks, and (3) mean change from baseline in the number of full panic attacks.

The following variables (mean change from baseline) were derived from the secondary assessments:

- MSPS-Fear Score
- MSPS-Avoidance Score
- AAA-% Time Worrying
- AAA-Intensity of Attacks
- SDS-Work Score
- SDS-Social Life Score
- SDS-Family Life Score

Patients were predominantly female (approximately 2/3), predominantly Caucasian, and the mean age was mid 30's. The treatment groups were comparable at baseline on the demographic and the key efficacy variables.

Summary of Significance Levels[1] (2-Sided) for Pairwise Comparisons (Paroxetine vs Placebo) in Study 120

Key Outcome Variables	Paroxetine Dose Groups														
	10 mg					20 mg					40 mg				
	Week[2]					Week					Week				
	2	4	6	8	10	2	4	6	8	10	2	4	6	8	10
No. Panic Attacks															
Proportion Zero															
LOCF	-	-	-	-	-	-	-	-	-	-	-	*	-	*	*
OC	-	-	-	-	-	-	-	-	-	-	-	*	-	-	*
Proportion ≥ 50% ↓															
LOCF	-	-	-	-	-	-	-	-	-	-	t	t	-	-	-
OC	-	-	-	-	-	-	-	-	-	-	t	t	t	-	-
Mean Δ Baseline															
LOCF	-	-	-	-	-	-	-	-	*	*	-	*	*	*	*
OC	-	-	-	-	-	-	t	-	t	-	-	*	*	*	*
CGI Severity															
LOCF	-	-	-	-	-	-	-	-	-	-	-	-	-	t	*
OC	-	-	-	-	-	-	-	-	-	-	-	-	t	t	*
MSPS-Fear Score															
LOCF		-		-			-		*			*			*
OC		-		-			-		*			*			*
MSPS-Avoidance Score															
LOCF		-		-			-		-			-			*
OC		-		-			-		-			-			-
AA-% Time Worrying															
LOCF	-	-	-	-	-	t	-	-	-	-	*	-	-	-	t
OC	-	-	-	-	-	t	-	-	-	-	*	-	*	-	-
AA-Intensity															
LOCF	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SDS-Work Score															
LOCF		-		-			-		*			-			*
OC		-		-			-		-			-			-
SDS-Social Life Score															
LOCF		-		-			-		t			-			t
OC		-		-			t		t			-			t
SDS-Family Life Score															
LOCF		-		-			-		*			-			-
OC		-		-			-		-			-			-

1 * = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$
* = $p \leq 0.019$ (criterion p-value for Dunnett's Test)

2 End of weeks 2, 4, 6, 8, and 10

Impression: I considered this study positive on 2 of the 3 panic attack variables and also for CGI severity and the MSPS fear score, but only for the 40 mg/day dose. [Note: Technically, this study didn't make it for zero panic attacks and CGI-Severity in the LOCF analyses at endpoint. However, in both cases, the p-values missed the Dunnet's criterion value by only a few hundredths of a percent, and I consider these results close enough. In support of this finding, in both cases there was a significant linear relationship between dose and response.] There was no demonstrable effect on the other secondary variables, however, this is not too surprising. The study duration may have been too short to expect to see behavioral changes, e.g., in avoidance and overall functioning (SDS). In addition, the assessment for anticipatory anxiety may not have been sensitive enough to detect change. The effect size seen in terms of change in panic attack frequency was actually quite impressive, with drug treated patients (40 mg/day) going from an average of about 10 attacks/2 weeks at baseline to about 2 attacks/2 weeks at endpoint, compared to a reduction from about 10 to 5 for placebo patients. I consider that a clinically meaningful effect and I consider this a positive study in support of the 40 mg/day dose.

5.1.1.2 Study 108

This was a randomized, 7-center (Danish), double-blind, parallel group, 12-week, flexible-dose study comparing paroxetine in a dose range of 20-60 mg/day (on a qd schedule) and placebo for the treatment of PD in adult outpatients meeting DSMIIIR criteria for PD. All patients also received standard cognitive behavior therapy. Patients were required to have at least 3 panic attacks (type not specified) in the 4 week period between screening and baseline. Patients could have sufficient depressive symptoms to meet criteria for major depressive disorder, providing the panic disorder symptoms were considered primary.

Patients completed a Panic Diary daily. Patients were rated at baseline and the ends of weeks 3, 6, 9, and 12 on the Panic Diary (investigator summarized the information from this instrument) and the CGI.

Reduction in the number of panic attacks was identified as the primary efficacy variable, using 3 approaches (all with reference to an interval of the previous 3 weeks): (1) proportion of patients having zero or 1 panic attack, (2) proportion of patients having $\geq$ 50% reduction from baseline in the mean number of panic attacks, and (3) mean change from baseline in the number of panic attacks.

Patients were predominantly female (approximately 3/4), and the mean age was mid 30's. The treatment groups were comparable at baseline on the demographic and the key efficacy variables. The mean paroxetine dose at 12 weeks in completers was 40 mg/day.

Size of Treatment Effect in Study 108			
Proportion of Patients with Panic Attacks ↓ to Zero or 1			
Group	Baseline[1]	Wks 9-12	Difference[2]
Placebo	-	14%	
Paroxetine	-	33%	19%
Proportion of Patients with ≥ 50% ↓ in Panic Attacks			
Group	Baseline[1]	Wks 9-12	Difference[2]
Placebo	-	47%	
Paroxetine	-	79%	32%
Number of Panic Attacks/3 Weeks			
Group	Baseline[3]	BL - Wk 12[4]	Difference[5]
Placebo	26.4	- 10.0	
Parox. 10 mg	21.2	- 15.0	5.0
CGI Severity Score			
Group	Baseline[3]	BL - Wk 12[4]	Difference[5]
Placebo	4.3	- 1.3	
Parox. 10 mg	4.3	- 2.1	0.8

1 Baseline score not relevant for this variable
2 Difference between drug and placebo in proportion of patients meeting criteria in weeks 9-12
3 Mean score at baseline
4 Mean Change from baseline to week 12 (LOCF)
5 Difference in mean change from baseline to week 12 endpoint (LOCF) between paroxetine and placebo

Impression: I considered this study positive on 2 of the 3 panic attack variables and also for CGI severity. It isn't clear why this study didn't make it on mean change from baseline in panic attack frequency. It may have been underpowered for this variable. In any case, the results were significant and clinically meaningful for both of the other panic attack variables. Thus, I consider this a second positive study in support of paroxetine in a dose range of 20-60 mg/day.

5.1.1.3 Study 137

This was a randomized, 39-center (international, mostly European), double-blind, parallel group, 12-week, flexible-dose study

Summary of Significance Levels[1] (2-sided) for Pairwise Comparisons (Parox. & Clomip. vs Placebo) in Study 187		
Key Outcome Variables	Parox. vs Pbo.	Clomip. vs Pbo
	Week[2] 3 6 9 12	Week 3 6 9 12
No. Panic Attacks		
Proportion Zero		
LOCF	- * * *	- - - *
OC	- t * -	- - - t
Proportion ≥ 50% ↓		
LOCF	- t * *	- - - -
OC	- - - -	- - - -
Mean Δ Baseline		
LOCF	- - t *	- - - -
OC	- - - -	- - - -
CGI Severity		
LOCF	t * * *	- * * *
OC	* * * *	- * * *
MSPS-Fear Score		
LOCF	- t * *	- * * *
OC	- * * *	- * - *
MSPS-Avoidance Score		
LOCF	- * t *	- - t *
OC	- * - *	- - t *
SDS-Work Score		
LOCF	* * * *	- * * *
OC	* * * *	- * * *
SDS-Social Life Score		
LOCF	* * * *	- * * *
OC	* * * *	- * * *
SDS-Family Life Score		
LOCF	* * * *	* * * *
OC	* * * *	* * * *

1 * = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$

2 End of weeks 3, 6, 9, and 12

would like to have seen an analyses of scores on these variables for dropouts from each of these groups (e.g., were paroxetine dropouts doing better than placebo dropouts?), I am not particularly troubled by this discrepancy, given the overwhelmingly positive findings on the CGI-Severity and all the secondary variables.] Consequently, I believe this study provides additional support for the effectiveness of paroxetine in panic disorder.

5.1.1.4 Study 223

This was a randomized, 16-center (US), double-blind, parallel group, 10-week, flexible-dose study comparing paroxetine (in a dose range of 10-60 mg/day; qd schedule), alprazolam (in a dose range of 1-6 mg/day; bid schedule), and placebo for the treatment of PD in adult outpatients meeting DSMIIIR criteria for PD. Patients were required to have at least 2 full panic attacks (i.e., ≥4 of the DSMIIIR criteria for a panic attack) in the 2 week period between screening and baseline. Patients could have sufficient depressive symptoms to meet criteria for major depressive disorder, providing the panic disorder symptoms were considered primary.

Patients completed a Panic Diary and an Anticipatory Anxiety Assessment (AAA) daily. Patients were rated at baseline and the ends of weeks 1, 2, 3, 4, 6, 8, and 10 on the following: Panic Diary and AAA (investigator summarized the information from these instruments); and CGI. Patients were rated at baseline and the ends of weeks 4 and 10 on the following: Marks-Sheehan Phobia Scale (MSPS); Sheehan Disability Scale (SDS).

Reduction in the number of full panic attacks was identified as the primary efficacy variable, using 3 approaches (all with reference to an interval of the previous 2 weeks): (1) proportion of patients having zero full panic attacks, (2) proportion of patients having ≥ 50%reduction from baseline in the mean number of full panic attacks, and (3) mean change from baseline in the number of full panic attacks.

The following variables (mean change from baseline) were derived from the secondary assessments:

MSPS-Fear Score
MSPS-Avoidance Score
AA-% Time Worrying
AA-Intensity
SDS-Work Score
SDS-Social Life Score
SDS-Family Life Score

Patients were approximately 2/3 female, predominantly Caucasian, and the mean age was late 30's. The treatment groups were generally comparable at baseline on the demographic and the key

Summary of Significance Levels[1] (2-sided) for Pairwise Comparisons (Parox. & Alpraz. vs Placebo) in Study 223										
Key Outcome Variables	Parox. vs Pbo.					Alpraz. vs Pbo				
	Week[2] 2	4	6	8	10	Week 2	4	6	8	10
No. Panic Attacks										
Proportion Zero										
LOCF	-	t	-	-	-	-	-	-	-	-
OC	-	t	-	-	-	-	-	-	-	-
Proportion ≥ 50% ↓										
LOCF	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-
Mean Δ Baseline										
LOCF	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-
CGI Severity										
LOCF	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-
MSPS-Fear Score										
LOCF	-		t			*		-		
OC	-		-			t		-		
MSPS-Avoidance Score										
LOCF	-		-			*		-		
OC	-		-			*		-		
AA-% Time Worrying										
LOCF	-	-	-	-	-	*	-	*	*	-
OC	-	-	-	-	-	*	-	*	-	-
AA-Intensity										
LOCF	-	-	-	-	-	*	-	*	t	-
OC	-	-	-	-	-	*	-	-	-	-
SDS-Work Score										
LOCF	*		t			-		-		
OC	t		-			-		-		
SDS-Social Life Score										
LOCF	t		*			-		-		
OC	t		-			-		-		
SDS-Family Life Score										
LOCF	*		*			-		-		
OC	*		-			-		-		

1 * = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$

2 End of weeks 2, 4, 6, 8, and 10

5.1.1.5 Study 228

This was an extension of study 187. Patients from any of the 3 treatment groups who completed study 187 and had no significant adverse events could be continued for up to 9 months, on a double-blind basis, on the same treatment and dose as in the short-term phase. Assessments were the same as in the short-term phase, but at 6-week intervals. In addition, definitions were provided for categorizing patients as having had partial or full relapse during the extension phase.

A major problem with this study was the fact that the original randomization was violated, in that only completers meeting the identified criteria were continued. Consequently, it is of descriptive value only, and I will not provide detailed comments. However, overall the results did not substantially favor paroxetine over placebo. There were few relapses and no statistically significant differences between groups in number of relapses or time to relapse.

5.1.1.6 Study 222

This was an extension of study 120. Patients who completed study 120, had no significant adverse events, and met criteia for being either partial or full responders could be entered into study 222. [Partial response = ≥ 50% reduction in full panic attacks during weeks 9-10; full response = no full panic attacks during weeks 9-10.]

The first 3 months of study 222 was a double-blind maintenance phase during which patients were continued on their previously assigned treatment and dose. Patients who were responders during the last 2 weeks of the maintenance phase and had not "relapsed" during that 3 month period could enter the 3-month re-randomization phase, which involved randomization to either their previous treatment and dose (placebo or paroxetine 10, 20, or 40 mg/day), or to placebo. The key outcomes during this phase were percent relapse and time to relapse. [A patient relapsed if frequency of full panic attacks per two weeks was ≥ that observed at baseline for study 120, or there was an increase of ≥ 2 points on CGI severity, relative to the score at week 12 of the maintenance phase.]

For the primary analysis, patients randomized from placebo to placebo were not included (not planned this way in protocol). The relapse rates for the remaining groups were as follows:

10 mg to pbo	2/12 (17%)
20 mg to pbo	2/12 (17%)
40 mg to pbo	7/13 (54%)
Total Parox to pbo	11/37 (30%)
10 mg to 10 mg	0/12 (0%)

Size of Treatment Effect in Three Panic Disorder Studies for Key Efficacy Variables at 10- or 12-Week Endpoint (LOCF)			
Study 120			
Variables	Paroxetine[1,2]	Placebo[2]	Difference[3]
# Panic Attack			
↓ to Zero	76%	44%	32%
≥ 50% ↓	89%	74%	15%
# Full PA	- 8.2	- 5.5	2.7
CGI Severity	- 1.8	- 1.3	0.5
Study 108			
Variables	Paroxetine[1,2]	Placebo[2]	Difference[3]
# Panic Attack			
↓ to 0/1	33%	14%	19%
≥ 50% ↓	79%	47%	32%
# Full PA	- 15.0	- 10.0	5.0
CGI Severity	- 2.1	- 1.3	0.8
Study 187			
Variables	Paroxetine[1,2]	Placebo[2]	Difference[3]
# Panic Attack			
↓ to Zero	51%	33%	18%
≥ 50% ↓	80%	62%	18%
# Full PA	- 12.2	- 8.5	3.7
CGI Severity	- 1.9	- 1.0	0.9

1 Data from 40 mg/day group

2 Proportions of patients meeting criteria for response in last observation interval, for zero panic attacks and ≥ 50% ↓ variables; mean change from baseline to 10- or 12-week endpoint for # panic attacks and CGI-Severity

3 Difference between paroxetine and placebo in proportions meeting criteria for zero panic attacks and ≥ 50% ↓ variables; difference between paroxetine and placebo in mean change from baseline to 10- or 12-week endpoint for # panic attacks and CGI-Severity

depression, and no reports were available for patients identified as being treated with paroxetine for Panic Disorder.

For the integrated PD database, paroxetine-exposed patients ranged in age from 18-74 (mean=36), were 65% female, and were 78% caucasian. The exposure tended to be short-term, however, about 29% were exposed for greater than 6 months. About 75% of patients received mean doses in a range of 16-60 mg/day.

There were no deaths among the paroxetine-exposed patients in the integrated database for the panic disorder studies.

A search of the integrated database for serious events yielded a total of 13 among paroxetine-exposed patients. Neither the numbers nor types of events were unexpected for this population. A search for suicidality also did not reveal any indication of a paroxetine-associated risk for suicidal behavior.

The common and drug-related adverse events leading to dropout (incidence $\geq$ 1% and at least twice the placebo rate) included: nausea, insomnia, and somnolence. This list overlapped with comparable lists for depression and OCD databases, however, included fewer adverse events overall.

The common and drug-related adverse events overall (from the integrated database; incidence $\geq$ 5% and at least twice the placebo rate) included: asthenia, decreased appetite, tremor, sweating, abnormal ejaculation, impotence, libido decreased, and female genital disorders (mostly anorgasmia or difficulty reaching orgasm). This list was also similar to the adverse events associated with paroxetine in the depression and OCD databases.

Three of the 4 short-term trials had a run-out phase during which assigned treatments were tapered and withdrawn (periods ranged from 3-6 weeks). Overall, 390 patients were discontinued in this manner, including 155 from paroxetine, 60 from alprazolam, 27 from clomipramine, and 148 from placebo. The incidence of dropout from this tapered withdrawl for adverse events was as follows:

Paroxetine	6/155	(4%)
Alprazolam	1/60	(2%)
Clomipramine	1/27	(4%)
Placebo	0	

The most common reasons for paroxetine patients leaving the scheduled tapering were headache, agitation, and depression.

Explorations of the integrated database for laboratory and vital signs variables, including analyses of change from baseline, analyses of proportions of patients meeting criteria for potentially clinically significant change on these variables, and

10.2 Foreign Labeling

To my knowledge, Paxil is not approved for PD anywhere at this time.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a safety update, a literature update, a regulatory status update, and a commitment to conduct a relapse prevention trial.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that SKB has submitted sufficient data to support the conclusion that Paxil is effective and acceptably safe in the treatment of Panic Disorder. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

cc:
Orig NDA
HFD-120
HFD-120/TLaughren/PLeber/GDubitsky/JKnudsen/MMille

DOC: MEMPAXPD.AE1

EXCLUSIVITY SUMMARY FOR NDA # 20-031 SUPPL # S-009 (SE1)

Trade Name PAXIL Generic Name PAROXETINE HCL

Applicant Name SmithKline Beecham HFD # 120

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /___/ NO /X/

b) Is it an effectiveness supplement?

YES /X/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA # ~~20-031~~. Drug Name ~~Paxil~~ _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /X/ NO /X/

Investigation #2 YES /X/ NO /X/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

____ _____

____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES /X/ NO /___/ Explain: _____

Investigation #2

IND # YES /X/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

_____ _____

Signature Date

Title: _____

_____ _____

Signature of Office/ Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Ward

SB
SmithKline Beecham
Pharmaceuticals

3 November 1994

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Rm. 2-14
12420 Parklawn Dr.
Rockville, MD 20857

Re.: NDA 20-031
Patent Information

The following patent information is being submitted pursuant to Title II of Pub. L. 98-417.

Patent information

Patent #	Expiry Date	Type of Patent	Patent Owner
4 721 723	Dec. 29, 2006	Drug, Drug Product, and Method of Use	Beecham Group p.l.c., Brentford, England

Declaration

The undersigned declares that U.S. Patent No. 4 721 723 covers the formulation, composition and method of use of paroxetine hydrochloride hemihydrate to treat depression. This product is currently approved under Section 505 of the Federal Food Drug and Cosmetic Act: NDA 20-031.

Respectfully submitted,
SmithKline Beecham Corporation

By: _____
Robert L. Powell, Ph.D.
V.P., U.S. Regulatory Affairs
and Product Professional
Services

SB
SmithKline Beecham

3 November 1994

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Rm. 2-14
12420 Parklawn Dr.
Rockville, MD 20857

Re.: Supplement to NDA 20-031
Patent Information

The following patent information is being submitted pursuant to Title II of Pub. L. 98-417.

Patent #	Expiry Date	Type of Patent	Patent Owner
4 721 723	Dec. 29, 2006	Drug	Beecham Group p.l.c., Brentford, England

Respectfully submitted,
SmithKline Beecham Corporation

By:
Robert L. Powell, Ph.D.
V.P., U.S. Regulatory Affairs
and Product Professional
Services

Debarrment Certification

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, SmithKline Beecham certifies that, to the best of it's knowledge and belief, we did not and will not use in any capacity, in connection with this application, the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act.

MINUTES OF MEETING
IN-HOUSE
NDA 20-031/ S-009

DRUG: PAXIL® (paroxetine HCl) Tablets

APPLICANT: SmithKline Beecham Pharmaceuticals

DATE/TIME: May 16. 1995 / 01:30 pm - 02:30 pm

LOCATION: Conference Room 4023/ WOC2

ATTENDEES:

P. Leber	G. Fitzgerald	S. Blum
T. Laughren	S. Sparenborg	
J. Knudsen	G. Dubitsky	M. Mille

Consultants: HFD-713/ E. Nevius; J. Choudhury
HFD-344/ R. Young

SUBJECT: File/ Refuse-to-file Meeting

BACKGROUND:

Submission S-009 is an efficacy supplement for the treatment of panic anxiety disorder. This supplement is subject to user fees and the user fee due date is March 29. 1996. It should be noted that an efficacy supplement (S-007) was submitted to this same NDA approximately 4-months earlier.

CHEMISTRY:

The chemistry and manufacturing controls portion of the application is fileable. This supplement does not contain any new CMC data. An environmental assessment review will be required. However, this review will be identical in content to that prepared for S-007. Mona Zarifa. Ph.D. has been assigned as chemist to this project. Establishment Evaluation Request (EER) is not required.

PHARMACOLOGY:

The application is fileable from the standpoint of preclinical requirements. This supplement contains no new preclinical data. A pharmacology memo containing the same text for S-007 will be available by 5/17/95.

BIOMETRICS ISSUES:

With regard to statistical concerns, the application is fileable.
Three efficacy studies appear to be nominally positive as presented by the firm. Analyses by race, gender, and age have been performed on the safety data. With

Tab

SB
SmithKline Beecham
Pharmaceuticals

NDA NO 20-031 REF. NO. SE1-009
NDA [illegible] FOR [illegible] (Panic)

March 29, 1995

NDA 20-031
PAXIL® (paroxetine hydrochloride) Tablets
Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products (HFD-120)
Document Control Room
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20850

Efficacy Supplements to NDA 20-031
Panic Disorder
PAXIL® (paroxetine hydrochloride) Tablets

Dear Dr. Leber:

Reference is made to our New Drug Application for Paxil® (paroxetine hydrochloride) tablets for the treatment of depression, NDA 20-031, which was submitted on November 22, 1989 and approved on December 29, 1992. Reference is also made to our Pre-sNDA meeting on February 16, 1994 and our Investigational New Drug Application, IND 23,280.

We are submitting an efficacy supplement to NDA 20-031 to support the use of Paxil in the treatment of Panic Disorder. Our efficacy claim is primarily based on data from a total of 991 patients (469 were assigned to receive paroxetine, 77 to receive alprazolam, 121 clomipramine and 324 placebo) randomized to treatment in four double-blind placebo controlled multicenter studies: Protocols 29060/120, 29060/223, 29060/208, and 29060/187.

All four studies in the Panic Disorder program were double-blind, placebo-controlled and 10-12 weeks in duration. Study 120 was a fixed-dose study comparing daily doses of paroxetine (10mg, 20mg and 40mg) to placebo and was conducted in the US and Canada. The other three studies were of flexible-dose designs which allowed for higher doses to be achieved through dose escalation. Study 223 compared daily doses of paroxetine (10mg-60mg) and alprazolam (1mg-6mg) to placebo and was conducted in the US. Study 108 compared daily doses of paroxetine (10mg-60mg) to placebo and was conducted in Denmark. Study 187 compared paroxetine (10mg-60mg) and clomipramine (50mg to 150mg) to placebo and was conducted throughout Europe.

Studies 108, 187 and 120 individually and collectively demonstrated that patients improved substantially with respect to the frequency and intensity of panic attacks. These trials also demonstrated improvement for other important clinical features such as generalized and anticipatory anxiety, phobia, fear, avoidance, depressive symptomatology and the disability associated with work, social life and family life. These three studies provide evidence for the overall efficacy of paroxetine in the treatment of Panic Disorder. We note that, in Study 108, a significant effect of paroxetine was demonstrated in patient receiving concomitant behavioral therapy.

In addition, we have included the clinical report of Protocol 29060/228 (Vol 51.053, page 000002), the 9 month, double-blind extension of Protocol 29060/187. The results of this study indicate that the efficacy of Paxil in the treatment of Panic Disorder was maintained for up to one year.

The submission comprises a total 305 volumes, with the majority of these volumes representing individual patient documentation in the form of Case Report Forms (Volumes 51.444 to 51.305). Indices to individual patient documentation are contained with Item 11 (Volume 51.118, page 00002) and Item 12 (Volume 51.144, page 000002).

A listing which summarizes the 50 submissions which have been made to NDA 20-031 since November 29, 1992 is provided in Volume 51.001, page 000012. Brief descriptions of these submissions are given in this listing. For purposes of cross-referencing these submissions, the convention that has been followed in this supplement is to refer to the submission number and volume number. For example, reference to 51.015, page 000002 refers to the data included on page 000002 of the Volume 15 within submission 51.

Chemistry and manufacturing and control data submitted within the original NDA and subsequent supplements to the NDA are included by cross-reference as shown in the table of contents to Item 3 (Volume 51.001, page 000191).

Updated summaries of Non-Clinical Pharmacology and Toxicology and Human Pharmacokinetics and Bioavailability were provided with the efficacy supplement submitted for Obsessive Compulsive Disorder on December 7, 1994. These updates provided brief summaries of studies conducted since the submission of the original NDA. These summaries are included by cross-reference in this submission. The reports of these studies are included by cross-reference to IND Reports which have been submitted to IND are listed in the table of contents to each of these sections and are included by cross-reference in this submission.

Within the section 8.6 Other Studies and Information, we have included a listing of all clinical study reports that were submitted within the original NDA and have identified studies in depressed patients that have been conducted and/or completed since the initial submission of NDA 20-031. The status of these reports is identified and reports submitted to IND are included by cross-reference

SB
SmithKline Beecham

August 15, 1995

Mr. Merill Mille
Consumer Safety Officer
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
Woodmont II, 4th Floor
1451 Rockville Pike
Rockville, Maryland 20852

Re: NDA 20-031, Supplement 009
Paxil® (paroxetine hydrochloride) Tablets
Desk Copy: Clinical Report,
Protocol 29060/222

Dear Mr. Mille:

Reference is made to our efficacy supplement to New Drug Application for PAXIL® (paroxetine hydrochloride) tablets, NDA 20-031, which was submitted on March 29, 1995.

As you requested, I am providing you with a copy of the clinical report of Protocol 29060/222 (SB Report No. MY-1050/BRL-029060/1/CPMS-222) for the statistical reviewer. The enclosed copy contains Volumes 1 to 3 and 25 to 28 of our submission of July 7, 1995. As you suggested, I have omitted the appendices containing case report forms (Appendix G: Volumes 04-21) and case report form tabulations (Appendix H: Volumes 22-24). If the statistical reviewer needs these volumes, we will provided them as requested. I would also note that the entire report and appendices are accessible on the electronic submission to the medical reviewer; access could also be arranged for the statistical reviewer.

Please do not hesitate to contact me at (610) 832-3712 should you have any questions regarding this submission.

Sincerely,

Michael J. Brennan, Ph.D.
Associate Director
U.S. Regulatory Affairs

1.0 Material Utilized in Review

1.1 Material from NDA Supplement 009

The following items were examined:

NDA Volume(s)	Date Submitted	Material Reviewed
51.001	March 29, 1995	Application Summary
51.017	March 29, 1995	Study Report: 120
51.027	March 29, 1995	Study Report: 223
51.035	March 29, 1995	Study Report: 108
51.039	March 29, 1995	Study Report: 187
51.053	March 29, 1995	Study Report: 228
51.060	March 29, 1995	Integrated Summary of Efficacy
51.061	March 29, 1995	Integrated Summary of Safety
51.144	March 29, 1995	Case Report Forms
52.1	July 3, 1995	Response to Agency Request
IND 23,280, Vol. 71.1	July 7, 1995	Study Report: 222
56.1-56.10	August 11, 1995	CRFs (for audit purposes)
58.1-58.2	September 15, 1995	Updated List of Publications

1.2 Related Reviews

NDA #20-031: Paxil in the treatment of depression, approved December 29, 1992
NDA #20-031-S-007: Paxil in the treatment of Obsessive Compulsive Disorder (OCD), submitted December 6, 1994 - approvable.

2.0 Background

2.1 Indication

Paroxetine is a selective serotonin reuptake inhibitor (SSRI) recently introduced into clinical practice in the United States for the treatment of depression. More recently, a supplemental NDA was submitted to the NDA to seek approval for the indication of OCD. The current supplemental submission is for the treatment of panic disorder.

Currently, only alprazolam (Xanax®), a benzodiazepine, is approved for the treatment of panic disorder in the United States. Alprazolam has been associated with physical and psychological dependence. Clomipramine (Anafranil®) is a TCA indicated for the treatment of OCD in the U.S. In Canada and some foreign countries, clomipramine is indicated for panic disorder. However, it is not approved for this indication in the United States. The safety profile of clomipramine is similar to other members of the TCA family. Another form of treatment of panic disorder is cognitive-behavioral therapy; this, however, involves considerable commitment by therapist and patient. Psychotherapy is not necessarily an alternative to pharmacotherapy, optimal treatment perhaps resulting from a culmination of the two.

Paroxetine has a different side-effect profile compared to alprazolam and clomipramine. Paroxetine has a side effect profile similar to other SSRIs and appears to be devoid of physical and psychological dependence.

2.2 Related INDs and NDAs

IND is the IND for paroxetine hydrochloride. There are no other INDs for the use of paroxetine in the treatment of panic disorder of which I am aware. There are no NDAs for other SSRIs in the treatment of panic disorder at the time of my review.

2.3 Administrative History

The following is a brief history of the IND and the NDA, including dates for submission of key amendments and critical meetings.

December 22,	1983	IND was submitted to study paroxetine in the treatment of depression.
November 22,	1989	NDA 20-031 was submitted for the treatment of depression.
December 29,	1992	Paroxetine was approved for the treatment of depression.
February 6,	1994	A pre-sNDA meeting ensued between the Smith Kline Beecham Company and the Division of Neuropharmacological Drug Products concerning the developmental programs for paroxetine in the treatment of obsessive compulsive disorder (OCD) and panic disorder.
March 29,	1995	sNDA 20-031/S-009 was received for paroxetine in the treatment of panic disorder.

2.4 Proposed Directions for Use

Paroxetine is indicated for the treatment of patients with panic disorder, with or without agoraphobia, as defined in DSM-IIIR for panic disorder.

The efficacy of paroxetine was established in three 10-12 week trials in patients with diagnoses which corresponded to the DSM-IIIR criteria for panic disorders with or without agoraphobia.

Usual initial dose:
Paroxetine should be administered at a single daily dose, usually in the morning. The recommended dose of paroxetine in the treatment of panic disorder is 40mg/day. The patient should be started on 10mg/day. Dose changes should occur in 10mg/day increments, according to the patient's response. Dose changes should occur in intervals of at least 1 week. Some patients may benefit from having their dose increased to a maximum of 60mg/day. In the clinical trials demonstrating the anti-panic effectiveness of paroxetine, patients were dosed in a range of 10-60mg/day.

While there are no systematic studies that indicate how long to continue paroxetine treatment, panic disorder is a chronic condition and it seems reasonable to consider continuation for a responding patient.

With respect to directions for use in the elderly, or debilitated, and patients with severe renal or hepatic impairment, it is indicated that the recommended initial dose be 10mg/day. Increases may then be made if indicated, however, dosage is recommended not to exceed 40mg/day.

As result of the new indication as well as an increase in the dosage range and extended use of paroxetine, three questions have arisen regarding use. Does the adverse event profile for paroxetine in the treatment of panic disorder patients vary from the adverse events commonly associated with the treatment of depression? With the dose increase to 60mg/day, is there in increase in the reporting frequency of adverse events? With the extension of use for 6 months or greater in panic disorder patients, particularly with an increase in dose, is there a greater frequency of adverse drug effects?

2.5 Foreign Marketing

As of July, 1995, paroxetine has not been approved for use in the treatment of panic disorder in foreign countries. However, as of January, 1995, paroxetine has been approved for the treatment of major depression in a total of 50 countries and marketed in 30 countries. The product has not been withdrawn from the market in any country for any reason.

3.0 Chemistry

Paroxetine is a marketed product. There are no chemistry, manufacturing or control issues to be addressed for this NDA supplement.

4.0 Animal Pharmacology

Updated summaries of non-clinical pharmacology and toxicology were provided with the efficacy supplements submitted for OCD on December 7, 1994. These summaries were included by cross-reference in the present submission for panic disorder. Pertinent findings from the evaluation of paroxetine in animal and biochemical models are summarized below. These data were submitted to the original NDA for the treatment of depression. Using an *in vitro*, model paroxetine has been demonstrated to be a potent inhibitor of [H^3]-5-HT uptake into synaptosomes prepared from rat and mouse whole brain, and selective regions of rat brain with a Ki in the low nanomolar concentrations. For comparison, the Ki (nM) for paroxetine has been 1.1 compared with fluvoxamine (6.2nM), clomipramine (7.4nM) and fluoxetine (25nM). Paroxetine has very weak effects on norepinephrine and dopamine reuptake and has little affinity for muscarinic, adrenergic, D_2, and H_1 receptors. This pharmacologic selectivity of paroxetine imparts potential advantages relative to a lack of cardiotoxicity and anticholinergic side-effects compared to tricyclics. Various animal models were used to assess cardiotoxicity and autonomic activity.

General toxicity studies conducted in rat and rhesus monkey for periods of up to 12 months did not reveal any findings that would be cause for concern. In a rat twelve month study only minimal toxic effects were observed at the 25mg/kg/day (approximately 25 times the maximum dose). Evidence of lipidosis was observed at this dose. This effect has also been demonstrated following administration of high dosages of lipophilic amines. There was no evidence of carcinogenicity in rats and mice following two years of dietary administration of paroxetine. No evidence of genotoxic potential was seen in a battery 5 *in vitro* and 2 *in vivo* tests.

Some segment II studies in the rat and rabbit did not indicate any teratogenic effect on the embryo, however, one rat study showed an increase in pup deaths during the first 4 days of lactation. This effect occurred at a dose equal, on a mg/kg basis, to a maximum human daily dose of 50mg/day. The "no effect dose" for rat pup mortality was not determined. It was not clear whether the observed deaths were related to an embryo toxic effect or due to exposure to paroxetine during lactation. There have been no controlled studies in pregnant women. Given this data, it is now recommended that paroxetine be used in pregnancy only if clearly indicated until this finding can be clarified. A change from Pregnancy Category B to Pregnancy Category C is now recommended.

Irreversible lesions were observed in the reproductive tracts of male rats after 2-52 weeks of dosing at 25X a maximum human dose (50mg/day) on a mg/kg basis, specifically vacuolation of epididymal tubular epithelium, atrophic changes in the seminiferous tubules, and arrested spermatogenesis.

The main feature of the metabolic and pharmacokinetic profile seen in the species examined was a similarity in profile to that seen in man. In all species, paroxetine was well absorbed and systemic availability was reduced by first-pass metabolism. The metabolism has been shown to be partially saturable, leading to disproportionate increases in plasma concentration on raising the dose. Paroxetine was extensively distributed. Clearance of paroxetine was almost entirely metabolic, via the same pathway in all species examined, with metabolites excreted in both urine and feces. *In vitro* studies have indicated that the metabolites of paroxetine are essentially inactive.

5.0 Description Of Clinical Data Sources

5.1 Primary Development Program

5.1.1 Study Type And Design/Patient Enumeration

The primary development program for paroxetine in the treatment of panic disorder consisted of four randomized double-blind, parallel group studies of 10-12 weeks in length. In addition, data from protocol 228, a double-blind extension of 187 and protocol 222, a double-blind extension of protocol 120 were submitted. All studies are summarized in Table 5.1.1.1, which follows.

Table 5.1.1.1

Table of Controlled Studies in Panic Disorder

Protocol [country(ies)]	Studies
108 (Denmark)	R, DB, parallel group, 7-center; 12 wk., flexible-dose trial, paroxetine vs. placebo, outpatients, panic disorder (N=approx. 60 in each 2 groups); paroxetine 10-60 mg/day and placebo. Both groups received standardized cognitive behavior therapy. PTs were discontinued abruptly at end of treatment phase.
120 (U.S./Canada)	R, DB, parallel group, 20-center; 10wk., fixed-dose trial, paroxetine vs. placebo; outpatients, panic disorder (N=approx. 70 in each of 4 treatment groups); paroxetine doses 10, 20 and 40mg/day, and placebo.
187 (Europe/Israel)	R, DB, parallel group, 39-center; 12 wk., flexible-dose trial, paroxetine vs. clomipramine vs. placebo; outpatients, panic disorder (N=approx. 122 in each of 3 treatment groups); paroxetine 10-60mg/day, clomipramine 10-150mg/day and placebo. Responders could continue DB therapy for an additional 9 mos. in study 228.
223 (U.S.)	R, DB, parallel group, 16-center; 10 wk., flexible-dose trial, paroxetine vs. alprazolam vs. placebo; outpatients, panic disorder (N=approx. 77 in each of 3 treatment groups); paroxetine 10-60mg/day, alprazolam 1-6 mg/day and placebo. After active treatment phase all patients down titrated during a 6-week run-out period.
228 (Europe/Israel)	DB, parallel group extension of 187, 32-center, 9-month study. Patients continued to receive same dose of medication as they had under study 187. Paroxetine, N-70; clomipramine N=64 and placebo N=46; paroxetine 20-60 mg/day, clomipramine 50-150 mg/day.
222 (U.S./Canada)	DB, parallel group extension of 120,18-center, 6-month study. Patients (N=approx. 35 in each of 4 treatment groups) continued to receive their respective treatment from study 120 during the 3 mo. maintenance phase. Responders entered "re-randomization" phase (3 mos. duration) and were re-randomized to their previous regimen (placebo, 10, 20, 40mg paroxetine) or to placebo.

The number of patients participating in the completed panic disorder trials is presented below.

Table 5.1.1.2

Enumeration by Treatment Groups in Controlled Panic Disorder Studies			
	PAROXETINE	PLACEBO	CONTROL+
Fixed Dose			
120	209*	69	0
222 (Ext. of 120)	(108)	(30)	(0)
Flexible Dose			
108	60	60	
187	123	123	121
223	77	72	77
228 (Ext. of 187)	(68)	(45)	(63)
TOTAL	469	324	198

* Paroxetine 10mg/day, N=67
Paroxetine 20mg/day, N=70
Paroxetine 40mg/day, N=72

\+ Clomipramine (studies 187 and 228) or, alprazolam (study 223).

( ) Denotes patients enrolled in extension trials and, therefore, not counted as part of the total, since they were counted in the short-term studies.

5.1.2 Demographics

Table 5.1.2 presents the demographic profile for patients participating in studies which make up the panic disorder integrated database.

As seen from table 5.1.2, the panic disorder patients were more often females, primarily Caucasian and less often elderly.

Table 5.1.2
Demographic Profile for Panic Disorder Studies

Overview of Demography All Studies								
Age	**Paroxetine N=469**		**Alprazolam N=77**		**Clomipramine N=121**		**Placebo N=324**	
(yrs)	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
16-24	52	11	11	14	17	14	36	11
25-34	170	36	18	23	42	35	110	34
35-44	149	32	23	30	40	33	107	33
45-54	75	16	17	22	20	17	54	17
55-64	18	4	5	7	2	2	16	5
≥65	5	1	3	4	0	0	1	0.3
Mean [+/-SD]	36 [+/10]		40 [+/-13]		35 [+/-9]		37 [+/-10]	
Range	18.0-74		18.0-71		19.0-57		18.0-67	
Gender								
Male	166	(35)	29	(38)	46	(38)	111	(34)
Female	303	(65)	48	(62)	75	(62)	213	(66)
Race								
Unk.	60	(13)	0	(0)		(0)	60	(19)
Cauc.	364	(78)	70	(91)		(100)	247	(76)
Non. White	45	(9)	7	(9)	0	(0)	17	(5)
Weight (kg)								
Mean [+/-SD]	73.3 [+/-17.7]*		76.0 [+/-16.5]		69.7 [+/-13.9]**		71.9 [+/-16.9]***	
Range	42-153		48-127		43-114		43-134	

Data source Adapted from Table 3 1a on p 12, volume 60
*n = 467
**n= 120 Data on weight was missing for 5 patients
***n = 322
Note In study 108 (n=120) which was conducted in Denmark, data on racial origin of the patients was not collected. This accounts for all of the patients whose racial origin was not collected

5.1.3 Extent of Exposure (dose/duration)

Table 5.1.3 is an enumeration of paroxetine-treated patients according to the mean total daily dose and duration of therapy for all studies (including 2 extension studies) in the panic disorder program. All patients started paroxetine treatment at a dose of 10mg daily. The maximum daily dose in study 120 was 40mg while it was 60mg/day in the remaining 3 studies. Ninety percent (420/469) of the patients received a mean daily paroxetine dose of at least 45mg. The majority of patients received treatment for up to 12 weeks. Twenty-nine percent of patients (137/469) received paroxetine for 6 months or more. Only 11 patients received upwards of 60mg/day of paroxetine for a year or longer.

Table 5.1.3
Enumeration of Paroxetine-Treated Patients According to Mean Daily Dose and Duration of Treatment

DURATION (in Weeks) **DOSE (Mean Daily Dose / mg)**

	0-15	16-25	26-35	36-45	46-55	56-60	Total	%
1	42	0	0	0	0	0	42	9.0
2	20	7	0	0	0	0	27	6.0
3	5	15	1	0	0	0	21	4.0
4	1	10	4	0	0	0	15	3.0
6	3	7	1	5	0	0	16	3.4
8	3	1	6	0	0	0	10	2.0
10	10	20	27	14	0	0	71	15.1
12	2	26	19	24	25	0	96	21.0
16	0	2	0	2	0	0	4	0.8
20	13	7	0	8	2	0	30	6.4
24	10	11	1	13	0	1	36	8.0
28	1	3	0	5	1	0	10	2.1
36	6	9	1	13	0	1	30	6.4
44	3	5	0	8	1	7	24	5.1
52	0	6	0	15	0	11	32	6.8
>52	0	1	0	4	0	0	5	1.0
Total	119	130	60	111	29	20	469	100
%	25	28	13	24	6	4	-	100

Adapted from Sponsor's table, submitted on September 28, 1995, in response to Agency's

request of September 6, 1995).

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REVIEW AND EVALUATION OF CLINICAL DATA

APPLICATION INFORMATION

NDA#	20-031 (S-009)
Sponsor:	SmithKline Beecham
Clock Date:	March 29, 1995

DRUG NAME:

Generic Name:	Paroxetine HCl
Trade Name:	Paxil®

DRUG CHARACTERIZATION

Pharmacological Category:	Selective Serotonin Reuptake Inhibitor
Proposed Indication:	Panic Disorder
NDA Classification:	6 S
Dosage Forms, Strengths & Route of Administration:	20mg and 30mg Tablets

REVIEWER INFORMATION:

Clinical Reviewer:	James F. Knudsen, M.D., Ph.D.
Review Completion Date:	December 28, 1995

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Table of Contents (continued)

The "windowing" convention is defined below for all the protocols. The visit windows were designed to handle any discrepancies between the visit number and the day on which the visit occurred.

Description of Duration in Weeks for Mean Daily Dose by Duration of Therapy Protocols 120, 223, 108, 187, 222, 228 follows:

Days on Therapy	Duration in Weeks
0 -- 10	1
11 -- 17	2
18 -- 24	3
25 -- 35	4
36 -- 49	6
50 -- 63	8
64 -- 77	10
78 -- 98	12
99 -- 126	16
127 -- 154	20
155 -- 182	24
183 -- 224	28
225 -- 280	36
281 -- 336	44
337 -- 367	52
> 367	>52

The table below provides the extent of exposure in the four short-term studies in the panic disorder program.

Treatment	N	Patient Exposure Years
Paroxetine	468*	83.9
Placebo	324	64.7
Alprazolam	77	17.5
Clomipramine	121	23.4

* 469 patients were exposed but the dosing and duration for one patient was unknown.

Patient exposure in years for the two extension studies in provided in the next table.

Patient Exposure in Years
by Treatment
Protocols 222 and 228

Treatment	N	Patient Exposure (years)
PAROXETINE	176	77.45
CLOMIPRAMINE	63	37.09
PLACEBO	75	45.68

5.1.4 Audit of Case Report Forms (CRFs)

As a component of my review of the NDA, ten case report forms for patients who dropped out for reasons other than an adverse event from the four short-term paroxetine clinical studies were audited. CRF's were compared with the line listings of non-adverse dropouts with respect to the reason for premature termination. The cases were selected at random by patient ID number.

The following table summarizes the audit.

Protocol Number	Patient Number	Treatment	Reason for Termination*
120	006.0017	Placebo	Lack of compliance
120	010.0102	Paroxetine (10mg)	Lack of efficacy
120	011.0065	Paroxetine (20mg)	Protocol violation (use of recreational drugs)
187	012.0100	Paroxetine	Improvement
187	023.0220	Clomipramine	Lost to follow-up
187	024.0175	Paroxetine	Lack of compliance
187	033.0237	Placebo	Lack of efficacy
223	001.0033	Placebo	Other reason (patient left country)
223	060.0190	Alprazolam	Protocol violation (urine drug screen unblinded)
223	017.0200	Paroxetine	Lost to follow-up

* Reason for termination as reported in the line listing of the individual studies.

There were no noticeable discrepancies.

5.2 Secondary Sources

5.2.1 Non-IND Studies

There are no non-IND studies.

5.2.2 Post-Marketing Experience

The sponsor states that the post-marketing experience reported in this submission reflects reports in depressed individuals. There were no ADR spontaneous reports involving patients with panic disorder available for review.

5.2.3 Literature

Profiles listing all SmithKline Beecham (SB) compounds from Phase II in development up to, and including, all marketed products have been established and are run against external databases which index biomedical literature. All references retrieved which mention any side effect or toxicity (preclinical as well as clinical) linked to an SB product are included in references input to the central product literature database SB Line. The main source of

references for SB Line is the Excerpta Medica database produced by Elsevier. This database covers approximately 3,500 biomedical journals. This source is supplemented by profiles run against the Medline and Biosis datasets, plus manual scanning of major journals. Updates form the profiles are received weekly. Additional in-house indexing is added by trained SB information staff working from the full text of the articles. Weekly alerts are issued throughout the company listing papers added within the last week which mention specific SB compounds or adverse events associated with any SB product. All adverse event papers are notified to the Central Safety Group through these weekly adverse event papers are notified to the Central Safety group through these weekly alerts. The database is also available for retrospective searching.

As a result of the above search, references were reported as part of the CANDA submission. An updated list of publications through July 1, 1995 was received on September 15, 1995 (Vol. 58.1 and 2).

Findings from a review of these articles are presented in Section 7 & 8.

6.0 Summary of Human Pharmacokinetics

An extensive summary of pharmacokinetic and bioavailability studies in man was submitted in the original NDA. Studies completed subsequently support the pharmacokinetic profile of paroxetine described previously. This is reflected in the current approved labeling for depression. Updated summaries of human pharmacokinetics and bioavailability studies were provided with the efficacy supplement for OCD submitted on December 7, 1994. I am unaware of any additional pharmacokinetic and bioavailability studies conducted in man and submitted to the present supplement for panic. A summary of the ADEM of paroxetine in humans is provided in this section.

The bioavailability, pharmacokinetics, and metabolism of paroxetine have been investigated in well over 70 studies in humans conducted both in normal healthy volunteers and in depressed patients. The pharmacokinetics of paroxetine after single dosages have been characterized across the therapeutic dose range. The pharmacokinetics in the elderly and in subjects with impaired hepatic and renal function have been examined as well the potential for pharmacokinetic interactions between paroxetine and a range of commonly administered drugs.

With respect to absorption and bioavailability, paroxetine is well absorbed from the gastrointestinal tract and undergoes extensive first pass metabolism in the liver. Single-dose studies have demonstrated that bioavailability of paroxetine is unaffected by the presence or absence of food, whether or not the food is high or low in fat content or by co-administration with milk or anti-acids.

Consistent with its lipophilic amine character, paroxetine is extensively distributed in tissues. Paroxetine is about 95% protein bound to plasma protein. However, the *in vitro* protein binding of warfarin or phenytoin is not altered.

On the basis of monitored plasma concentrations, steady-state paroxetine concentrations are usually achieved by approximately 10 days for most subjects. At steady-state, the diurnal range of plasma concentrations is small in most subjects, with a Tmax occurring at around 4-6 hours. The average terminal half-life on cessation of multiple dosing is about one day, although inter-subject variability is pronounced (range: 9-44 hours). Doses in the elderly produced plasma levels that were 70-80% greater than in younger cohorts. Patients with renal or hepatic impairment exhibited a two-fold increase in Cmax and AUC compared to normals. Mean plasma concentrations in patients with a creatinine clearance of <30ml/min was 4-fold higher than observed in normal volunteers.

Elimination is achieved almost entirely by metabolism, involving oxidation, methylation and conjugation, with less than 2% of an oral dose eliminated as unchanged paroxetine. The major metabolites are sulfate and glucuronide conjugates, which are excreted in urine and feces. Renal clearance of unchanged drug has been reported to be negligible. The data indicate that the metabolites have no more than 1/50th in the potency of the parent compound at inhibiting serotonin uptake, *in vitro*.

The metabolism of paroxetine is accomplished, in part, by cytochrome $P_{450}IID_6$. The role of this enzyme in paroxetine metabolism also suggests potential drug/drug interactions. Like other drugs of this class, paroxetine has been shown to inhibit cytochrome $P_{450}IID_6$, one of the many isoenzymes of the human P_{450} enzyme system. This may lead to increased plasma concentration of those co-administered drugs which are metabolized mainly by this isoenzyme. If the other drug shows a narrow therapeutic window, and where $P_{450}IID_6$ is responsible for a substantial portion of the total clearance (for example, certain TCAs, phenothiazine neuroleptics, and type IC antiarrhythmics) increased plasma concentrations could result in adverse experiences. Recently a study has been conducted using an (*in vitro*) model of human liver microsome preparations to evaluate the inhibiting effects of paroxetine on the activity of two specific cytochromes: P_{450}-3A4 and P_{450}-IID_6. (Von Moltke, Greenblatt et al J Clin Psychopharmacol 15:125,1995). According to the data, paroxetine's inhibiting activity, with respect to P_{450}-3A4 (as quantitated by the inhibition Ki), was no greater than that of sertraline and fluoxetine. Paroxetine was determined to be a potent IID_6 inhibitor, having Ki values smaller than those of fluoxetine. Paroxetine itself is a substrate for P_{450}-IID_6. Hence, as both a substrate and an inhibitor of the same cytochrome, paroxetine has non-linear pharmacokinetic properties in humans. (Sindrup et al., Clin Pharmacol Thes 51:228,1992).

7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

This NDA supplement contains the results of four short-term studies and two extension studies as support for the claim of effectiveness of paroxetine in the treatment of panic disorder; one 20-center, placebo-controlled, fixed-dose trial (study 120) and 3 multi-center, flexible-dose (108, 187 and 223) studies in which paroxetine was compared with placebo (study 108), placebo and clomipramine (study 187) and placebo and alprazolam (study 223). These short-term studies were 10-12 weeks in duration and were conducted in Europe (108) Europe/Israel (187), the United States/Canada (120) and the United States (223). Patients recruited into the studies had a diagnosis of panic disorder according to the DSM-III-R criteria (with or without

agoraphobia). Additional data were collected during a long-term extension phase of study 120 designated study 222 and the extension phase of study 187 designated study 228. The short-term studies as well as the extension studies will be discussed.

7.2 Summary of Studies Pertinent To Efficacy

7.2.1 Panic Disorder Program - Short-Term Studies

7.2.1.1 Fixed-Dose Study 120

Investigators and Locations

Appendix table 7.2.1.1 lists the principal investigators for each site in the fixed-dose study, 120.

Objectives

The objectives of this study were to assess the safety and efficacy of three dose levels of paroxetine relative to placebo in the treatment of panic disorder.

Population

Two hundred seventy-eight (278) patients from 20 centers were randomized to one of three paroxetine doses (67 patients to 10mg/day paroxetine, 70 patients to 20mg/day paroxetine and 72 patients to 40mg/day paroxetine) and placebo (N=69 patients).

Relevant inclusion criteria were:

- Males and females, 18 years of age or older
- Diagnosis of panic disorder as defined by DSM III-R criteria and as diagnosed according to the *Structural Clinical Interview for the DSM III-R* (SCID)
- At least two full panic attacks in the two week period between screening and baseline Full panic attacks were defined as attacks containing at least four of the DSM III-R symptoms during the attack.

Relevant exclusion criteria were:

- Current major depression as defined by DSM III-R unless panic disorder dominates the clinical picture and preceded affective symptoms chronologically, in other words, patients should have panic disorder as primary diagnosis, not depression.
- Any other Axis I disorder
- Severe or uncontrolled medical condition
- High risk of suicide
- Patients who have received:

a) MAOIs, TCAs, oral neuroleptics or type Ic anti-arrhythmics within the preceding 2 weeks;
b) Investigational drugs or SSRIs within the preceding 4 weeks;
c) Lithium or depot neuroleptics within the preceding 12 weeks;
d) ECT within the preceding 6 months

- Concurrent psychotropic medication
- History of substance abuse by DSM III-R criteria within 6 months prior to screening
- Emergence of benzodiazepine withdrawal symptoms in the placebo run-in phase
- Patients with a history of non-compliance
- History of sensitivity to the SSRIs

Design

Study 120 was a randomized, double-blind, placebo-controlled, fixed dose, comparison of 3 doses of paroxetine (10mg, 20mg and 40mg/day) and placebo. The study was conducted in the US/Canada. All patients who completed a two-week placebo washout and qualified were randomized to one of four treatment groups. The dosing schedule is provided in Table 7.2.1.1.

Table 7.2.1.1
Dosage Schedule (Study 120)

Week	Placebo	Paroxetine		
		10 mg/day	20 mg/day	40 mg/day
Run-in Period (two weeks)	Placebo	Placebo	Placebo	Placebo
Medication Phase				
Week 1	Placebo	10	10	10
Week 2	Placebo	10	20	20
Weeks 3-10	Placebo	10	20	40
Run-Out period (For patients not entering Extension Study)				
Week 11	Placebo	Placebo	10	20
Week 12	Placebo	Placebo	Placebo	10
Weeks 13-14	Placebo	Placebo	Placebo	Placebo

Data source adapted from table in volume 18, p. 13.

Patients not entering the 6 month extension protocol 222 followed the 10-week medication phase with a 4-week double-blind run-out phase where the dose of paroxetine was reduced according to the dosing schedule in Table 7.2.1...

Patients were required to maintain their dosing regimen for the duration of the 10-week study. They were not permitted to decrease medication dosage. Compliance was monitored by pill count.

Post baseline visits were scheduled weekly for the first month and every two weeks up until week 10. Patients who met the criteria for a therapeutic response at week 10 visit had the option of entering the 6 month extension study, 222. A therapeutic response was defined as zero full panic attacks over the last 2 week period of the coded medication phase or a 50% or more reduction from baseline in the number of full panic attacks over the last 2 week period of the coded medication phase.

Assessments

The efficacy scales evaluated and the intervals during which measurements were made are enumerated in the following table. All efficacy scales were administered at baseline as well as weeks 1, 2, 3, 4, 6, 8 and 10 and one run-out visit. The frequency of assessments was modeled after the original alprazolam study by Ballenger et al. (Ballenger et al, Arch. Gen Psychiatry 45:413,1988). Analyses were performed at 2-week intervals. Visit 1 and 2 were

combined for the 1st 2-week interval and visits 3 and 4 were combined for the 2nd 2-week interval. Visits 6, 8 and 10 covered a two week period and made up the remaining 2-week intervals for the analyses. Patients missing one week of data within a given interval were excluded.

Efficacy Evaluations+ Study 120											
	Run In		Base Line	Treatment Phase							Run Out*
WEEK	-2	-1	0	1	2	3	4	6	8	10	14
Panic Diary Information and A.A.A.	X	X	X	X	X	X	X	X	X	X	X
MSPS			X				X			X	
SDS			X				X			X	
CGI			X	X	X	X	X	X	X	X	X

Data source adapted from Table 2 in volume 17, p. 82.

* For those patients not continuing in the extension protocol 222.

\+ A.A.A. = anticipatory anxiety assessment
MSPS = Mark-Sheehan Phobia Scale
SDS = Sheehan Disability Scores
CGI = Clinical Global Impression - (seventy of illness item)

For data derived from the panic inventory and A.A.A. means were given for every two weeks (patient visits scheduled every 2 weeks after the first month) in the treatment and run-out phases. Thus, mean values for weeks 2 and 4 were the result of combining data for each patient at visits 1 and 2 and 3 and 4, respectively.

Patients were given a diary card which was to be filed out every day. A copy of which is located in the Appendix 7.2.1.1

A panic inventory was used to determine mean number of full and limited symptom panic attacks during the run in and coded medication phase of the study. The panic inventory contains all the DSM III-R criteria for a panic attack. Four of the DSM III-R symptoms are required for the diagnosis of a full panic attack.

The investigator summarized the diary data for the panic inventory and A.A.A. since the previous visit. A copy of this form is in the Appendix 7.2.1.1.

Analysis Plan

The sponsor defined the ITT population as any patient randomized and receiving study medication. Hence, the patient counts for number randomized and ITT population could be (and generally are) the same. For demographic, safety, medical history and patient completion/withdrawal counts, these are the numbers of patients used as the denominator. The efficacy ITT population consists of patients as defined above who have at least one on-therapy assessment. This number differs from the overall ITT population due to the fact that some patients may have a baseline assessment, but withdraw prior to their first on-therapy assessment.

The principal assessment of efficacy was a reduction in the number of full panic attacks which were recorded daily by the patient. Panic attack frequency was determined from the following:

- proportion of patients having zero full panic attacks (4 of the DSM III-R symptoms are required for a diagnosis of full panic attack) during the last 2-week interval
- proportion of patients with a 50% or more reduction from baseline in the mean number of full panic attacks during the last 2-week interval
- mean change from baseline in the number of full panic attacks during the last 2-week interval

Other efficacy variables considered were the CGI-severity score, the MSPS, anticipatory anxiety and the SDS.

Two types of datasets were used to analyze the data: visit-wise dataset (observed cases, OC) and the extender (LOCF) dataset. The OC dataset consisted of each patient's observation for each week of the study (only for the timepoint when it was collected). No data were carried forward to estimate missing data points. The LOCF dataset consisted of each patient's last observation. Missing data for a given visit were estimated by bringing forward (extending) the data from the previous visits. The LOCF dataset was considered to be the primary dataset, and the primary time-point of interest (endpoint) was the week 10 visit in the LOCF dataset.

The proportion of patients achieving a dichotomous response, such as the proportion having zero full panic attacks and those with a 50% reduction from baseline in the number of panic attacks, was analyzed using a Logistic Regression Methodology. The remaining efficacy results were analyzed using the analyses of variance model (ANOVA), with treatment, investigators, and treatment by investigator interaction effects. The interactions were tested at an alpha level of 0.10. Otherwise, statistical testing was performed at the 5% significance level and were two-tailed. Pair-wise comparisons between each paroxetine dose and placebo were made using Dunnett's test (which adjusted for multiple comparisons) to maintain an overall α = 0.05 ($p<0.019$).

Baseline Demogra

The four patient [illegible] comparable with respect to mean age, age range and gender at baseline. Incompl[illegible]e data [illegible]sted for racial distribution. (See **Appendix** 7.2.1.1, Table 1).

Baseline Illness Severity

There were no statist[illegible]ificant differences at baseline with respect to the mean number of panic attacks or CGI se[illegible]y scores across the treatment groups. Mean baseline CGI was 4.4 for all treatment grou[illegible] The mean frequency of panic attack at baseline was generally consistent between the ind[illegible]vidual treatment groups (vol. 60, p. 232).

Patient Disposition

Appendix Table 7.2.1.1, Table 2, gives the distribution of patients by treatment group. A total of 278 patients were randomized to 4 treatment arms. There were no differences between the treatment groups with respect to completion rates. At least two-thirds of the patients in all groups were still in the study at week 10.

Use of Concomitant Medications

A summary of concomitant medications by WHO ATC class was supplied by the sponsor (vol. 17, p. 96, table 11). Concomitant medications taken during the study were numerous. The most frequently used concomitant medications were analgesics taken by 40 (58%) of placebo and 37 (55.2%) of the 10 mg/day paroxetine, 35 (50%) of the 20 mg/day paroxetine and 34 (47.2%) of the 40 mg/day paroxetine-treated groups.

More paroxetine-treated patients 8 (11.9%), 4 (5.7%), 8 (11.1%) for the 10 mg/day, 20 mg/day and 40 mg/day dose, respectively, reported taking antipruritics (mainly diphenhydramine for insomnia) than the placebo-treated patients 2 (2.9%). Sex hormones were mainly estrogen and were used more frequently by the placebo-treated patients, 22 (31.9%) relative to the paroxetine-treated patients where 12 (17.9%), 20 (28.6%) and 12 (16.7%) of the patients treated with 10 mg/day, 20 mg/day and 40 mg/day of paroxetine, respectively reported use of sex hormones.

The line listing of concomitant medications (Appendix 5A) was examined to evaluate the extent of benzodiazepine or tricyclic antidepressant use during double-blind treatment, since these two classes of drugs are thought to possess anti-panic activity. Most use of these drugs was of brief duration (1 or 2 days), early in double-blind treatment (first 5 weeks), and no such use was noted in the paroxetine 40mg dose group, which was the only group to manifest statistically significant superiority over placebo.

Efficacy Results

Appendix 7.2.1.1, tables 3-13, summarize the efficacy of study 120. At the endpoint of the study (week 10), the percent of patients with zero full panic attacks was not statistically significant between any of the treatment groups in the LOCF analysis, although there was a

strong trend exhibited for the 40mg/day paroxetine group. Statistical significance was achieved for the paroxetine 40mg/day vs placebo group at the second and fourth 2-week periods ($p<0.017$ and $p<0.016$, respectively). The OC analysis revealed statistical significance for only the 40mg/day paroxetine dose at endpoint ($p<0.011$) and the second 2-week period ($p<0.014$).

With respect to the percentage of patients with a 50% reduction in the number of full panic attacks (table 4), there were no statistically significant differences noted at any timepoint for either the LOCF or OC analyses.

Comparisons of the group mean change from baseline in the number of panic attacks (table 5) at endpoint of study (week 10) revealed statistical significance for the 40mg/day paroxetine group (vs placebo) in the LOCF and OC analyses. Statistically significant differences between the 40mg/day paroxetine-treated group and placebo were demonstrated at the second, third, fourth, and final 2-week periods. Results for the OC analysis were consistent with those for the LOCF.

With respect to the CGI-severity of illness scores (table 6), statistically significant differences ($p<0.007$) between the paroxetine 40mg/day dose vs placebo were reported at endpoint for OC analysis. A strong trend was noted for LOCF analysis at endpoint.

The MSPS-fear score (table 7) showed statistically significant improvement at endpoint for the 20mg paroxetine group vs placebo and for the 40mg paroxetine group vs placebo for both LOCF and OC analyses. The MSPS-avoidance score revealed no statistically significant differences for any group for either datasets.

With respect to anticipatory anxiety (table 9), the mean change from baseline in the percent of time and intensity of worrying about panic attacks showed no statistically significant differences at any time for any dose for either the LOCF on OC datasets.

For all items included in the SDS (tables 11-13), there were no statistically significant differences between treatment groups. Results of the OC dataset analysis were consistent with the LOCF analysis.

There were no treatment-by-center interactions.

Conclusion

Overall demonstration of efficacy in study 120 was not robust. This is considered a marginally positive study. Only the 40mg/day paroxetine dose using LOCF analysis showed a modicum of consistently statistically significant differences (vs placebo) in the outcome measures used to assess efficacy. At study endpoint (week 10), LOCF analysis of the reduction in the frequency of panic attacks showed statistically significant differences in favor of the 40mg/day paroxetine group only for the mean change from baseline in the number of panic attacks (paroxetine 9.6 to 1.4 vs placebo 11.6 to 6.1).

7.2.1.2 Flexible Dose Studies

Three multiple-center, flexible-dose, short-term studies (10-12 weeks in duration) were conducted as part of the panic disorder program (studies 108, 187 and 223) and are discussed in this section.

Study 108

Investigators/Location

Appendix table 7.2.1.2 lists the principal investigators for study 108.

Objectives

This study was conducted to compare the reduction in the number of panic attacks and the tolerance of therapy in patients with panic disorder, with or without agoraphobia treated with either paroxetine or placebo in combination with psychotherapy.

Population

A total of 120 patients from 7 centers were randomized equally to one of two treatment groups, (60 paroxetine and 60 placebo).

The inclusion criteria for study 108 differs from study 120 with respect to the frequency of panic attacks. In the previous US/Canadian study, 120, patients had to meet the criterion of having at least two full panic attacks in the two week period between screening and baseline, whereas, in study 108, the criterion was at least 3 panic attacks (full or limited not specified) in the previous four weeks. Exclusion criteria were similar to those of study 120.

Design

This multi center study was a randomized, double-blind, placebo-controlled, flexible-dose, parallel design comparison study conducted in Denmark and completed February 1, 1992. The screening visit was followed by a single-blind, placebo wash-out phase lasting three weeks, after which patients were randomly allocated to receive either paroxetine or placebo tablets. The baseline day was defined as the day in which the active treatment was started. Treatment lasted for 12 weeks and was followed by an additional 2 weeks of placebo treatment for both

groups. All paroxetine-treated patients received 10mg/day for the first week, 20mg/day for the following week and then either 20 or 40mg/day for the next three weeks. For the remaining seven weeks, 20, 40 or 60mg/day could be dispensed, selected by judging the response to treatment and the tolerability to treatment.

All patients had psychotherapy standardized according to principals established by Hawton A et al (Cognitive Behavior Therapy for Psychiatric Problems, Oxford Periodical Publications, No publishing date available at this time). In order to ensure standardization of psychotherapy, investigators were given training and required to meet regularly to discuss treatment methods.

Assessments

Efficacy evaluations performed are enumerated in the table below. The Zung/self-rating scale and the HAM-A were also done but not considered in this review. The A.A.A., MSPS and SDS were not performed. This may be due to the fact that study 108 was the first study implemented to study paroxetine in the treatment of panic and that modalities to assess panic disorder had not been clearly delineated at that time.

Efficacy Evaluations
Study 108

	Screen	Baseline	Treatment Phase							Run Out Phase
Week		-3 to -1	1	2	3	4	6	9	12	14
Panic Diary Information		X	X	X	X	X	X	X	X	X
CGI-Severity	X	X	X	X	X	X	X	X	X	X

Adapted from Table on page 10, vol. 36.

The panic attacks were counted for the four week period prior to entry to a 3 week placebo run-in period. Subsequently, the panic attacks were totaled over, 3-week periods (including baseline days -20 to day 0) where the baseline period consisted of the 3 weeks during the placebo run-in. The first 3-week treatment period consisted of days 1 to 21. The second 3-week period consisted of days 22 to 42. The third 3-week period consisted of days 43-63 and the fourth 3-week period consisted of days 64-84. In this study, unlike the previous study, the patients had no formal checklist of panic symptoms. According to the sponsor, the physicians educated their patients with respect to recognition of panic attack symptoms. A copy of a patient's diary card is in appendix 7.2.1.2 followed by a copy of the panic inventory which was to be completed by the physician.

Analysis Plan

The ITT population consisted of all patients who were randomized.

The principal assessment of efficacy outcome was a reduction in the number of panic attacks which were recorded daily by the patient. No formal checklist of symptoms was provided to the patients in this study, hence, unable to discern full vs limited panic attack. Panic attacks frequency was determined from the following:

- proportion of patients having 0 or 1 panic attack in each of the 3-week periods and the end-point
- proportion of patients with a 50% or greater reduction in the number of panic attacks between baseline and each of the 3-week periods and the endpoint
- the mean change in the number of panic attacks between baseline and each of the 3-week periods and the endpoint.

Other efficacy variables considered were the CGI-severity score.

Two types of datasets were used to analyze the efficacy data: observed cases dataset (OC) which consisted of each patient's observation at each week and the extender dataset (LOCF). The endpoint was defined as the last day of active medication before placebo run-out, i.e., at week 12. Analyses of variance was performed to assess differences in continuous variables between treatment groups. A two-tailed significance level of 5% was used to determine whether or not the result was to be regarded as statistically significant. The Cochran-Mantel-Haenszel Chi Square Tests were used to analyze categorical data. The Breslow-Day Tests for homogeneity of the odds ratios were performed to test homogeneity over the centers.

In the appendix tables, the paroxetine "n" in the LOCF row for the 1st 3-weeks should be 56 since there were only 56 paroxetine patients with valid 1st 3-weeks assessments as can be seen in the OC row. If a patient has a missing assessment, the last measurement was brought forward only if that patient had a previous post-baseline assessment.

The baseline means quoted in the tables cited above are based on 58 patients which is the total number with a baseline assessment as opposed to a mean based solely on patients who had a further assessment on-treatment. This was the convention at that time.

The reason why the "N's" in Table 17 (Efficacy Response Rates) do not exactly match Table 15 (Patient Completion Rates) are as follows:

- to be included in the week 12 column of table 15 a patient must have completed the study
- to be included in the 4th 3-weeks column of table 17 a patient must have completed the study and had the 4th 3-weeks assessment (i.e. completed at least 14 of the 21 days diary data).
- there are 3 patients who completed the study but did not have the 4th 3-weeks assessment. (2 paroxetine patients 108.001.0199 and 108.007.0073 and 1 placebo patient 108.005.0005)

As above, the reasons for the inconsistencies in the "N's" across variables are that there are different requirements for the different tables. For example:

- to be included in the 4th 3-weeks column of Table 17 a patient must have the 4th 3-weeks assessment (i.e., completed at least 14 of the 21 days diary data).
- to be included in the 4th 3-weeks column of Table 18 a patient must have the 4th 3-weeks assessment and the baseline assessment.

Baseline Demographics

Appendix 7.2.1.2 table 14 depicts baseline demographic characteristics. There were 48 (80%) females in the paroxetine-treated group and 43 (72%) females in the placebo group; this difference was not statistically significant (p= 0.394, 2-tailed Fisher's exact test).. Other baseline characteristics of age and age range were comparable across the two treatment groups. In this study, demographic data on race were not collected.

Baseline Illness Severity

Pair-wise comparisons of paroxetine with placebo revealed no statistical significant differences at baseline with respect to baseline CGI severity of illness score or the number of full panic attacks where comparable (vol 60, p 231)

Patient Disposition

Appendix 7.2.1.2 Table 15 depicts the patient disposition. The ITT was composed of 120 patients, distributed evenly between the paroxetine and placebo-treated patients. Fifty-five (92%) of paroxetine-treated patients completed the 12-week study. Fifty-two (87%) of the placebo-treated patients completed the 12-week study.

Dosing Information

Appendix 7.2.1.2 table 16, includes a table depicting a mean dose over time. The mean dose at the completion of the study was 40mg.

With respect to maximum daily dose, 1 (2%) patient took a maximum dose of 10mg, 14 (23%) patients took a maximum dose of 20mg, 17 (28%) patients took a maximum dose of 40mg and 28 (47%) patients took a maximum dose of 60mg.

Use of Concomitant Medications

Concomitant medication use during the study was reported more frequently by the paroxetine-treated patients (27%) compared with the placebo-treated patients (10%). The most frequently used medications were analgesics and allergy medications used by 8 (13.3%) of the paroxetine-treated patients and 4 (6.7%) of the patients in the placebo group.

The line listing of concomitant medications (Appendix 5.1.1) was examined to evaluate the extent of benzodiazepine or tricyclic antidepressant use during double-blind treatment, since these two classes of drugs are thought to possess anti-panic activity. Only one paroxetine-treated patient had such use, namely alprazolam 1.5 mg/day from day 20 for an unspecified period of time. It is unlikely that this use biased the efficacy findings in this study.

Efficacy Results

Appendix 7.2.1.2 Tables 17-20 provides summary tables of the efficacy results from study 108. With respect to the numbers of responders (full panic attacks reduced to 1 or less) at endpoint 33% of the paroxetine-treated patients compared to 14% of the placebo-treated patients in the LOCF dataset experienced a reduction in panic attacks to 1 or less relative to baseline. The difference was statistically significant for both LOCF and OC datasets. The paroxetine group had a statistically significantly higher proportion of responders compared to placebo, achieving a 50% reduction in panic attacks at the second, third and fourth 3-week totals and endpoint for both LOCF and OC datasets. The mean change from baseline to endpoint in the number of panic attacks was -15 for the paroxetine group and -10 for the placebo group in the LOCF group. The difference between treatments was not statistically significant (both LOCF and OC analyses).

With respect to the CGI-severity of illness scores, the differences between treatment groups (in favor of paroxetine) was statistically significantly different at weeks 4, 6 and 12 for both LOCF and OC analyses; in addition, paroxetine was superior to placebo at week 9 in the OC data set..

There were no treatment-by-center interactions reported.

Conclusion

Improvement was seen for patients treated with paroxetine plus cognitive therapy compared with placebo with cognitive therapy with respect to the number of full panic attacks reduced to 1 or less at endpoint and also with respect to a 50% reduction in the number of full panic attacks using either LOCF or OC datasets. Mean changes from baseline in the number of panic attacks were numerically superior in the paroxetine-treated group compared to the placebo-treated group from the second 3-week assessment onwards but did not attain statistical significance. A trend was noticed at week 12 in the OC analysis. Sample size calculation was based on the predicted response rates for the other 2 primary variables (≥50% reduction in full panic attacks / reduced to 0 or 1 full panic attack). The study was not powered for the comparison of the mean change from baseline in full panic attacks.

If one attempts to estimate the power of the study to detect a statistically significant difference between the treatments, based on the following assumptions:

- Significance Level (∝) = 5%
- Detectable difference = 5 full panic attacks
- Standard Deviation = 18 (From the s.d. of change from baseline in no. of full panic attacks at endpoint, for all patients)
- Number of patients per group = 55
- Then, Power (1-β) = 30.8%

Further evidence of efficacy came from the CGI-severity score with a mean decrease in severity in the paroxetine plus cognitive therapy group relative to the placebo-treated groups.

Overall, a positive study would be one in which the change in the number of panic attacks and the change in CGI-Severity score for panic both show significant drug-placebo differences, as exhibited here. Both are adequate measurements which have been widely used in psychopharmacological studies. Nevertheless, there is an important qualification, that the data being collected is reliable. In this Danish study 108, patients were not referred to a formal symptom checklist for recognition of panic attack symptoms although apparently the patients were educated to recognize panic attack symptoms. Overestimating or underestimating panic attack frequency would be expected to be distributed evenly between paroxetine and placebo-treated groups.

Data from this study have been published (Br. J. Psychiatry 167:374,1995).

Study 187

Investigator/Location

Appendix table 7.2.1.3 lists principal investigator for each site in the flexible-dose study 187.

Objectives

The objectives of this study were to compare the effect of paroxetine, clomipramine and placebo on efficacy and safety in the treatment of patients with panic disorder.

Population

A total of 368 patients from 39 centers were randomized to one of three treatment groups: paroxetine, placebo or clomipramine. Although the inclusion and exclusion criteria were similar to the previous fixed-dose study, 120 and flexible-dose study 108, some differences were evident. With respect to the frequency of panic attacks in study 187 the patients were required to have had at least 3 full panic attacks in the 3 week period between screening and baseline. Exclusion criteria varied somewhat in study 187 relative to previous studies, with respect to medication history, in particular, recent administration of MAOIs, TCAs, oral neuroleptics or type 1C antiarrhythmics. In study 187, patients who had taken these medications within four weeks of the double-blind period (versus within two weeks of start of study 120) were considered to be ineligible for the studies.

Design

This study was a randomized, double-blind, placebo and active-controlled, parallel group study conducted over 12 weeks in Europe/Israel and completed on December 7, 1993. After a three week single-blind, placebo run-in phase, patients proceeded to the active phase of the study during which the dose of study medication could be changed. Patients not wishing to enter the extension study were titrated down during a three week period.

A screening phase was used to evaluate potential study participants. Eligible patients entered into a 21 day period of placebo treatment. At the end of three weeks of the placebo run-in phase baseline evaluations were made and patients were randomized to double-blind treatment. Patients took two capsules in the morning, with food, and one capsule in the evening, also with food. The paroxetine capsule(s) were taken only in the morning, whereas the active clomipramine capsules were taken both morning and evening, except for week one when they were taken only in the morning. The dosing schedule for study 187 follows.

Patients started treatment with either paroxetine (10mg/day), clomipramine (10mg/day, increasing to 25mg/day for three days) or placebo. After this titration, and at the end of week two, patients were receiving a daily dose of either paroxetine 20mg, clomipramine 50mg or placebo. At the end of the second week, the study medication could be increased so that patients in the paroxetine group were either receiving 20mg or 40mg/daily and patients in the clomipramine group were receiving either 50mg or 100mg/day. At the end of week three, the daily dose could be increased again, so that within each treatment group there were low, medium and high dose groups. Dosage could be increased to 40mg and 60mg paroxetine or 100mg and 150mg clomipramine at the end of the fifth, sixth, seventh and ninth week, respectively (if the patient was receiving low or medium dose), or decreased (if the patient was receiving medium or high dose). The investigator made the decision on whether or not to increase or decrease the dose using as a guide the CGI efficacy index grid as shown in the following scheme provided by the sponsor (Vol. 39, p. 39).

Therapeutic Effect	Adverse Events			
	None	No significant interference	Significant interference	Outweighs therapeutic effect
Marked	N	N	N	D
Moderate	I	N	D	D
Minimal	I	I	D	D
Worse/unchanged	I	I	D	D

'N' represents no change in daily dose, 'I' represents an increase and 'D' represents a decrease. In the case of adverse events, the dose could be decreased between study visits, in which case the patient contacted the investigator first.

Assessments

The timing of the study visits and the efficacy measurements carried out at each visit are shown in the table below.

Patients recorded daily details of any panic attacks in a diary for a three-week period. The daily records consisted of the number of panic attacks, the type of panic attacks, as well as the total number and type of symptoms which occurred on each occasion, and the intensity of each attack. From a symptoms check list, the total number of symptoms was recorded. Panic attacks were classified as situational, unexpected or anticipatory. The diary card information was used in each clinical visit after screening to record weekly summary information in the CRF. A copy of the patient diary is in the appendix.

Baseline assessment (Day 0) occurred at the end of 3 weeks of the placebo run-in phase (week -1 in table). Eligible patients were randomized.

Efficacy Evaluations

Study 187

	Screen	Run-in Phase			Treatment Phase							Run-Out Phase
Week (visit is at *end of week*)		-3	-2	-1	1	2	3	4	6	9	12	15
Panic Diary Information		X	X	X	X	X	X	X	X	X	X	X
MSPS		X	X	X	X	X	X	X	X	X	X	X
SDS	X			X	X	X	X	X	X	X	X	X
CGI				X			X		X	X	X	X

Data Source: Adapted from Table 2, P. 37, Vol. 39

Analysis Plan

The ITT population consisted of patients randomized to treatment, and for whom at least one post-baseline assessment was available after treatment.

The principal measurement of efficacy outcome was a reduction in the number of full panic attacks which were recorded daily by the patient in a panic attack diary. Full panic attacks were defined as attacks containing at least four symptoms during the attack. Panic attack frequency was determined from the following measures:

- the percentage of patients with 0 full panic attacks in each third 3-week interval
- the percentage of patients with a 50% or greater reduction in the number of full panic attacks from baseline.
- the mean change from baseline in the number of full panic attacks during each 3-week interval.

Since there were fewer than 70% of patients with a valid fourth 3-week (or week 12) assessment, the primary time-point in this study was the third 3-week (or week 9) time-point. Other efficacy variables were the following:
CGI-severity, Mark-Sheehan Phobia Scale (MSPS, fear and avoidance as separate variables) and the Sheehan Disability Scale (SDS).

Two types of datasets were used by the sponsor to analyze the efficacy data: Observed cases (OC) and extender datasets (LOCF). The observed cases (visitwise) data set consisted of each patient's observation at each visit. The LOCF dataset were generated from the visitwise data set: missing data were estimated by extending forward the data from the previous visit. If the first visit on active treatment was missing, then the baseline visit was not used to extend forward. (If the first visit on active treatment is missing, then there is no on-active treatment assessment to extend forward. One does not extend forward the baseline data). The LOCF data set were considered to be the primary data set, and the primary time-point of interest in this study was the third 3-week (or week 9) time-point, since there were fewer than 71% of patients with a valid fourth 3-week (or week 12) assessment; a valid assessment is one for which panic diary data was recorded for at least 2 of the 3 weeks in an interval. Although 71% (261/367) of the patients completed the study, not all patients who completed the study had evaluable efficacy assessments at all timepoints. There were 256/367 (69.8%) patients who had a valid 4th 3-weeks assessment of which only 254/367 (69.2%) patients had a valid baseline assessment. Therefore, as stated in the report, "Since there were fewer than 70% of the patients with a valid fourth 3-week (i.e. week 12) assessment, the primary timepoint in this study is the third 3-week (i.e. week 9) time-point."

Although these above percentages are not much (<70%), the sponsor notes that when they looked at the individual treatment group the situation was worse for the placebo group where only 78/123 (63.4%) of the placebo patients had a valid 4th 3-weeks assessment. Therefore the 3rd 3-week assessment was used as the primary timepoint.

In this study, the following statistical tests were used:

- two-sample t-tests were used to analyze variables whose distributions did not differ markedly from normal
- Mann-Whitney U-Tests were used as a non-parametric alternative to the t-tests
- Fishers Exact Tests were used to analyze binary data
- Mantel Haenszel chi-square tests were used to analyze ordinal data
- Cochran-Mantel-Haenszel chi-square tests, adjusting for factor (e.g., gender), were used to analyze binary data, where a factor was used in the analyses
- Breslow-Day tests for homogeneity of the odds ratios were performed in tests for homogeneity over the factors
- Log-rank tests were used to test the difference in survival curve distributions

All p-values quoted are based on two-sided α=0.05 level.

Baseline Demographics

Baseline demographic characteristics are displayed in Appendix 7.2.1.3, Table 21. There were no statistically significant differences in mean age, age range, or gender between the three treatment groups. Caucasians comprised the vast majority of the population.

In this study, the ratio of males to females (1:1.5) was higher than for the overall population of patients participating in the other studies (1:2).

Baseline Illness Severity

The mean frequency of panic attacks at baseline may be used as an indicator of the baseline severity of panic disorder. In the present study, the mean number of panic attacks at baseline (paroxetine 17.9, clomipramine 15.3, placebo 18.5) indicated a slightly lower baseline severity of panic disorder in the clomipramine group. Between 47% and 49% of patients in each group had attacks of moderate intensity and between 50% and 53% of patients in each group had attacks of severe intensity. The CGI severity of illness score at baseline was slightly higher in the paroxetine-treated patients than in the placebo-treated group (4.6 vs 4.5), and equal to the clomipramine-treated group (4.6 vs 4.65.0).

Patient Disposition

A total of 368 patients were randomized to the three treatment arms, 123 were randomized to receive paroxetine, 122 to receive clomipramine, and 123 to receive placebo. One clomipramine patient (187.003.0017) had no evaluable assessments during active treatment and was excluded from the ITT population, leaving 123 paroxetine, 121 clomipramine and 123 placebo patients eligible for inclusion in the ITT population. (See Appendix 7.2.1.1, table 21 for a summary table of patient disposition). By week 12 there were more withdrawals in the placebo group (34%) than in the paroxetine (28%) or clomipramine (25%) groups.

Dosing Information

Appendix 7.2.1.3 includes a table depicting mean dose over time. The mean paroxetine dose at study completion was 43mg/day.

Use of Concomitant Medication

Thirty-six patients (29.3%) in the paroxetine-treated group, 38 (31.4%) in the clomipramine-treated and 45 patients (36.6%) in the placebo-treated group used concomitant medications during the study (Data from Sponsor's Table 5.1.4.2, vol. 40, page 29). The most commonly used concomitant medication was a CNS acting drug. used by 19.5% (paroxetine), 21.5% (clomipramine) and 20.3% (placebo) patients. The line listing of concomitant medications (Appendix 2, Listing 5.1.4) was examined to evaluate the extent of benzodiazepine or tricyclic antidepressant use during double-blind treatment, since these two classes of drugs are thought to possess anti-panic activity. Most use of these drugs was of brief duration (1 or 2 days) and early in this period (first 6 weeks). Therefore, it is felt to be unlikely that this use significantly affected the efficacy findings.

Chloral hydrate was used by approximately twice as many paroxetine-treated patients (10/123, 8.1%) as placebo (5/123, 4.1%) and more than clomipramine-treated patients (6/121, 5%). The drug was used infrequently and therefore would not likely have an effect on the efficacy requests.

Efficacy Results

Appendix 7.2.1.3, tables 24-32, summarize the efficacy results of study 187.

With respect to zero full panic attacks, statistically significant differences between paroxetine and placebo treatment groups occurred from the second, third and fourth 3-week time periods in the LOCF analysis and at only the third 3-week timepoint for the OC analysis.

At the third 3-week time periods, 83 paroxetine-treated patients (76%) had a reduction of at least 50% in the total number of attacks, compared with 69 patients (60%) in the placebo and 69 clomipramine-treated patients (65%). Pairwise comparisons showed paroxetine to be better than placebo at the third and fourth 3-week periods and better than clomipramine at the second 3-week time period for the LOCF analysis. There were no statistically significant differences between paroxetine and placebo treatment groups in the OC analysis.

Mean changes from baseline in the total number of full panic attacks in the LOCF dataset were statistically significantly larger for paroxetine versus placebo in the fourth 3-week period. Using OC analysis, no significance was attained at any time period.

A statistically significant mean change of -1.7 was observed in the CGI severity of illness score from baseline (week 9) in the paroxetine ITT population. Statistically significant differences were noted as early as week 6. Clomipramine was also better then placebo at these time points. There was no difference between clomipramine and paroxetine. Using the OC analysis, paroxetine vs placebo significance was attained as early as week 3.

The MSPS was analyzed for fear and avoidance. The mean reduction in total fear score at week 9 was 21.1 in the paroxetine group, compared with 12.6 in the placebo and 18.9 in the clomipramine group and was statistically significantly larger in the paroxetine group (vs placebo) for the LOCF analysis. OC results were similar. There was a consistent trend toward greater fear reduction in all treatment groups for each visit for both LOCF and OC datasets. The mean reduction in total avoidance score was significantly larger in the paroxetine group than in the placebo group at week 6 and 12, but not week 9. The results for the OC datasets were similar for each component.

For all components of the SDS, the mean reduction in score was significantly larger in the paroxetine vs placebo group at weeks 3, 6, 9 and 12. OC datasets were similar.

Due to the large numbers of centers with small numbers of patients in study 187, it was felt that the data would be inadequate to assess any treatment by investigator interactions. (For the primary efficacy data, there are 25/36 (69%) of the investigators which have ≤1 patient in one or more treatment groups).

Two investigators were the primary investigators in more than one center (Dr. Van Dyck for centers 006, 007 and 008 and Dr. Ljubomir for Centers 017 and 018).

Conclusions

LOCF analysis presented robust evidence of the superiority of paroxetine compared to placebo at 6 and 12 weeks for multiple rating scales. There was weaker evidence of efficacy in the OC datasets, particularly for the reduction in number of panic attacks to zero, % with 50% decrease and mean change from baseline in the number of panic attacks. Although clomipramine was significantly more effective than placebo in lowering the mean severity of illness and avoidance scores, there was no statistically significant change in the reduction of panic attacks. Incidentally, according to the sponsor, the dosing recommendations (versus the "usual effective dose") for clomipramine in the treatment of panic disorder was based on the guidance in the British formulary for dosing clomipramine in panic disorder (British National Formulary No. 28, September, 1994. British Medical Association/Royal Pharmaceutical Society of Great Britain. Anne B. Prasad (ed). the Royal Pharmaceutical Press. London, England). This dosing regimen was employed during the conduct of studies 187 and 228 and is shown below.

"Clomipramine is indicated for depressive illness, phobic and obsessional states"

"Dose 25mg initially, increased gradually, over 2 weeks, as necessary to 100mg-150mg daily in divided doses as a single dose at bedtime. Starting dose should be 10mg in sensitive or elderly."

Overall, the study provides evidence of efficacy for paroxetine.

Study 223

Investigator/Location

Appendix table 7.2.1.4 lists principal investigators for each site in this flexible-dose study, 223.

Objectives

The objectives of this study were to compare the safety and efficacy of paroxetine relative to placebo in the treatment of panic disorder, using alprazolam as a positive control, and to assess the effect of paroxetine and alprazolam on anticipatory anxiety and phobic avoidance.

Population

A total of 226 patients were randomized to double-blind medication (77, paroxetine; 72, placebo; 77, alprazolam). Inclusion and exclusion criteria were similar to the previous flexible-dose study, 187, discussed previously in my review. Patients who had received MAOIs, TCAs, oral neuroleptics or type 1C anti-arrhythmics within 2 weeks of baseline visit were excluded from these studies (versus 4 weeks in study 187).

Design

This study was a multi center (16) randomized, double-blind, placebo and alprazolam controlled study conducted over 10 weeks in the U.S. and completed on April 21, 1994.

A single-blind, placebo-controlled (washout) pre-treatment phase was used to screen potential candidates. Candidates were administered single-blind doses of placebo t.i.d. for 14 days, at the end of which baseline evaluations were made and eligible patients were randomized into one of the three treatment groups. At baseline, patients had to have had at least 2 full panic attacks over the previous 2 weeks to be eligible for the treatment phase. The table which follows displays double-blind medication dosing information.

Schedule Of Maximum Doses: Study 223

Week	Alprazolam*	Paroxetine*	Placebo
1 - (Day 1-3)	1.0	10	placebo
(Day 4-7)	1.5	10	placebo
2 - (Day 8-10)	2.0	20	placebo
(Day 11-14)	2.5	20	placebo
3-10	3.0	30	placebo
4-10	4.0	40	placebo
5-10	5.0	50	placebo
6-10	6.0	60	placebo

Data Source: Adapted from Table 1, p. 14, vol. 28.
* Dose is mg/day.

Over a 3 week period, patients were allowed to increase their paroxetine and alprazolam daily doses from 10mg/day and 1mg/day to 30mg/d and 3mg/d, respectively. At the beginning of week 4, the paroxetine and alprazolam daily doses could be increased in 10mg and 1mg increments, respectively, no more frequently than every 7 days in the event of an inadequate therapeutic response. Decisions regarding dose increases were made based on therapeutic

response, apparently independent of drug tolerance. The maximum paroxetine and alprazolam daily doses were 60mg and 6mg, respectively. This double-blind treatment phase was followed by a 6 week double-blind dose reduction or run-out phase. By the beginning of week 16, all patients were dispensed placebo. In the event of intolerability, the dose level was reduced or medication discontinued at any time during the study. Dose reductions were permitted only once during the treatment phase. Weekly visits were scheduled for the first month and bi-weekly for the remaining 3 visits for a total of 7 visits during the 10-week treatment phase.

Assessments

The timing of the study visits and the efficacy measurements carried out at each visit are shown in the table which follows. Patients were evaluated at baseline, and 7-on therapy visits during treatment and at end of weeks 12, 14 and 16 of run-out period. Assessments were made by telephone at end of weeks 11, 13 and 15.

Patients were given a diary card which was to be filled in every time the patient experienced a panic attack. Four of the DSMIII-R symptoms were required for the diagnosis of a full panic attack. The diary recorded a panic inventory or the number of full and limited panic attacks per day, the duration and intensity of each attack and whether an attack was unexpected or situational (brought on by a situation known from experience to bring on an attack). Additionally, the diary recorded the intensity of and percent of time each day engaged in anticipatory anxiety (worrying about attacks or situations that might bring on an attack). A copy of the diary card is in the appendix 7.2.1.4.

Efficacy Evaluations Study 223																
	Pretreat Phase		Base Line	Treatment Phase							Run Out Phase					
WEEK:	-2	-1	0	1	2	3	4	6	8	10	11	12	13	14	15	16
Evaluation																
Panic Inventory and AAA	X	X	X	X	X	X	X	X	X	X		X		X		X
MSPS			X				X			X						
SDS			X				X			X						
CGI			X	X	X	X	X	X	X	X		X		X		X

Data Source: Adapted from Table 2, p. 114, Vol. 27.

Analyses Plan

The ITT population was defined as any patient randomized and receiving study medication. Hence, the patient counts for number randomized and ITT population could be (and generally are) the same. For demographic, safety, medical history, and patient completion/withdrawal count, these are the patients included as the denominator.

The efficacy ITT population (*including baseline data*) consists of patients as defined above who have at least one on-therapy assessment. This number differs from the overall ITT population due to the fact that some patients may have a baseline assessment, but withdraw prior to their first on-therapy assessment. If a patient did not have at least one on-therapy assessment for all efficacy variables of interest, the sample size may not be consistent for each efficacy variable of interest. For example, if a patient had HAMD assessed at visit 1 and 2, but did not have any panic data for visit 1 and 2 before withdrawing, then that patient would be included in the HAMD summaries but no included in panic summaries. Hence, the differences in patient population counts.

The primary efficacy variables were considered to be the following;

- the percentage of patients with 0 full panic attacks during the last 2 weeks of the treatment phase
- the percentage of patients with a 50% or more reduction from baseline in the number of full panic attacks during the last 2 weeks of treatment phase
- the mean change from baseline in the number of full panic attacks during the last 2 weeks of the treatment phase.

The study endpoint for this study was the week 10 visit assessment. For this study, as was the case for study 187 there were fewer than 70% of the patients with a valid final active treatment assessment, so the 70% endpoint for this study was the week 8 visit, even though only 66% of the paroxetine patients completed week 8.

Other efficacy variables considered in this review of protocol 223 were the following: CGI-severity, MSPS (fear and avoidance as separate variables) and the SDS and anticipatory anxiety scales.

Data derived from the panic inventory and anticipatory anxiety assessment, means are given for every 2 weeks in the treatment and run-out phases. Thus, mean values for weeks 2 and 4 are the results of combined data from each patient at visits 1 and 2, and 3 and 4, respectively.

Two sets of efficacy data were used, the visit-wise (OC) dataset and the extender dataset (LOCF). The OC dataset consisted of each patient's data evaluated only for the timepoint when it was collected. No data were carried forward to estimate missing data points. In the LOCF dataset, a patient's last available observation was carried forward to estimate the missing data. The LOCF was considered to be the primary dataset.

Treatment by investigator interaction was significant for the mean change from baseline for many of the variables. Thus, where significant, this term was included in the statistical model. Mean change from baseline for all variables relating to the panic inventory were analyzed using the nonparametric Mann Whitney U Test. Statistical tests were two-tailed and performed at $\alpha = 0.05$ level.

Baseline Demographics

Appendix 7.2.1.4, Table 33, depicts baseline demographics. All three treatment groups were comparable with respect to mean age and age distribution (mean = 39.0, 39.1, and 39.5 years). Females were roughly twice as prevalent as males in each group. The predominant race was Caucasian.

Baseline Illness Severity

The mean frequency of panic attacks at baseline may be used as an indicator of the baseline severity of panic disorder between the individual treatment groups. The mean numbers of panic attacks at baseline for paroxetine were 8.8, for placebo 7.9, and for alprazolam 9.8; these was no statistically significant difference (p=0.675). Likewise, the mean CGI-severity scores at baseline were similar.

Patient Disposition

Appendix 7.2.1.4, table 34, depicts the patient disposition. A total of 226 patients: 77, 72 and 77 patients were randomized at baseline to paroxetine, placebo and alprazolam groups, respectively. However, 10 patients had no on-therapy efficacy data after baseline and were not included in the efficacy analyses (paroxetine = 4; placebo = 2; alprazolam = 4) Thus at baseline, 73, 70 and 73 patients in the paroxetine, placebo and alprazolam groups (N=216) were included in the efficacy analyses. Of the 216 patients with post-baseline efficacy data, 10 were excluded from analysis of panic inventory and anticipatory anxiety data because they did not have data after the week one visit (paroxetine = 5; placebo = 3; alprazolam N = 2). A minimum of 2 weeks of data for these variables was required because mean values for 2 weeks were presented for each 2 week interval. Therefore, the number of patients in which panic inventory and anticipatory anxiety were evaluated were N=206. More alprazolam-treated patients completed the study (78% of 77 patients) than placebo-treated patients (69% of 72 patients) than paroxetine-treated patients (62% of 77 patients).

Dosing Information

Appendix 7.2.1.4 includes a table 35, depicting mean dose over time for the completed cohorts for the two active drug groups, paroxetine and alprazolam. After week 3, patients were allowed to increase their daily dose no more frequently than every 7 days from 30mg of paroxetine and 3mg alprazolam by 10mg and 1mg increments, respectively. The mean daily dose increased throughout the entire 10-week study interval for the paroxetine-treated patients, whereas in the alprazolam-treated patients the mean daily dose plateaued from week 4, onwards. During the 6-week run-out phase, patients were to decrease paroxetine and alprazolam daily dose every 7 days until they received placebo during week 16.

Use of Concomitant Medications

Concomitant medications taken during the treatment and run-out phases of the study were numerous and quite varied (Data source, vol. 27, page 123, table 12).

The most frequently used concomitant medications were analgesics. In the paroxetine-treated group 28 (36.4%) used analgesics, whereas 26 (36.1%) of the placebo-treated group and 35 (45.5%) of alprazolam-treated patients used analgesics. Almost twice as many placebo and alprazolam-treated patients used antacids/antiflat/antipeptic. Antibiotics were used by twice as many paroxetine-treated patients (18.2%) compared to placebo-treated patients (9.7%) and also more frequently than alprazolam-treated patients (10.4%). The most frequently used concomitant medication was ibuprofen.

The line listing of concomitant medications (Appendix 5A) was examined to evaluate the extent of benzodiazepine or tricyclic antidepressant use during double-blind treatment, since these two classes of drugs are thought to possess anti-panic activity. Only one paroxetine- and one placebo-treated patient had such use, both of which were of brief duration (up to 3 days) and early in the study (first 4 weeks). This use is not felt to substantially bias the efficacy results of this trial.

Efficacy Results

Appendix 7.2.1.4 provides summary tables with the efficacy results for this study.

There were no statistically significant differences between the paroxetine and placebo treatment groups in either datasets at any visit with the exception of SDS work, social life and family life measures.

Conclusion

This study did not demonstrate the superiority of either paroxetine or alprazolam over placebo. The lack of statistically significant effects with paroxetine and alprazolam may be due in part to the large placebo response. Also, the mean alprazolam doses were considerably below the maximum allowed in this protocol (i.e. 6 mg/day) and well below the maximum labeled dose for alprazolam in the treatment of panic disorder (i.e. 10 mg/day); therefore, one cannot rule out the possibility that inadequate alprazolam dosing contributed to lack of assay sensitivity. Overall, it is difficult to conclude whether this trial represents a failed study or a negative study.

7.2.2 Extension Studies

There were two extension studies submitted to this NDA. Study 228 was an extension study of 187 and study 222 was an extension study of 120. These extension studies will be discussed separately.

7.2.2.1 Study 228

Investigator/Locations

Appendix table 7.2.2.1 lists the principal investigator for each site in study 228.

Objectives

The stated objective of this extension study was to compare the long-term efficacy and safety of paroxetine, clomipramine and placebo in the treatment of patients with panic disorder.

Population

Patients who had completed the 12 weeks of treatment in study 187 and who did not have significant adverse experiences were eligible to continue treatment and made up the study population. A total of 180 patients in 32 centers and 11 countries entered this study. Therefore the inclusion and exclusion criteria were the same as those in study 187 with the additional inclusion criteria being that patients had to have completed 12 weeks of treatment in study 187 and did not have a significant adverse experience. Patients who had used benzodiazepine during treatment in study 187 were excluded.

Design

This was a double-blind, placebo-controlled, parallel group, 36 week, extension study of study 187. Patients were not re-randomized and proceeded with no interruption in administration of study medication from study 187. Patients received the same dose regimen that they received during the last weeks of the short-term treatment period. The active phase of this 9 month extension study was followed by a 3-week run-out period, during which patients on the higher dose levels were down-titrated off medication.

The daily dosages of paroxetine were 20mg, 40mg or 60mg. The daily dosages of clomipramine were 50mg, 100mg or 150mg.

Assessments

The study visits and the assessments carried out at each visit are provided in the accompanying table. After screening and enrollment (visit 1), patients returned to the clinic at the end of 6, 12, 18, 24, 30 and 36 weeks of treatment (visits 2, 3, 4, 5, 6, and 7) for evaluation.

Efficacy Evaluation
Study 228

	Treatment Phase							Run-out Phase
Week (visit is at end of week)	1[1]	6	12	18	24	30	36	39
Panic Diary Information	X	X	X	X	X	X	X	X
CGI	X	X	X	X	X	X	X	X
MSPS	X	X	X	X	X	X	X	X
SDS	X	X	X	X	X	X	X	X

Data Sources Adopted from Table 3, p. 26, vol. 53.

[1] this visit is at the start of week 1, the remainder (6-39) are at the end of week.

Patients entered study 228 based solely on their willingness to continue and absence of significant adverse events. Some key points to bear in mind.

- A therapeutic response in 187 was not an entry criteria to 228.
- The group of patients who responded in 187 is a subset of the ITT.
- The definitions of full and partial relapse were defined a priori in the protocol.

Response was defined as a ≥ 50% reduction from baseline in the number of full panic attacks (attacks containing at least 4 symptoms during the attack) over the last 3-week period in study 187. Relapse was defined by the sponsor as a return to (or an increase to more than) the number of full panic attacks experienced during the study 187 during any of the 3-week periods. Partial relapse was defined as an increase in the number of full panic attacks during the second, fourth, sixth, eighth, tenth or twelfth 3-week periods during study 228, plus an increase in the CGI severity illness score by 2 points from the 187 end-point interval during the same period in study 228 (that is, week 6, 12, 18, 24, 30 and 36, respectively).

Analysis Plan

The ITT population consisted of all patients who had received study medication and who had data from at least one on-therapy assessment in this study 228. The ITT database was composed of 176 patients distributed as follows: 68 in the paroxetine-treated group, 63 in the clomipramine-treated group and 45 in the placebo-treated group.

The number of panic attacks was totaled over each 3-week period. The primary variables considered in the analyses were;

- the proportion of patients with zero full panic attacks (4 of the DSM III-R symptoms are required for a diagnosis of full panic attack)
- the proportion of patients with a 50% or greater reduction in the number of full panic attacks
- the mean change from baseline in the number of full panic attacks. Baseline for this study was considered to be the baseline of study 187.

Other outcome measures were: CGI-severity score, the MSPS (fear and avoidance) and SDS.

Two datasets were considered in the analyses, the visit-wise dataset (OC) and the extender dataset (LOCF). These datasets also include the baseline and end-point (i.e., fourth 3-week) assessments from study 187. Baseline of this study was considered to be the baseline of study 187. The OC dataset consisted of each patient's observation at each visit. The LOCF dataset was generated from the OC dataset: missing data were estimated by extending forward the data from the previous visit. If the first visit on active treatment was missed then the last visit from study 187 was not used to extend forward. The LOCF dataset was used at the timepoint at which at least 70% of the patients remained in the study. Since there were fewer than 70% of the patients in the placebo group with a valid tenth or twelfth 3-week (or week 30/36) assessment, the primary timepoint in this study was the eighth 3-week (or week 24) period.

The Mann-Whitney U Test was used to analyze continuous data; Fisher's Exact Tests were used to analyze the binary data; Log-rank tests were used to analyze the differences of survival curve distributions. The paroxetine group was compared with both the clomipramine group and the placebo group: a significance level was set at $P \leq 0.05$.

Parenthetically, treatment comparisons under this protocol will be of suspect validity because randomization was lost at the end study 187. Patients entering study 228 were self-selected, as entry of eligible patients were based on willingness to continue and absence of significant adverse events.

Baseline Demographics

Appendix Table 7.2.2.1 depicts baseline demographic characteristics. There were fewer females in the placebo-treated group, 25 (55.6%) than in the paroxetine-treated group, 43 (63.2%); this difference was not statistically significant (p= 0.438, 2-tailed Fisher's exact test). There are no differences in either mean age or race among the three treatment groups.

Baseline Illness Severity

Mean CGI-severity scores for these patients at the beginning of Study 187 were comparable (paroxetine= 4.6, placebo= 4.4, and clomipramine= 4.6).

Patient Disposition

Appendix Table 7.2.2.1 depicts the patient disposition. The ITT population of 176 patients was distributed as follows: 68 patients in the paroxetine-treatment group, 63 patients in the clomipramine-treatment group and 45 patients received placebo.

Of patients in the paroxetine group, 74% completed the study, compared with 68% in the clomipramine group and 60% in the placebo group.

Dosing Information

Appendix Table 7.2.2.1 includes a table depicting mean dose over time. The mean daily paroxetine dose for completers was 42mg and for clomipramine, 105mg.

Use of Concomitant Medications

Concomitant medication use reported during the study was reported by 26 patients (38.2%) in the paroxetine group, 24 patients (38.1%) in the clomipramine group and 13 patients (28.9%) in the placebo group. The most frequently used medications were those drugs with a CNS effect (11.8%, 22.2% and 17.8% of the paroxetine, clomipramine, and placebo-treated patients, respectively). Medications with anti-panic effects (other than the agents under study) were not allowed during study 228. As in Study 187, Protocol 228 specifically prohibited the concomitant use of benzodiazepines. Some patient (2/68 paroxetine patients, 3/63 clomipramine patients, 2/44 placebo patients) took them in spite of the prohibition (usually as an isolated incident) or benzodiazepines may have been administered for the treatment of panic attacks after the patients were withdrawn from the study.

Efficacy Results

Appendix 7.2.2.1 summarizes the efficacy results of study 228.

The percentage of patients in the paroxetine group responding with a reduction in the total number of full panic attacks to zero, was significantly better than placebo at last visit, for the LOCF analysis and OC analysis. There was no statistically significant differences in the other pairwise comparisons.

When the percentage of patients with a reduction of at least 50% in the total number of full panic attacks was examined, there was no statistically significant differences between any of the treatment groups for either LOCF or OC analyses. There was a trend at final visit (LOCF analysis only). There was a higher placebo response rate during treatment (85-88%) in study 228.

Significant differences between paroxetine and placebo groups at weeks 6, 12, 18, 24 and 36, with respect to mean change from baseline in total number of full panic attacks were noted (LOCF analysis). OC analysis revealed statistical significance (paroxetine vs placebo) only at week 6. There was no significant difference between comparisons of paroxetine vs clomipramine or comparisons between clomipramine vs placebo with respect to mean change from baseline in the total number of full panic attacks for either datasets.

Other outcome measures were CGI-severity, MSPS, fear and avoidance (as separate variables) and the SDS. Results are displayed in Appendix Table 7.2.2.1. There was a statistically significant mean change in CGI-severity of illness score at all time periods for paroxetine vs placebo and clomipramine vs placebo comparisons. Data were consistent in the LOCF and OC analyses.

Mean changes from baseline in MSPS total fear scores in paroxetine vs placebo comparisons were statistically significant (in favor of paroxetine) at all time periods for both LOCF and OC dataset analyses. In the clomipramine group, statistical significance over placebo was obtained only at week 18 (LOCF analysis).

There were no statistically significant differences between any group comparisons in the mean change from baseline in MSPS total avoidance score.

A favorable response to treatment with paroxetine vs placebo was also recorded for the SDS work, social life, and family life/home responsibility scores at all timepoints. (LOCF analyses). Clomipramine was less effective.

Of the patients who responded in study 187 (defined as those who had at least a 50% reduction from baseline in the number of full panic attacks in the last 3-week period), 5 (8.3%) in the paroxetine group, 3 (6.0%) in the clomipramine group and 4 (10.8%) in the placebo group suffered a full relapse. There was no statistically significant differences between the groups.

Conclusions

LOCF analysis did reveal patterns of statistically significant differences in the panic inventory as well as in the majority of the secondary measuring scales. Only small numbers of patients experienced a full or partial relapse in the active treatment groups; 5 patients (8%) with full relapse and one patient (2%) with partial relapse in the paroxetine group, and three patients (6%) with full and two patients (4%) with partial relapse in the clomipramine group. In the placebo group, 4 patients (11%) experienced a full relapse and the same number a partial relapse. Although this study was not designed to collect relapse data, there was evidence hinting at a higher incidence of relapse in placebo-treated patients. There were, however, no significant differences between the treatment groups, and no significant difference in the time to full relapse. The main problem with this study was the potential bias secondary to non-random samples. Overall, no conclusions can be drawn from this data regarding long-term anti-panic efficacy, primarily because of the probability of selection bias in the non-randomized groups which were compared.

Extension Study 222

Investigators and location

There were a total of 18 sites in the United States and Canada in study 222. Appendix Table 7.2.1.1 lists the principal investigator for each site in study 120. With the exception of study sites 18 and 19, the investigators and sites were the same in this extension study of 120.

Objectives

There were two stated objectives of this extension of the fixed dose study 120. The first was to evaluate the long-term (6 month) efficacy and safety/tolerance of paroxetine in the treatment of out-patients with panic disorder. A second objective was to assess the relapse of panic disorder in patients receiving either placebo or one of 3 doses of paroxetine after a positive response, then discontinuation of paroxetine.

Population

A total of 138 patients entered study 222. The number of patients per site ranged from 2 to 17. Important criteria for inclusion into study 222 consisted of completion of the 10-week treatment phase of study 120 with no significant ongoing adverse events. In addition, patients were required to have met the criteria for either full or partial responder (during the last two weeks of the 10-week treatment phase of study 120 (partial responder had to have a $\geq$50% reduction in the number of full panic attacks during the last 2 weeks of study 120 relative to study 120 baseline; full responder = no full panic attacks during latter 2-week interval.) Relevant exclusion criteria have been discussed previously in study 120.

Design

Study 220 was a 6-month, randomized, double-blind, parallel design clinical trial conducted in two phases. The first phase, termed the maintenance phase, was a 3-month extension of the dose ranging study 120. In the maintenance phase, patients continued on their respective treatment regimens which consisted of 10mg, 20mg, or 40mg paroxetine daily or placebo for three months.

Patients who were "responders" during the last two weeks of the maintenance phase of study 222 and did not relapse during the course of the maintenance phase, that is the frequency of full panic attacks was equal to or greater than the frequency observed at baseline in study 120, were permitted to enter the second phase, the so-called "re-randomization phase". In the re-randomization phase, patients were re-randomized to either their previous treatment regimen (placebo or 10, 20 or 40mg/day of paroxetine) or to placebo. The re-randomization phase was of 3 months duration. Patients who completed the entire 24 weeks of treatment ended a 4-week-run-out period, during which the paroxetine dose was reduced by 10mg increments at weekly intervals. By the beginning of week 28, all patients were dispensed placebo. All doses were taken as single oral doses.

Clinical visits were scheduled every four weeks during the 12-week maintenance phase, every two weeks for the first four weeks of the re-randomization phase, every four weeks for the last eight weeks of the re-randomization phase and at the end of the run-out phase (week 28), as noted in the outline of study procedures as shown in the below in the assessment section of this review.

Assessments

A schedule of the assessments during protocol 222 are outlined in the table below.

Efficacy Evaluation
Study 222

		Maintenance -Phase-			Re-Randomization -Phase-				Run-Out Phase
WEEK:	Initial Visit	4	8	12	14	16	20	24	28
Screen Evaluations									
Inclusion/Exclusion Criteria	X								
Efficacy Evaluation									
Panic Inventory and AAA	X	X	X	X	X	X	X	X	X
CGI-severity	X	X	X	X	X	X	X	X	X
MSPS	X	X	X	X	X	X	X	X	X
SDS	X	X	X	X	X	X	X	X	X

The initial visit to ascertain eligibility for entry into the study was the final visit, week 10 of study 120. As displayed in the table, assessments were made at end of weeks 4, 8, 12 (maintenance phase), 14, 16, and weeks 20, 24 (re-randomization phase) and at the end of week 28 (run-out period). The sponsor prospectively defined in the protocol the following efficacy variables:

- Percentage of patients who relapsed during the re-randomization phase
- Time until relapse, measured from the beginning of the re-randomization phase.

During the re-randomization phase, a patient was categorized as having experienced a relapse if the frequency of full panic attacks per two weeks was equal to or greater than the frequency observed at baseline in study 120, and/or an increase of two or more points on the CGI severity of illness score from the week 12 visit of maintenance phase.

The sponsor considered the following variables of secondary interest:

- Percentage of patients having zero full panic attacks per 2-week period
- Percentage of patients with a 50% or more reduction from study 120 baseline and the number of full panic attacks per 2-week period
- Mean change from study 120 baseline in the number of full panic attacks per 2-week period
- CGI (severity of illness).

Other variables assessed, and discussed in my review were: MSPS, anticipatory anxiety and the SDS.

Analyses Plan

The intent-to-treat (ITT) population consisted of those patients who received any double-blind medication and entered the maintenance phase. All patients in the ITT population, for whom at least one valid post-treatment efficacy evaluation was available, were included in the ITT efficacy analyses. The ITT population for the Randomization phase of Study 222 received the following treatments.

- Placebo n=62
- 10 mg Paroxetine n=12
- 20 mg Paroxetine n=13
- 40 mg Paroxetine n=18

Two sets of efficacy data were examined, the visit-wise (OC) dataset and the endpoint dataset (LOCF). In the former dataset, efficacy data were evaluated only for the timepoint when it was collected. No data were carried forward to estimate missing data points. The latter dataset consisted of each patient's last available observation in the re-randomization phase, one observation per patient. The LOCF dataset was considered to be the primary dataset by the sponsor.

The pool of all three paroxetine-to-paroxetine dose groups versus the paroxetine-to-placebo groups at the end of the re-randomization phase was the primary comparison of interest. Of secondary consideration were comparisons of these pools at each visit and also paroxetine-to-paroxetine versus paroxetine-to-placebo within each dose level at the final visit. These placebo-treated patients randomized to placebo during the entire study were excluded from the statistical analyses. In the maintenance phase of study 222, mean changes in number of panic attacks, percent of time engaged in and intensity of anticipatory anxiety, CGI-severity of illness score, MSPS and SDS were based on differences from study 120 baseline value for patients. For the re-randomization phase, mean changes in these efficacy scales were expressed as change from last visit at the end of the maintenance phase.

With respect to statistical methodology, either the Cni Square test or Fisher's Exact test was used to analyze the proportion of patients achieving a response per two-week interval, including the proportion having zero full panic attacks and achieving a 50% or greater reduction in the number of full panic attacks, as well as including the proportion relapsing. Relapse during the randomization phase was defined as patients having a number of full panic attacks greater than or equal to the paroxetine 120 study baseline number of full panic attacks and/or greater than or equal to 2 point increase from the last maintenance schedule CGI severity of illness score.

Survival analysis of clinical time to relapse during the randomization phase was to be analyzed using the Cox proportional hazards methodology. Patients not experiencing a relapse were censored. However, due to the small amount of patients who relapsed in the paroxetine-to-paroxetine group (2/43, 4.7%), the time to relapse analysis was not done.

The calculation of change from baseline (change = score - baseline score) required a baseline value. Therefore, if a patient was missing a baseline evaluation for a variable, anv subsequent data was not analyzed. Mean change in CGI severity of illness and the additional efficacy variables was analyzed using parametric analysis of the variance model. Mean change in the number of full panic attacks and other panic inventory variables were analyzed using the nonparametric Mann Whitney U test, which performs analyses on the ranked data.

All statistical comparisons were 2-tailed and perform at the 5% significance level.

Baseline Demographics

Appendix 7.2.2.2, tables 1A and 1B provide baseline demographic characteristics. In the maintenance phase which consisted of the placebo and 3 paroxetine treatment groups, the four treatment groups were comparable with respect to mean age and age distribution (mean = 34 to 38 years). Females were roughly twice as prevalent as males in all groups, except for the 40mg/day group where 58% of the patients were female. The four treatment groups were comparable with respect to race distribution; the predominant race was Caucasian (77 to 93%).

In the re-randomization phase (N=105), the placebo group (paroxetine-to-placebo and placebo-to-placebo combined) and the 3 paroxetine-to-paroxetine treatment groups were comparable with respect to mean age and age distribution (mean = 34 to 39 years). Females were roughly twice as prevalent as males in all groups except for the paroxetine to paroxetine 10mg groups where 83% were females. All four groups were comparable with respect to race distribution; the predominant race was Caucasian (75 to 94%).

Baseline Illness Severity

For the cohort of study 120, patients that entered study 222, the number of panic attacks per two weeks at baseline in the paroxetine 40mg/day dosing group was greater than the other 3 groups.

Patient Disposition

Appendix 7.2.2.2, tables 2-4, provide a summary of the patient disposition. Of a total of 188 patients who completed 120, 138 or 74% entered the maintenance phase of study 222. The ITT population comprised these 138 patients. Of the 138 patients, 116 (84%) completed this 12 week maintenance phase, and 105 patients (76%) entered the re-randomization phase. Of the original 138 patients, 70 (51%) completed the 12 week re-randomization phase. The percentage of patients in each paroxetine group at the end of study 120 who qualified for and entered the maintenance phase tended to be greater than placebo, particularly for the paroxetine 40mg group dose. It appears that slightly more paroxetine-treated patients completed the maintenance phase.

Use of Concomitant Medications

Concomitant medications were numerous and varied with no discernable pattern of use apparent across the treatment groups. During the maintenance phase, the most frequently used concomitant medication (≥10% in any treatment group) were analgesics (53 to 59%) and anti-inflammatory/anti-rheumatic products (25 to 37%).

The most frequently used concomitant medications (≥10% in any treatment group) during the re-randomization phase included analgesics (42 to 69%), anti-inflammatories/anti-rheumatic products (33 to 46%) and systemic antihistamines (11 to 42%).

The line listings of concomitant medications (Appendices 3B, 4,and 5A) were examined to evaluate the extent of benzodiazepine or tricyclic antidepressant use during the re-randomization phase, since these two classes of drugs are thought to possess anti-panic activity. There was one patient in the paroxetine-to-placebo group and 2 patients in the paroxetine-to-paroxetine group who had such use. All of this use was of brief duration (up to 3 days) and, hence, was not felt to significantly impact on the efficacy findings.

Efficacy Results for Protocol 222

The percentage of patients relapsing during the 12-week re-randomization phase is shown in the table on the next page.

Summary of Relapse During Randomization Phase Study 222			
Treatment Group	Relapse		Mean Time (days)
		%	
10 MG -> PLACEBO	2/12	16.7	11.0
20 MG -> PLACEBO	2/12	16.7	24.5
40 MG -> PLACEBO	7/13	53.8	18.9
TOTAL PAROXETINE -> PLACEBO	11/37	29.7	18.5
PAROXETINE 10 MG	0/12	0.0	-
PAROXETINE 20 MG	1/13	7.7	28.0
PAROXETINE 40 MG	1/18	5.6	14.0
PAROXETINE TOTAL	2/43	4.7	21.0
Treatment P-value, % Relapse Par vs Pla: 0.002[a]			

Data Source: Adapted from Table 15, p. 171 in Volume 1 of July 7, 1995 submission

Relapse = Number of Full Par : Attacks >= Study 120 baseline AND/OR >= 2 point increase from last maintenance CGI Severity of Illness.

[a] Treatment p-value comparing % Relapse Total Paroxetine -> Placebo vs Paroxetine Total from Chi-square test,significant for alpha=0 05

In this 6 month study more than 50% of the patients treated daily with doses of the 40mg paroxetine dose and re-randomized to placebo relapsed. Whereas fewer patients (17%) treated with the less efficacious doses of 10 and 20mg/day were reported to have relapsed. In contrast, only 5.6% of patients continuing to take paroxetine at the 40mg/day dose relapsed during the re-randomization phase, and the two smaller and less efficacious doses of 10 and 20mg/day were characterized by a 0 and 8% relapse rate during the re-randomization phase.

Time to relapse was addressed by the sponsor. As shown in the above table, the mean time to relapse after crossing over to placebo occurred for most patients within the first 4 weeks, ranging from 11 to 25 days. Time to relapse in those paroxetine patients continuing to take paroxetine ranged from 14 to 28 days.

Appendix 7.2.2.2 summarizes the other efficacy results of this trial.

Table 5A of Appendix 7.2.2.2 displays the percentage of patients responding with zero full panic attacks over 2-week intervals in a 12-week maintenance phase for the OC dataset only. Table 5B summarizes the percentage of patients responding with zero full panic attacks over two week intervals in the twelve week re-randomization phase for the observed cases. In the first part of this table, data are shown for patients in each of the three paroxetine dose groups who were re-randomized to placebo or continued paroxetine treatment. Despite that fact that a trend existed with regards to a consistently greater response among patients continuing on the paroxetine compared to paroxetine-treated patients crossing over to placebo, none of these differences in response within each paroxetine dose group was statistically significant. The primary comparison was the placebo vs. Paroxetine contrast pooled over the three active arms at the end of the re-randomization phase, as stated in the original protocol (p. 21, section entitled, "Statistical Methodology"). As shown in the second part of this table, when data are combined across the three paroxetine doses and comparisons made between paroxetine to placebo and paroxetine to paroxetine groups for the percentage of patients with zero full panic attacks, the percentage of patients in the paroxetine to paroxetine group with zero panic attacks remained above 85% between end of maintenance and endpoint (86% to 91%), whereas the percentage of responders in the paroxetine to placebo group fell from 81 to 73%. The difference between these two combined groups at endpoint was statistically significant (91 vs 73%, respectively; p = 0.044). In the OC dataset, there was a statistically significant difference between these two groups at the seventh and eighth two-week periods.

The percentage of patients responding with a 50% or greater reduction from baseline in the number of full panic attacks during the maintenance phase is presented in table 6A for the observed cases dataset. The percentage of patients responding was similar between the placebo and three paroxetine dose groups during the majority of the two week intervals in this twelve week maintenance phase. Re-randomization phase data are presented in two parts in Table 6B.

In the first part of the table, their last visit in the maintenance phase all patients who were rerandomized for placebo or continued paroxetine responded with a 50% reduction in attack frequency. In the second part of Table 6B, the data were combined across the three paroxetine dosages and comparisons were made between the paroxetine to placebo and paroxetine to paroxetine groups for the percentage of patients with at least a 50% reduction in number of full panic attacks. The differences between these two groups at endpoint was not statistically significant, whereas a comparison of paroxetine-placebo vs. Paroxetine total, revealed a p-value of 0.05.

The mean change from baseline in number of full panic attacks over two-week intervals in the 12-week maintenance phase is presented in Table 7A for the observed cases dataset. The mean number of full panic attacks at baseline in Study 120 was between 6.48 and 6.75 in the placebo and paroxetine 10mg and 20mg groups, whereas in the paroxetine 40mg group the mean value was higher. At Study 120 endpoint, the mean decrease in number of full panic attacks relative to baseline was between 5.86 and 6.23 in the placebo and paroxetine 10mg and 20mg groups, whereas in the paroxetine 40mg group the mean decrease was higher (8.18).

The mean change from end of maintenance phase in number of full panic attacks over two-week intervals in the 12-week re-randomization phase is presented in Table 7B for the observed cases and endpoint datasets. In the first part of Table 7B data are shown only for patients in each of the three paroxetine dose groups who were re-randomized to placebo or continued paroxetine treatment. At the last visit in maintenance phase there was no appreciable difference between the groups when one considers the standard errors between the groups compared. At endpoint, the mean number of full panic attacks among patients continuing on paroxetine 10, 20, or 40mg did not change appreciably from end of maintenance. The mean number of attacks among patients re-randomized to placebo increased by 0.79, 1.33, and 3.73 in the 10, 20, and 40mg paroxetine groups, respectively. However, because of overlapping standard errors and lack of power the significance, if any remains questionable.

The mean change from end of maintenance phase in CGI severity of illness score in the 12-week *re-randomization phase* is presented in Table 8, data are shown only for patients in each of the three paroxetine dose groups who were re-randomized to placebo or continued paroxetine treatment. At the last visit in maintenance phase, the mean CGI severity of illness scores in the paroxetine 10, 20 and 40mg groups that were re-randomized to placebo were slightly less than values in the corresponding paroxetine-to-paroxetine groups. Patients crossing over to placebo showed a mean increase in severity of illness at endpoint. In contrast, patients continuing on paroxetine treatment showed no change in CGI severity of illness score.

The mean change from end of maintenance phase in intensity of anticipatory anxiety over two-week intervals in the 12-week *re-randomization phase* is presented in Table 9B for the OC and LOCF datasets. There were no differences between any of the treatment groups.

The mean change from end of maintenance phase in overall MSPS fear score in the 12-week *re-randomization phase* is presented in Table 10A for the observed cases and endpoint datasets. At endpoint, the mean MSPS fear score among patients continuing on paroxetine 10, 20 and 40mg increased by 0.42 and 0.09, and decreased by 0.16, respectively. For the combined paroxetine-to-paroxetine groups, the mean value at endpoint was an increase of 0.07, whereas patients in the combined paroxetine-to-placebo group showed a mean increase in score of 1.69. The difference between these two combined groups at endpoint in mean MSPS fear score was statistically significant, ($p \leq 0.006$).

The mean change from end of maintenance phase in overall MSPS avoidance score in the 12-week *re-randomization phase* is presented in Table 11 for the OC and LOCF. There were no statistically significant differences.

The mean change from end of maintenance phase in SDS work score in the 12-week *re-randomization phase* for OC and LOCF datasets failed to demonstrate statistical significance (table 12).

Conclusions

When all paroxetine-to-paroxetine groups are pooled and compared to all paroxetine-to-placebo groups, there is a statistically significant difference in terms of percent relapse (4.7% vs. 29.7%, respectively; p= 0.002). Mean times to relapse are comparable (21.0 vs. 18.5 days, respectively).

Additionally, when one compares groups within the 40mg/day dose level, patients continuing paroxetine (paroxetine-paroxetine) treatment relapsed at a rate 9-fold higher than patients discontining paroxetine (paroxetine-placebo (54 vs 6%). Due to the small number of paroxetine patients relapsing at the other dose levels, statistical testing for those comparisons were not performed. The vast majority of all patients relapsed within the first month after crossover.

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

Sub-group analyses of three efficacy variables, namely mean change from baseline in the number of full panic attacks, number of patients having zero full panic attacks and reduction ≥ 50% from baseline of number of panic attacks were performed on each of the four short-term studies; 108, 120, 187 and 223, with the following covariants: gender and baseline severity of illness. For all four studies, there was no significant effect of these covariants on the three efficacy variables at primary endpoint, as defined previously in my review, except for the zero full panic attacks in study 223, where alprazolam-treated males demonstrated a high rate of response. In all four studies, there were statistically significant covariant effects for baseline severity for one or more efficacy variables. For change in mean number of full panic attacks, the patients in the more severe cohort showed more improvement, whereas higher proportions of patients in the less severe cohort showed zero full panic attacks and reductions of ≥ 50% in number of full panic attacks. As pointed out by the sponsor, this is not surprising, in light of the fact that patients with a higher frequency of panic attacks at baseline would be expected to have the greater margin to reduce the number of their panic attacks. There were no other consistent statistically significant findings across these studies.

7.3.2 Size of Treatment Effect

The efficacy data for study 120, 187 and 108 were examined to estimate the magnitude of the treatment effect size, with respect to the efficacy variable mean change from baseline in the number of panic attacks and are summarized in the table which follows. The efficacy data for study 223 was not included because of the fact that it was a failed study. The evaluation of treatment effect size in study 120 focused on the 40mg dose group. Clomipramine, which was used as an active control drug for protocol 187, is also incorporated into this table for comparisons. Clomipramine is not an established treatment for panic by our standards.

The differences between paroxetine and placebo in the mean change from baseline at the final study week favored paroxetine over placebo.

Summary of Treatment Effect Sizes* in Positive Panic Disorder Short-Term Trials		
Treatment Group	**Mean Change from Baseline in Number of Panic Attacks**	**Absolute Change from Baseline to Endpoint in Number of Panic Attacks**
120 (40mg dose)	-3**	9.6 to 0.5
187	-3	17.9 to 3.8
187 clomipramine	+0.1	15.3 to 4.6
108	-6	21.2 to 5.2

* Difference between drug and placebo means at final week in panic disorder datasets. OC at last visit, paroxetine/placebo difference (negative numbers indicate paroxetine was superior to placebo and positive numbers indicate placebo was superior).
** Note that the time interval for recording panic attacks was 2 weeks for 120 and 3 weeks for both 187 and 108. Hence, these figures are not directly comparable.
A 50% reduction in the frequency of panic attacks and the proportion of patients who are panic-free are often regarded as indices of clinical improvement in panic disorder trials. Recently, a meta-analysis by Boyer (Int. Clin Psychopharmacol,10:45,1995) was conducted which evaluated the treatment effect size of a number of anti-panic agents, based on the proportion of patients considered to be panic-free at endpoint. The conclusion from their analyses was that the treatment effect sizes for paroxetine were comparable to or even exceeded those for fluvoxamine, clomipramine, imipramine and alprazolam.

7.3.3 Choice of Dose

Based on one fixed-dose study (study 120), the minimum effective dose of paroxetine in the treatment of panic disorder is 40mg per day. In this study, pairwise comparisons of outcome measures between placebo and the 10 or 20mg paroxetine doses were not statistically significant. The only pairwise comparisons which were statistically significant were the 40mg paroxetine vs placebo comparisons. Nevertheless, the dosing recommendation by the sponsor is for patients to begin treatment with a 10mg/day dose of paroxetine with titration based on efficacy and tolerability to 60mg/day. These dosing recommendations are similar to those which exist for patients with depression.

7.3.4 Duration of Treatment

Study 222 was a six month extension of study 120 to assess the long-term efficacy of paroxetine in the treatment of panic disorder. This study was divided into a three month maintenance phase followed by a three month re-randomization phase. Overall, based on the response of paroxetine-treated patients by such measurements as zero panic attacks, ≥50% reduction in number of full panic attacks and mean change from baseline in the number of full panic attacks there was inconclusive evidence for efficacy in this extension study. For the most part, paroxetine was not consistently superior to placebo in comparisons of the efficacy measures. However, in terms of relapse prevention, the findings demonstrate that paroxetine, particularly at the 40mg/day dose, was effective in preventing relapse of panic disorder symptoms after 22 weeks of treatment (paroxetine relapse rate = 5.6% vs. placebo rate= 53.8%).

7.4 Conclusions Regarding Efficacy Data

Table 7.4 summarizes the efficacy results for the four panic disorder studies at week 10 in the two ten-week studies (120 and 223) and at week 12 in the two twelve-week studies (108 and 187).

Table 7.4
Summary of Efficacy Results for the Panic Disorder Program Short-Term Trials
(Significance of Drug/Placebo Comparisons)

Study	Active Drug Group	Panic Inventory							
		% Reduction[2]		% 50 % [2]		Mean Δ From Baseline[2]		CGI Severity	
		LOCF[3]	OC[3]	LOCF	OC	LOCF	OC	LOCF	OC
120	PAR 10	ns	ns	ns	ns	ns	ns	ns	ns
	PAR 20	ns	ns	ns	ns	tr	ns	ns	ns
	PAR 40	tr	*	ns	ns	*	*	tr	*
108	PAR	*	*	*	*	ns	tr	*	*
187	PAR	*	ns	*	ns	*	ns	*	ns
	CLO	*	ns	ns	ns	ns	ns	ns	ns
223	PAR	ns	ns	ns	ns	ns	ns	ns	ns
	APZ	ns	ns	ns	ns	ns	ns	ns	ns

1)Significance Codes For Studies 108, 187 and 223: ns=non-significant, tr=trend ($0.05<p\leq.10$), *=significant ($p\leq0.05$)
Significant Codes For Study 120: ns=non-significant, tr=trend ($0.019 < p \leq 0.05$), *=significant ($p \leq 0.019$)

2) Panic inventory consists of 3 items:

- percentage of patients with zero or 1 panic attack
- percentage of patients with a 50% or greater reduction
- Mean change from baseline in the number of panic attacks

3) LOCF = Last Observation Carried Forward
OC = Observed Cases

Table 7.4
Summary of Efficacy Results for the Panic Disorder Short-Term Trials
(Significance of Drug/Placebo Comparisons)

Study	Active Drug Group	Panic Inventory					
		MSPS-Fear		MSPS-Avoid		Anticip.Anx	
		LOCF[3]	OC[3]	LOCF	OC	LOCF	OC
120	PAR 10	ns	ns	ns	ns	ns	ns
	PAR 20	*	*	ns	ns	ns	ns
	PAR 40	*	*	ns	tr	ns	ns
108	PAR	not measured					
187	PAR	*	*	*	ns	not measured	
	CLO	*	*	*	*	not measured	
223	PAR	ns	tr	ns	ns	ns	ns
	APZ	ns	ns	ns	ns	ns	ns

1)Significance Codes For Studies 108, 187 and 223: ns= non-significant, tr=trend ($0.05<p\leq0.10$)
* = significant ($p\leq0.05$)

Significant Codes For Study 120: ns= non-significant, tr=trend ($0.019 < p \leq 0.05$)
* = significant ($p \leq 0.019$)

2) LOCF = Last Observation Carried Forward
OC = Observed Cases

In the fixed-dose study (study 120), the 40mg dose group showed significant improvement in two of the three panic inventory measures, as well as the CGI severity score and phobic fear scale. Study 120 was a marginally positive study.

Study 108 provided evidence to support the efficacy of paroxetine in the treatment of panic disorder with respect to two of the panic inventory categories and the CGI-S. Study 108 was a positive study.

Study 187 provided strong evidence to support the efficacy of paroxetine in the treatment of panic disorder across multiple domains of panic disorder including: panic frequency, CGI-S, phobic avoidance and fear (in LOCF but not OC analyses). Additionally, statistically significant differences were recorded at many time points in addition to the endpoint.

Study 223 was considered either a failed or negative trial, depending on whether one considers the administered doses of alprazolam sufficient to produce a therapeutic response. There was no evidence of superiority for either paroxetine or alprazolam over placebo. While it is not possible to fully explain the outcome of this trial, strong existent placebo responses may have been one of the factors.

In summary, 3 of the 4 studies demonstrated varying degrees of efficacy for paroxetine in the treatment of panic disorders. Significant improvement in a preponderance of outcome variables measured at endpoint occurred in studies 187 and 108, both European studies. Of the two U.S. studies, study 120 was marginally positive and study 223 was a failed or a negative study.

8.0 Safety Findings

8.1 Methods

The clinical safety of paroxetine used in the treatment of panic disorder was evaluated through the analysis of adverse experience reports, clinical laboratory analytes, vital signs and ECGs. The search for serious events included on evaluation of death(section 8.2), dropouts due to adverse events (section 8.3) and an evaluation of other events identified as serious by the sponsor (section 8.4). In addition, routine withdrawal phenomena and abuse potential are discussed in section 8.5.6, available information pertaining to human reproduction experiences is provided in section 8.5.7. Overdose experience in patients exposed to paroxetine is discussed in section 8.5.8. Section 8.6 provides a summary of adverse experiences to be considered both important and possibly/ probably related to exposure to paroxetine. Serious events considered unlikely to be drug-related are displayed in section 8.7. Drug-demographic, drug-disease, drug-drug interaction are summarized in section 8.8.

Additionally, the data base were examined to determine if there were any gender-related differences as well as age and race-related differences in adverse experience rates. Potential dose-response relationships were examined.

As a component of this review, an audit of randomly selected CRFs was done. The CRFs which were audited are identified in the Appendix 8.1. Ten volumes were submitted and reviewed. Results are presented in 5.1.4.

TABLE 43
Study: 223
Mean Change from Baseline in Intensity of Anticipatory Anxiety

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week									
	BL Mean		Wk 1 and 2		Wk 3 and 4		Wk 5 and 6		Wk 7 and 8	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ
Paroxetine	68	3.36	66	2.92	67	1.53	67	-0.53	67	-0.59
Alprazolam	70	3.89	69	1.94+	69	1.18	69	1.57*+	59	-1.47
PLA	67	3.36	67	2.21	67	1.67	67	-0.59	67	-1.06
2-sided p-values for pairwise comparisons										
Paroxetine vs. PLA	N/S		.100		.680		.824		.414	
Par. vs. Alprazolam	N/S		.013*		.499		.042*		.082	
Alprazolam vs. PLA	N/S		.542		.285		.022*		.344	

OBSERVED CASE ANALYSIS

Treatment Groups	Treatment Week									
	BL Mean		Wk 1 and 2		Wk 3 and 4		Wk 5 and 6		Wk 7 and 8	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ
Paroxetine	68	3.36	66	2.92	57	1.31	53	-1.37	51	-1.47
Alprazolam	70	3.89	69	1.94+	63	1.12	62	-1.94*	61	-1.87
PLA	67	3.36	67	2.21	59	1.69	59	-0.77	53	-1.33
2-sided p-values for pairwise comparisons										
Paroxetine vs. PLA	N/S		.100		.383		.135		.819	
Pa. vs.Alprazolam	N/S		.013*		.812		.205		.291	
Alprazolam vs. PLA	N/S		.542		.259		.008*		.209	

Significant for alpha = 0.05: * active drug vs. placebo, + alprazolam vs. paroxetine N/S = Not Significant

TABLE 43
Study:223
Mean Change from Baseline in Intensity of Anticipatory Anxiety

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week					
	Wk 9 and 10					
	n	X	n	Δ	n	Δ
Paroxetine	68	-0.94				
Alprazolam	70	-1.59				
PLA	67	-1.08				
2-sided p-values for pairwise comparisons						
Paroxetine vs. PLA	.988					
Par. vs. Alprazolam	.268					
Alprazolam vs. PLA	.247					

OBSERVED CASE ANALYSIS

Treatment Groups	Treatment Week					
	Wk 9 and 10					
	n	X	n	Δ	n	Δ
Paroxetine	53	-1.70				
Alprazolam	60	-1.98				
PLA	51	-1.26				
2-sided p-values for pairwise comparisons						
Paroxetine vs. PLA	.191					
Par vs. Alprazolam	.653					
Alprazolam vs. PLA	.095					

TABLE 44
Study:223
Mean Change from Baseline in SDS Work

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week									
	BL Mean		Wk 4		Wk 10					
	n	X	n	Δ	n	Δ				
Paroxetine	60	4.31	57	-2.94	58	-3.08				
Alprazolam	65	3.98	61	-2.30	65	-2.66				
PLA	64	4.23	57	-1.85	64	-2.17				
2-sided p-values for pairwise comparisons										
Paroxetine vs. PLA	.880		.025*		.059					
Par. vs. Alprazolam	.534		.186		.386					
Alprazolam vs. PLA	.630		.359		.306					

OBSERVED CASE ANALYSIS

Treatment Groups	Treatment Week									
	BL Mean		Wk 4		Wk 10					
	n	X	n	Δ	n	Δ				
Paroxetine	60	4.31	55	-2.91	48	-2.88				
Alprazolam	65	3.98	59	-2.33	58	-2.63				
PLA	64	4.23	55	-1.92	50	-2.59				
2-sided p-values for pairwise comparisons										
Paroxetine vs. PLA	.880		.051		.590					
Par. vs. Alprazolam	.534		.255		.622					
Alprazolam vs. PLA	.630		.412		.934					

* Significant for alpha = 0.05

TABLE 45
Study: 223
Mean Change from Baseline in SDS Social Life

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week									
	BL Mean		Wk 4		Wk 10					
	n	X	n	Δ	n	X	n	Δ	n	Δ
Paroxetine	61	4.86	59	-2.45	60	-3.24				
Alprazolam	66	4.67	62	-2.09	66	-2.65				
PLA	65	5.03	58	-1.58	65	-2.18				
2-sided p-values for pairwise comparisons										
Paroxetine vs. PLA	.737		.055		.024*					
Par. vs. Alprazolam	.702		.418		.207					
Alprazolam vs. PLA	.465		.262		.309					

OBSERVED CASE ANALYSIS

Treatment Groups	Treatment Week									
	BL Mean		Wk 4		Wk 10					
	n	X	n	Δ	n	Δ	n	Δ	n	Δ
Paroxetine	61	4.86	57	-2.53	49	-3.30				
Alprazolam	66	4.67	59	-2.11	58	-2.65				
PLA	65	5.03	55	-1.61	50	-2.42				
2-sided p-values for pairwise comparisons										
Paroxetine vs. PLA	.737		.052		.104					
Par. vs. Alprazolam	.702		.383		.194					
Alprazolam vs. PLA	.465		.284		.664					

* - Significant for alpha = 0.05

APPENDIX 7.2.2.1

STUDY 228

TABLE 46
Study:223
Mean Change from Baseline in SDS Family Life

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week									
	BL Mean		Wk 4		Wk 10					
	n	X	n	Δ	n	Δ	n	Δ	n	Δ
Paroxetine	61	3.97	59	-2.14	60	-2.65				
Alprazolam	66	4.04	62	-1.71	66	-2.39				
PLA	65	3.76	58	-1.06	65	-1.73				
2-sided p-values for pairwise comparisons										
Paroxetine vs. PLA	.664		.042*		.045*					
Par. vs. Alprazolam	.896		.415		.572					
Alprazolam vs. PLA	.565		.218		.141					

OBSERVED CASE ANALYSIS

Treatment Groups	Treatment Week									
	BL Mean		Wk 4		Wk 10					
	n	X	n	Δ	n	Δ	n	Δ	n	Δ
Paroxetine	61	3.97	57	-2.23	49	-2.69				
Alprazolam	66	4.04	59	-1.87	58	-2.60				
PLA	65	3.76	55	-1.07	50	-2.21				
2-sided p-values for pairwise comparison										
Paroxetine vs. PLA	.664		.036*		.374					
Par. vs. Alprazolam	.896		.507		.859					
Alprazolam vs. PLA	.565		.151		.461					

* - Significant for alpha = 0.05

Appendix 7.2.2.1
Principal Investigators (Study 228)

Investigator	City, Country
Carlos Ballus	Barcelona, Spain
Istvan Bitter	Budapest, Hungary
Michel Bourin	Nanges, France
Battista Cassano	Pisa, Italy
Poul Ernst Christiansen	Aarhus, Denmark
J. M. G. Coppens	Amersfoort, The Netherlands
André de Nayer	Montigny-sur-Sambre, Belgium
Christian Gaussares	Bordeaux, France
Miguel Gutierrez	Vitoria, Spain
John Haug	Fredrikstad, Norway
Fred Holsten	Bergan Norway
Antal Kasas	Bellelay, Switzerland
Nicole Lantieri-Kieffer	Porto Vecchio, France
Seth Kindler	Tel-Hashomer, Israel
Y. Lecrubier	Paris, France
David Nutt	Bristol, UK
Frank O'Donoghue	Dublin, Ireland
Søren Øhrberg	Aalborg, Denmark

Appendix 7.2.2.1
Principal Investigators (Study 228)

Investigator	City, Country
Myriam Peeters	Lier, Belgium
A Querido	Amersfoort, The Netherlands
Arlette Seghers	Brussels, Belgium
Pierre Le Boubey Michel Rigaud	Caen, France
Birgit Severin	Copenhagen, Denmark
Ilan Treves	Hod Hasharon, Israel
Richard Van Dijk	Amsterdam, The Netherlands
Myriam Van Moffaert	Gent, Belgium
József Varga	Pecs, Hungary
Tim Webb	Bury St Edmunds, UK
Paul Willemse	Mouscron, Belgium
Jean Wilmotte	Marchienne-au-Pont, Belgium

TABLE 47
Study : 228
Demographic Characteristics of Extension Sample at Baseline*

Treatment Groups		Age (years)		Sex [n(%)]		Race [n(%)]	
	n	Mean	Range	Male	Female	White	Non-White
PAR	68	35.0	20 - 66	25 (36.8)	43 (63.2)	68 (100.0)	0 (0.0)
PLA	45	36.7	19 - 62	20 (44.4)	25 (55.6)	45 (100.0)	0 (0.0)
CLO	63	34.9	20 - 53	28 (44.4)	35 (55.6)	63 (100.0)	0 (0.0)

TABLE 48
Study : 228
Patient Completion Rates

Treatment Groups	Number Extended	Intent to Treat Sample	Completers [n(%)]					
			Wk 6	Wk 12	Wk 18	Wk 24	Wk 30	Wk 36
PAR	70	68	64 (94.1)	61 (89.7)	57 (83.8)	55 (80.9)	51 (75.0)	50 (73.5)
PLA	46	45	39 (86.7)	39 (86.7)	35 (77.8)	31 (68.9)	29 (64.4)	27 (60.0)
CLO	64	63	56 (88.9)	54 (85.7)	48 (76.2)	44 (69.8)	44 (69.8)	43 (68.3)

TABLE 49
Study : 228
Dosing Information

Treatment Groups	Mean Dose (mg) for Completers in Active Drug Groups						
	BL*	Wk 6	Wk 12	Wk 18	Wk 24	Wk 30	Wk 36
PAR		42.0	42.0	42.0	42.0	42.0	42.0
CLO		104.9	104.9	104.9	104.9	104.9	104.9

* Baseline for this study is considered to be the baseline of Study 187.

TABLE 50
Study : 228
Response Rates - Number of Full Panic Attacks Reduced to Zero

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week							
	BL* Mean		2nd 3-weeks		4th 3-weeks		6th 3-weeks	
	n	X	n	N (%)	n	N (%)	n	N (%)
PAR	66	17.5	64	44 (68.8)	65	47 (72.3)	65	45 (69.2)
PLA	43	14.3	42	26 (61.9)	43	28 (65.1)	43	30 (69.8)
CLO	63	16.0	58	43 (74.1)	58	41 (70.7)	58	43 (74.1)
2 - sided p - values for pairwise comparisons								
PAR vs PLA	0.20		0.53		0.52		1.00	
CLO vs PLA	0.34		0.27		0.66		0.66	
PAR vs CLO	0.73		0.55		0.85		0.69	

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week							
	BL* Mean		2nd 3-weeks		4th 3-weeks		6th 3-weeks	
	n	X	n	N (%)	n	N (%)	n	N (%)
PAR	66	17.5	64	44 (68.8)	61	44 (72.1)	58	41 (70.7)
PLA	43	14.3	40	26 (65.0)	36	25 (69.4)	35	26 (74.3)
CLO	63	16.0	57	42 (73.7)	52	37 (71.2)	51	39 (76.5)
2 - sided p - values for pairwise comparisons								
PAR vs PLA	0.20		0.83		0.82		0.81	
CLO vs PLA	0.34		0.38		1.00		1.00	
PAR vs CLO	0.73		0.69		1.00		0.52	

* Baseline for this study is considered to be the baseline of Study 187.

TABLE 50
Study : 228
Response Rates - Number of Full Panic Attacks Reduced to Zero

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week					
	8th 3-weeks		10th 3-weeks		12th 3-weeks	
	n	N (%)	n	N (%)	n	N (%)
PAR	65	48 (73.8)	65	45 (69.2)	65	55 (84.6)
PLA	43	28 (65.1)	44	29 (65.9)	44	26 (59.1)
CLO	58	45 (77.6)	58	39 (67.2)	58	42 (72.4)
2 - sided p - values for pairwise comparisons						
PAR vs PLA	0.39		0.84		0.004	
CLO vs PLA	0.18		1.00		0.20	
PAR vs CLO	0.68		0.85		0.12	

OBSERVED CASE ANALYSIS

Treatment Groups	Treatment Week					
	8th 3-weeks		10th 3-weeks		12th 3-weeks	
	n	N (%)	n	N (%)	n	N (%)
PAR	54	39 (72.2)	50	34 (68.0)	49	41 (83.7)
PLA	31	21 (67.7)	29	21 (72.4)	25	15 (60.0)
CLO	45	37 (82.2)	43	29 (67.4)	42	31 (73.8)
2 - sided p - values for pairwise comparisons						
PAR vs PLA	0.81		0.80		0.043	
CLO vs PLA	0.18		0.90		0.93	
PAR vs CLO	0.34		1.00		0.31	

* Baseline for this study is considered to be the baseline of Study 187.

TABLE 51
Study : 228
Response Rates - 50% reduction from baseline in number of Full Panic Attacks

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week							
	BL* Mean		2nd 3-weeks		4th 3-weeks		6th 3-weeks	
	n	X	n	N (%)	n	N (%)	n	N (%)
PAR	66	17.5	64	59 (92.2)	65	61 (93.8)	65	62 (95.4)
PLA	43	14.3	41	35 (85.4)	42	36 (85.7)	42	36 (85.7)
CLO	63	16.0	58	50 (86.2)	58	51 (87.9)	58	54 (93.1)
2 - sided p - values for pairwise comparisons								
PAR vs PLA	0.20		0.33		0.19		0.15	
CLO vs PLA	0.34		1.00		0.77		0.31	
PAR vs CLO	0.73		0.38		0.35		0.71	

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week							
	BL* Mean		2nd 3-weeks		4th 3-weeks		6th 3-weeks	
	n	X	n	N (%)	n	N (%)	n	N (%)
PAR	66	17.5	64	59 (92.2)	61	58 (95.1)	58	56 (96.6)
PLA	43	14.3	39	34 (87.2)	35	30 (85.7)	34	29 (85.3)
CLO	63	16.0	57	49 (86.0)	52	46 (88.5)	51	47 (92.2)
2 - sided p - values for pairwise comparisons								
PAR vs PLA	0.20		0.50		0.14		0.096	
CLO vs PLA	0.34		1.00		0.75		0.47	
PAR vs CLO	0.73		0.38		0.30		0.42	

* Baseline for this study is considered to be the baseline of Study 187.

TABLE 51
Study : 228
Response Rates - 50% reduction from baseline in number of Full Panic Attacks

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week					
	8th 3-weeks		10th 3-weeks		12th 3-weeks	
	n	N (%)	n	N (%)	n	N (%)
PAR	65	61 (93.8)	65	62 (95.4)	65	63 (96.9)
PLA	42	37 (88.1)	43	38 (88.4)	43	37 (86.0)
CLO	58	54 (93.1)	58	53 (91.4)	58	54 (93.1)
2 - sided p - values for pairwise comparisons						
PAR vs PLA	0.31		0.26		0.057	
CLO vs PLA	0.49		0.74		0.32	
PAR vs CLO	1.00		0.47		0.42	

OBSERVED CASE ANALYS

Treatment Groups	Treatment Week					
	8th 3-weeks		10th 3-weeks		12th 3-weeks	
	n	N (%)	n	N (%)	n	N (%)
PAR	54	51 (94.4)	50	48 (96.0)	49	48 (98.0)
PLA	30	26 (86.7)	28	25 (89.3)	25	22 (88.0)
CLO	45	42 (93.3)	43	39 (90.7)	42	39 (92.9)
2 - sided p - values for pairwise comparisons						
PAR vs PLA	0.24		0.34		0.11	
CLO vs PLA	0.43		1.00		0.66	
PAR vs CLO	1.00		0.41		0.33	

* Baseline for this study is considered to be the baseline of Study 187.

TABLE 52
Study : 228
Mean Change from Baseline* in Number of Full Panic Attacks
LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week							
	BL* Mean		2nd 3-weeks		4th 3-weeks		6th 3-weeks	
	n	X	n	Δ	n	Δ	n	Δ
PAR	66	17.5	64	-15.6	65	-15.8	65	-15.8
PLA	43	14.3	41	-9.6	42	-9.8	42	-9.4
CLO	63	16.0	58	-13.3	58	-14.0	58	-13.0
2 - sided p - values for pairwise comparisons								
PAR vs PLA	0.20		0.031		0.032		0.049	
CLO vs PLA	0.34		0.14		0.18		0.17	
PAR vs CLO	0.73		0.49		0.45		0.49	

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week							
	BL* Mean		2nd 3-weeks		4th 3-weeks		6th 3-weeks	
	n	X	n	Δ	n	Δ	n	Δ
PAR	66	17.5	64	-15.6	61	-15.8	58	-15.2
PLA	43	14.3	39	-9.9	35	-11.0	34	-9.9
CLO	63	16.0	57	-13.3	52	-14.1	51	-12.6
2 - sided p - values for pairwise comparisons								
PAR vs PLA	0.20		0.042		0.13		0.14	
CLO vs PLA	0.34		0.21		0.57		0.40	
PAR vs CLO	0.73		0.42		0.40		0.44	

* Baseline for this study is considered to be the baseline of Study 187.

TABLE 52
Study : 228
Mean Change from Baseline* in Number of Full Panic Attacks
LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week					
	8th 3-weeks		10th 3-weeks		12th 3-weeks	
	n	Δ	n	Δ	n	Δ
PAR	65	-16.1	65	-15.9	65	-16.3
PLA	42	-10.2	43	-11.0	43	-10.3
CLO	58	-14.3	58	-14.0	58	-13.4
2 - sided p - values for pairwise comparisons						
PAR vs PLA	0.038		0.084		0.039	
CLO vs PLA	0.16		0.24		0.20	
PAR vs CLO	0.51		0.56		0.40	

OBSERVED CASE ANALYSIS

Treatment Groups	Treatment Week					
	8th 3-weeks		10th 3-weeks		12th 3-weeks	
	n	Δ	n	Δ	n	Δ
PAR	54	-16.4	50	-15.5	49	-17.0
PLA	30	-10.8	28	-11	25	-10.7
CLO	45	-14.6	43	-14.8	42	-14.3
2 - sided p - values for pairwise comparisons						
PAR vs PLA	0.068		0.21		0.080	
CLO vs PLA	0.30		0.27		0.20	
PAR vs CLO	0.44		0.87		0.51	

* Baseline for this study is considered to be the baseline of Study 187.

TABLE 53
Study : 228
Mean Change from Baseline* in CGI Severity of Illness

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week							
	BL* Mean		Wk 6		Wk 12		Wk 18	
	n	X	n	Δ	n	Δ	n	Δ
PAR	68	4.6	67	-2.6	67	-2.7	67	-2.7
PLA	45	4.4	44	-1.8	44	-1.9	44	-2.0
CLO	63	4.6	60	-2.4	61	-2.5	61	-2.6
2 - sided p - values for pairwise comparisons								
PAR vs PLA	0.29		0.003		0.001		0.002	
CLO vs PLA	0.36		0.029		0.029		0.013	
PAR vs CLO	0.91		0.37		0.27		0.77	

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week							
	BL* Mean		Wk 6		Wk 12		Wk 18	
	n	X	n	Δ	n	Δ	n	Δ
PAR	68	4.6	67	-2.6	60	-2.7	58	-2.7
PLA	45	4.4	44	-1.8	39	-2.1	38	-2.1
CLO	63	4.6	60	-2.4	56	-2.5	53	-2.7
2 - sided p - values for pairwise comparisons								
PAR vs PLA	0.29		0.003		0.007		0.013	
CLO vs PLA	0.36		0.029		0.088		0.026	
PAR vs CLO	0.91		0.37		0.33		0.90	

* Baseline for this study is considered to be the baseline of Study 187.

TABLE 53
Study : 228
Mean Change from Baseline* in CGI Severity of Illness

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week					
	Wk 24		Wk 30		Wk 36	
	n	Δ	n	Δ	n	Δ
PAR	67	-2.9	67	-2.9	67	-3.0
PLA	44	-1.9	44	-1.9	44	-2.1
CLO	61	-2.7	61	-2.7	61	-2.7
2 - sided p - values for pairwise comparisons						
PAR vs PLA	< 0.001		< 0.001		< 0.001	
CLO vs PLA	0.004		0.004		0.018	
PAR vs CLO	0.47		0.35		0.23	

OBSERVED CASE ANALYSIS

Treatment Groups	Treatment Week					
	Wk 24		Wk 30		Wk 36	
	n	Δ	n	Δ	n	Δ
PAR	55	-2.9	50	-2.9	51	-3.0
PLA	33	-2.1	30	-1.8	29	-2.0
CLO	44	-2.9	41	-2.8	43	-2.8
2 - sided p - values for pairwise comparisons						
PAR vs PLA	0.001		< 0.001		< 0.001	
CLO vs PLA	0.003		< 0.001		0.005	
PAR vs CLO	0.94		0.80		0.34	

* Baseline for this study is considered to be the baseline of Study 187.

TABLE 54
Study : 228
Mean Change from Baseline* in MSPS Total Fear score
LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week							
	BL* Mean		Wk 6		Wk 12		Wk 18	
	n	X	n	Δ	n	Δ	n	Δ
PAR	68	45.5	67	-31.0	67	-33.7	67	-35.4
PLA	44	46.5	41	-20.8	44	-22.7	44	-22.5
CLO	62	51.5	59	-29.2	59	-30.6	59	-32.1
2 - sided p - values for pairwise comparisons								
PAR vs PLA	1.00		0.012		0.004		0.001	
CLO vs PLA	0.33		0.076		0.080		0.038	
PAR vs CLO	0.18		0.80		0.58		0.65	

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week							
	BL* Mean		Wk 6		Wk 12		Wk 18	
	n	X	n	Δ	n	Δ	n	Δ
PAR	68	45.5	67	-31.0	59	-33.8	58	-37.8
PLA	44	46.5	41	-20.8	38	-24.7	37	-24.4
CLO	62	51.5	59	-29.2	55	-30.9	51	-34.6
2 - sided p - values for pairwise comparisons								
PAR vs PLA	1.00		0.012		0.030		0.004	
CLO vs PLA	0.33		0.076		0.23		0.048	
PAR vs CLO	0.18		0.80		0.49		0.65	

* Baseline for this study is considered to be the baseline of Study 167.

TABLE 54
Study : 228
Mean Change from Baseline* in MSPS Total Fear score
LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week					
	Wk 24		Wk 30		Wk 36	
	n	Δ	n	Δ	n	Δ
PAR	67	-36.3	67	-36.8	67	-37.6
PLA	44	-25.3	44	-25.7	44	-25.6
CLO	59	-33.3	59	-33.6	59	-33.4
2 - sided p - values for pairwise comparisons						
PAR vs PLA	0.006		0.006		0.006	
CLO vs PLA	0.061		0.077		0.079	
PAR vs CLO	0.56		0.50		0.48	

OBSERVED CASE ANALYSIS

Treatment Groups	Treatment Week					
	Wk 24		Wk 30		Wk 36	
	n	Δ	n	Δ	n	Δ
PAR	54	-39.9	47	-35.8	49	-40.4
PLA	32	-28.2	29	-25.0	28	-29.6
CLO	43	-36.9	40	-38.8	41	-37.3
2 - sided p - values for pairwise comparisons						
PAR vs PLA	0.010		0.015		0.047	
CLO vs PLA	0.081		0.027		0.20	
PAR vs CLO	0.57		0.62		0.65	

* Baseline for this study is considered to be the baseline of Study 187.

TABLE 55
Study : 228
Mean Change from Baseline* in MSPS Total Avoidance score
LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week							
	BL* Mean		Wk 6		Wk 12		Wk 18	
	n	X	n	Δ	n	Δ	n	Δ
PAR	67	14.7	66	-9.3	66	-10.0	66	-10.4
PLA	44	16.5	41	-7.5	44	-8.2	44	-8.1
CLO	61	18.4	58	-9.8	58	-10.3	58	-10.5
2 - sided p - values for pairwise comparisons								
PAR vs PLA	0.33		0.24		0.25		0.14	
CLO vs PLA	0.35		0.23		0.28		0.19	
PAR vs CLO	0.032		0.77		0.86		0.94	

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week							
	BL* Mean		Wk 6		Wk 12		Wk 18	
	n	X	n	Δ	n	Δ	n	Δ
PAR	67	14.7	66	-9.3	59	-9.9	57	-10.9
PLA	44	16.5	41	-7.5	38	-8.5	37	-8.8
CLO	61	18.4	58	-9.8	54	-10.1	50	-11.2
2 - sided p - values for pairwise comparisons								
PAR vs PLA	0.33		0.24		0.56		0.23	
CLO vs PLA	0.35		0.23		0.55		0.25	
PAR vs CLO	0.032		0.77		0.91		0.88	

* Baseline for this study is considered to be the baseline of Study 187.

TABLE 55
Study : 228
Mean Change from Baseline* in MSPS Total Avoidance score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week					
	Wk 24		Wk 30		Wk 36	
	n	Δ	n	Δ	n	Δ
PAR	66	-10.6	66	-10.8	66	-11.2
PLA	44	-8.6	44	-9.1	44	-9.0
CLO	58	-11.2	58	-11.2	58	-11.6
2 - sided p - values for pairwise comparisons						
PAR vs PLA	0.21		0.32		0.18	
CLO vs PLA	0.17		0.28		0.17	
PAR vs CLO	0.68		0.79		0.79	

OBSERVED CASE ANALYSIS

Treatment Groups	Treatment Week					
	Wk 24		Wk 30		Wk 36	
	n	Δ	n	Δ	n	Δ
PAR	53	-11.4	46	-10.[illegible]	48	-11.4
PLA	32	-9.8	29	-9.[illegible]	28	-10.2
CLO	42	-12.0	39	-12.6	40	-12.2
2 - sided p - values for pairwise comparisons						
PAR vs PLA	0.41		0.68		0.55	
CLO vs PLA	0.33		0.17		0.39	
PAR vs CLO	0.71		0.19		0.67	

* Baseline for this study is considered to be the baseline of Study 187.

TABLE 56
Study : 228
Mean Change from Baseline* in SDS Work score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week							
	BL* Mean		Wk 6		Wk 12		Wk 18	
	n	X	n	Δ	n	Δ	n	Δ
PAR	66	5.6	66	-3.7	66	-3.9	66	-4.0
PLA	44	5.6	42	-1.9	44	-2.8	44	-2.7
CLO	63	5.9	60	-3.4	61	-3.4	61	-3.5
2 - sided p - values for pairwise comparisons								
PAR vs PLA	0.96		0.007		0.063		0.051	
CLO vs PLA	0.64		0.020		0.35		0.23	
PAR vs CLO	0.66		0.72		0.38		0.42	

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week							
	BL* Mean		Wk 6		Wk 12		Wk 18	
	n	X	n	Δ	n	Δ	n	Δ
PAR	66	5.6	66	-3.7	57	-3.9	57	-4.0
PLA	44	5.6	42	-1.9	38	-3.3	38	-3.2
CLO	63	5.9	60	-3.4	56	-3.4	52	-3.8
2 - sided p - values for pairwise comparisons								
PAR vs PLA	0.96		0.007		0.26		0.26	
CLO vs PLA	0.64		0.020		0.80		0.36	
PAR vs CLO	0.66		0.72		0.36		0.80	

* Baseline for this study is considered to be the baseline of Study 187.

TABLE 56
Study : 228
Mean Change from Baseline* in SDS Work score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week					
	Wk 24		Wk 30		Wk 36	
	n	Δ	n	Δ	n	Δ
PAR	66	-4.2	66	-4.2	66	-4.4
PLA	44	-2.6	44	-2.8	44	-2.9
CLO	61	-3.9	61	-3.9	61	-3.9
2 - sided p - values for pairwise comparisons						
PAR vs PLA	0.023		0.034		0.028	
CLO vs PLA	0.090		0.11		0.16	
PAR vs CLO	0.55		0.59		0.40	

OBSERVED CASE ANALYSIS

Treatment Groups	Treatment Week					
	Wk 24		Wk 30		Wk 36	
	n	Δ	n	Δ	n	Δ
PAR	52	-4.2	47	-4.0	47	-4.5
PLA	30	-3.2	30	-3.0	29	-3.4
CLO	44	-4.3	41	-4.2	41	-4.4
2 - sided p - values for pairwise comparisons						
PAR vs PLA	0.18		0.14		0.15	
CLO vs PLA	0.14		0.086		0.22	
PAR vs CLO	0.92		0.84		0.79	

* Baseline for this study is considered to be the baseline of Study 187.

TABLE 57
Study : 228
Mean Change from Baseline* in SDS Social Life score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week							
	BL* Mean		Wk 6		Wk 12		Wk 18	
	n	X	n	Δ	n	Δ	n	Δ
PAR	66	6.0	66	-4.3	66	-4.4	66	-4.6
PLA	44	5.5	42	-2.4	44	-2.5	44	-2.8
CLO	63	6.1	60	-4.0	61	-4.1	61	-4.1
2 - sided p - values for pairwise comparisons								
PAR vs PLA	0.28		0.003		0.004		0.004	
CLO vs PLA	0.21		0.012		0.010		0.034	
PAR vs CLO	0.94		0.65		0.64		0.30	

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week							
	BL* Mean		Wk 6		Wk 12		Wk 18	
	n	X	n	Δ	n	Δ	n	Δ
PAR	66	6.0	65	-4.3	57	-4.3	57	-4.8
PLA	44	5.5	42	-2.4	38	-3.0	38	-3.3
CLO	63	6.1	60	-4.0	56	-4.1	52	-4.2
2 - sided p - values for pairwise comparisons								
PAR vs PLA	0.28		0.003		0.052		0.023	
CLO vs PLA	0.21		0.012		0.083		0.13	
PAR vs CLO	0.94		0.65		0.67		0.28	

* Baseline for this study is considered to be the baseline of Study 187.

TABLE 57
Study : 228
Mean Change from Baseline* in SDS Social Life score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week					
	Wk 24		Wk 30		Wk 36	
	n	Δ	n	Δ	n	Δ
PAR	66	-4.8	66	-4.9	66	-5.1
PLA	44	-2.4	44	-2.8	44	-2.8
CLO	61	-4.3	61	-4.3	61	-4.3
2 - sided p - values for pairwise comparisons						
PAR vs PLA	< 0.001		< 0.001		< 0.001	
CLO vs PLA	0.006		0.013		0.018	
PAR vs CLO	0.3[illegible]		0.23		0.12	

OBSERVED CASE ANALYSIS

Treatment Groups	Treatment Week					
	Wk 24		Wk 30		Wk 36	
	n	Δ	n	Δ	n	Δ
PAR	52	-5.0	47	-4.9	47	-5.3
PLA	30	-2.8	30	-2.[illegible]	29	-3.2
CLO	44	-4.2	41	-4.[illegible]	41	-4.4
2 - sided p - values for pairwise comparisons						
PAR vs PLA	0.005		0.003		0.005	
CLO vs PLA	0.068		0.021		0.10	
PAR vs CLO	0.18		0.38		0.13	

* Baseline for this study is considered to be the baseline of Study 187.

TABLE 58
Study : 228
Mean Change from Baseline* in SDS Family Life / Home Responsibilities score
LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week							
	BL* Mean		Wk 6		Wk 12		Wk 18	
	n	X	n	Δ	n	Δ	n	Δ
PAR	66	5.2	66	-3.6	66	-3.7	66	-4.0
PLA	44	4.7	42	-2.3	44	-2.1	44	-2.1
CLO	62	5.5	59	-3.4	60	-3.8	60	-3.7
2 - sided p - values for pairwise comparisons								
PAR vs PLA	0.35		0.029		0.014		0.005	
CLO vs PLA	0.084		0.044		0.002		0.009	
PAR vs CLO	0.50		0.70		0.83		0.61	

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week							
	BL* Mean		Wk 6		Wk 12		Wk 18	
	n	X	n	Δ	n	Δ	n	Δ
PAR	66	5.2	66	-3.6	57	-3.4	57	-4.0
PLA	44	4.7	42	-2.3	38	-2.6	38	-2.6
CLO	62	5.5	59	-3.4	55	-3.7	51	-3.7
2 - sided p - values for pairwise comparisons								
PAR vs PLA	0.35		0.029		0.17		0.038	
CLO vs PLA	0.084		0.044		0.036		0.073	
PAR vs CLO	0.50		0.70		0.61		0.60	

* Baseline for this study is considered to be the baseline of Study 187.

APPENDIX 7.2.2.2

STUDY 222

TABLE 58
Study : 228
Mean Change from Baseline* in SDS Family Life / Home Responsibilities score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week					
	Wk 24		Wk 30		Wk 36	
	n	Δ	n	Δ	n	Δ
PAR	66	-3.9	66	-4.2	66	-4.4
PLA	44	-1.9	44	-2.2	44	-2.3
CLO	60	-4.0	60	-4.0	60	-3.9
2 - sided p - values for pairwise comparisons						
PAR vs PLA	0.003		0.003		< 0.001	
CLO vs PLA	< 0.001		0.003		0.005	
PAR vs CLO	0.84		0.72		0.31	

OBSERVED CASE ANALYSIS

Treatment Groups	Treatment Week					
	Wk 24		Wk 30		Wk 36	
	n	Δ	n	Δ	n	Δ
PAR	52	-3.7	47	-3.9	47	-4.2
PLA	30	-2.3	30	-2.3	29	-2.6
CLO	43	-3.9	40	-3.8	40	-3.8
2 - sided p - values for pairwise comparisons						
PAR vs PLA	0.063		0.030		0.034	
CLO vs PLA	0.012		0.046		0.092	
PAR vs CLO	0.76		0.74		0.48	

* Baseline for this study is considered to be the baseline of Study 187.

Table 7.2.2.2

Paroxetine - Protocol 222
Table 8A
Summary of Patient Demographic Data
For the Maintenance Phase

Intent-to-Treat Population

	PLACEBO N = 30 n (%)	PAROXETINE 10 MG N = 34 n (%)	PAROXETINE 20 MG N = 34 n (%)	PAROXETINE 40 MG N = 40 n (%)	PAROXETINE TOTAL N = 108 n (%)
Age (Yrs)					
< 16	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
16 - 24	6 (20.0%)	3 (8.8%)	5 (14.7%)	5 (12.5%)	13 (12.0%)
25 - 34	4 (13.3%)	10 (29.4%)	15 (44.1%)	11 (27.5%)	36 (33.3%)
35 - 44	11 (36.7%)	11 (32.4%)	9 (26.5%)	13 (32.5%)	33 (30.6%)
45 - 54	8 (26.7%)	9 (26.5%)	5 (14.7%)	7 (17.5%)	21 (19.4%)	
55 - 64	1 (3.3%)	1 (2.9%)	0 (0.0%)	4 (10.0%)	5 (4.6%)
>= 65	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mean Age (+/- S.D.)	37.9 (+/-10.8)	38.2 (+/-9.9)	31.4 (+/-10.0)	38.4 (+/-10.6)	37.. (+/-10.3)
Minimum Age	20	19	20	20	19
Maximum Age	59	63	54	58	63
Sex					
Male	8 (26.7%)	9 (26.5%)	11 (32.4%)	17 (42.5%)	37 (34.3%)
Female	22 (73.3%)	25 (73.5%)	23 (67.6%)	23 (57.5%)	71 (65.7%)
Race					
Caucasian	25 (83.3%)	26 (76.5%)	29 (85.3%)	37 (92.5%)	92 (85.2%)
Black	2 (6.7%)	7 (20.6%)	2 (5.9%)	2 (5.0%)	11 (10.2%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oriental	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hispanic	2 (6.7%)	1 (2.9%)	3 (8.8%)	0 (0.0%)	4 (3.7%)
Other	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (0.9%)

Data Source: Appendix 2
Data displayed in this table were collected at the baseline of PAR-120.

Paroxetine - Protocol 222

Table 8

Summary of Patient Demographic Data

For the Randomization Phase

Intent-to-Treat Population

	PLACEBO	PAROXETINE 10 MG	PAROXETINE 20 MG	PAROXETINE 40 MG	PAROXETINE TOTAL
	N = 62	N = 12	N = 13	N = 18	N = 43
	n (%)	n (%)	n (%)	n (%)	n (%)
Age (Yrs)					
< 16	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
16 - 24	6 (9.7%)	3 (25.0%)	2 (15.4%)	3 (16.7%)	8 (18.6%)
25 - 34	17 (27.4%)	2 (16.7%)	5 (38.5%)	6 (33.3%)	13 (30.2%)
35 - 44	18 (29.0%)	3 (25.0%)	4 (30.8%)	6 (33.3%)	13 (30.2%)
45 - 54	17 (27.4%)	3 (25.0%)	2 (15.4%)	2 (11.1%)	7 (16.3%)
55 - 64	4 (6.5%)	1 (8.3%)	0 (0.0%)	1 (5.6%)	2 (4.7%)
>= 65	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mean Age (+/- S.D.)	39.2 (+/-10.1)	37.8 (+/-12.9)	34.4 (+/-11.0)	35.1 (+/-10.5)	35.7 (+/-1
Minimum Age	20	19	20	20	19
Maximum Age	59	63	54	56	63
Sex					
Male	21 (33.9%)	2 (16.7%)	4 (30.8%)	7 (38.9%)	13 (30.2%)
Female	41 (66.1%)	10 (83.3%)	9 (69.2%)	11 (61.1%)	30 (69.8%)
Race					
Caucasian	53 (85.5%)	9 (75.0%)	12 (92.3%)	17 (94.4%)	38 (88.4%)
Black	6 (9.7%)	2 (16.7%)	0 (0.0%)	1 (5.6%)	3 (7.0%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oriental	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hispanic	3 (4.8%)	1 (8.3%)	1 (7.7%)	0 (0.0%)	2 (4.7%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Data Source: Appendix 2

Data displayed in this table were collected at the baseline of PAP-120.

The PLACEBO group includes both paroxetine->placebo and placebo->placebo.

Paroxetine Protocol 222 - Intent-to-Treat Population

Table 1a

Summary of Patient Population

PAR-120 Treatment	PAR-120 Entered	PAR-120 Completed	PAR-222 Entered Maintenance		PAR-222 Entered Randomization PLACEBO		PAR-222 Entered Randomization PAROXETINE	
	n	n	n	(%)*	n	(%)**	n	(%)**
PLACEBO	69	46	30	(65.2%)	19	(63.3%)	0	(0.0%)
PAROXETINE 10 MG	67	45	34	(75.6%)	15	(44.1%)	12	(35.3%)
PAROXETINE 20 MG	70	47	34	(72.3%)	13	(38.2%)	13	(38.2%)
PAROXETINE 40 MG	72	50	40	(80.0%)	15	(37.5%)	18	(45.0%)
TOTAL	278	188	138	(73.4%)	62	(44.9%)	43	(31.2%)

Data Source: Appendix 1

* Percent of patients completing PAR-120 who entered PAR-222

** Percent of patients who entered PAR-222 maintenance phase

Paroxetine - Protocol 222
Table 3
Summary of Patient Withdrawals
For the Maintenance Phase
Intent-to-Treat Population

REASON FOR WITHDRAWAL	PLACEBO N = 30 n (%)	PAROXETINE 10 MG N = 34 n (%)	PAROXETINE 20 MG N = 34 n (%)	PAROXETINE 40 MG N = 40 n (%)
Lack of efficacy / relapse	4 (13.3%)	0 (0.0%)	2 (5.9%)	2 (5.0%)
Lack of efficacy plus adverse events	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Significant adverse events	0 (0.0%)	1 (2.9%)	1 (2.9%)	1 (2.5%)
Total Adverse Experiences	1 (3.3%)	1 (2.9%)	1 (2.9%)	1 (2.5%)
Lack of patient compliance	3 (10.0%)	2 (5.9%)	3 (8.8%)	1 (2.5%)
Patient lost to follow-up	1 (3.3%)	2 (5.9%)	1 (2.9%)	0 (0.0%)
Patient improvement	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
Protocol violation	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other reason	1 (3.3%)	2 (5.9%)	1 (2.9%)	1 (2.5%)
TOTAL	11 (36.7%)	7 (20.6%)	8 (23.5%)	7 (17.5%)

Data Source: Appendix 1
PLA = PLACEBO; PAR = PAROXETINE Table includes patients who did not enter the randomization phase.

Paroxetine Protocol 222 - Intent-to-Treat Population

Table 4

Summary of Patients Remaining in the Study at Each Visit

Maintenance Phase Treatment Group	Entered Maint	--- Maintenance Phase --- Week 4	Week 8	Week 12*	Completed Maint**	Entered Rand		------ Randomization Phase ------ Week 14		Week 16		Week 20		Week 24		Completed Study***		Entered Run-Out	
						PLA	PAR	PLA	PAR	PLA	PAR	PLA	PAR	PLA	PAR	PLA	PAR	PLA	PAR
CEBO	30	27	23	19	23	19	0	17	0	14	0	14	0	14	0	14	0	12	0
OXETINE 10 MG	34	33	30	27	30	15	12	9	10	9	9	9	9	9	9	9	9	9	9
OXETINE 20 MG	34	29	26	26	26	13	13	10	11	8	11	7	9	7	9	7	9	6	8
OXETINE 40 MG	40	39	37	33	37	15	18	10	18	10	16	7	15	7	15	7	15	7	14
OXETINE TOTAL	108	101	93	86	93	43	43	29	39	27	36	23	33	23	33	23	33	22	31

a Source: Appendix 1

= PLACEBO; PAR = PAROXETINE

nt = Maintenance Phase; Rand = Randomization Phase

xcludes patients who withdrew from the study during the defined week 12 window

Patients are considered to have completed the maintenance phase if they took study medication for at least 71 days or ered the randomization phase.

Completed the randomization phase (week 24)

The ITT population for the Randomization phase of Study 222 received the following treatments:

- Placebo n=62
- 10 mg Paroxetine n=12
- 20 mg Paroxetine n=13
- 40 mg Paroxetine n=18

Paroxetine Protocol 222 - Intent-to-Treat Population
Table 5A
Summary of Percentage of Patient Responding
Zero Full Panic Attacks
Maintenance Phase

	PLACEBO	%	PAROXETINE 10 MG	%	PAROXETINE 20 MG	%	PAROXETINE 40 MG	%	PAROXETINE TOTAL	%
Endpoint (PAR120)	19 /30	63.3	26 /34	76.5	27 /34	79.4	36 /40	90.0	89/108	82.4
2nd 2 weeks	21 /29	72.4	18 /31	58.1	22 /32	68.8	29 /39	74.4	69/102	67.6
4th 2 weeks	18 /26	69.2	24 /28	85.7	20 /28	71.4	28 /39	71.8	72 /95	75.8
6th 2 weeks	13 /20	65.0	23 /27	85.2	18 /21	85.7	24 /32	75.0	65 /80	81.3
7th 2 weeks	1 /3	33.3	2 /2	100.0	3 /5	60.0	4 /4	100.0	9 /11	81.8
8th 2 weeks	0 /0	.	0 /0	.	1 /1	100.0	0 /0	.	1 /1	100.0

Data Source: Appendix 8

Paroxetine Protocol 222 - Intent-to-Treat Population
Table 5 8
Summary of Percentage of Patient Responding
Zero Full Panic Attacks
Randomization Phase

	10 MG**				20 MG**				40 MG**			
	PLACEBO	%	PAROXETINE	%	PLACEBO	%	PAROXETINE	%	PLACEBO	%	PAROXETINE	%
End of Maintenance	13 /15	86.7	11 /11	100.0	9 /13	69.2	12 /13	92.3	13 /15	86.7	13 /18	72.2
7th 2 weeks	7 /10	70.0	10 /10	100.0	6 /10	60.0	8 /8	100.0	8 /11	72.7	12 /15	80.0
8th 2 weeks	7 /9	77.8	10 /11	90.9	5 /10	50.0	9 /10	90.0	6 /8	75.0	15 /17	88.2
10th 2 weeks	7 /9	77.8	7 /7	100.0	6 /8	75.0	8 /10	80.0	6 /9	66.7	12 /15	80.0
12th 2 weeks	8 /8	100.0	9 /9	100.0	5 /6	83.3	9 /9	100.0	6 /6	100.0	13 /15	86.7
Endpoint	10 /12	83.3	12 /12	100.0	8 /12	66.7	12 /13	92.3	9 /13	69.2	15 /18	83.3
Treatment P-value at Endpoint		0.478				0.160				0.413		

Data Source: Appendix 8

End of Maintenance = Last maintenance value prior to entering randomization phase.
** Maintenance phase treatment groups.
7th 2-week interval also includes patients falling in the 6th 2-week interval visit window.
Excludes run-out phase data

Treatment P-value comparing Paroxetine vs Placebo within maintenance phase treatment group from Fisher's Exact test.
* significant for overall alpha=0.05 (p<0.017)

Paroxetine Protocol 222 - Intent-to-Treat Population
Table 5 B
Summary of Percentage of Patients Responding
Zero Full Panic Attacks
Randomization Phase

	PLACEBO->PLACEBO	%	PAROXETINE->PLACEBO	%	PAROXETINE TOTAL	%	Treatment P-value Par vs Pla
End of Maintenance	13 /19	68.4	35 /43	81.4	36 /42	85.7	0.771
7th 2 weeks	15 /19	78.9	21 /31	67.7	30 /33	90.9	0.030*
8th 2 weeks	12 /15	80.0	18 /27	66.7	34 /38	89.5	0.031*
10th 2 weeks	12 /13	92.3	19 /26	73.1	27 /32	84.4	0.3
12th 2 weeks	10 /14	71.4	19 /20	95.0	31 /33	93.9	1.000
Endpoint	13 /18	72.2	27 /37	73.0	39 /43	90.7	0.044*

Data Source: Appendix 8

End of Maintenance = Last maintenance value prior to entering randomization phase.
7th 2-week interval also includes patients falling in the 6th 2-week interval visit window.

Excludes run-out phase data

Treatment p-value comparing Paroxetine->Placebo vs Paroxetine Total from Fisher's Exact test.
* significant for alpha=0.05

Paroxetine Protocol 222 - Intent-to-Treat Population
Table 6 A
Summary of Percentage of Patient Responding
50% Reduction from Baseline in Number of Full Panic Attacks
Maintenance Phase

	PLACEBO	%	PAROXETINE 10 MG	%	PAROXETINE 20 MG	%	PAROXETINE 40 MG	%	PAROXETINE TOTAL	%
dpoint (PAR120)	30 /30	100.0	34 /34	100.0	33 /34	97.1	39 /40	97.5	106/108	98.1
1 2 weeks	28 /29	96.6	30 /31	96.8	29 /32	90.6	39 /39	100.0	98/102	96.1
n 2 weeks	24 /26	92.3	27 /28	96.4	26 /28	92.9	38 /39	97.4	91 /95	95.8
n 2 weeks	17 /20	85.0	27 /27	100.0	21 /21	100.0	31 /32	96.9	79 /80	98.8
n 2 weeks	2 /3	66.7	2 /2	100.0	5 /5	100.0	4 /4	100.0	11 /11	100.0
n 2 weeks	0 /0	.	0 /0	.	1 /1	100.0	0 /0	.	1 /1	100.0

ta Source: Appendix 8

Paroxetine Protocol 222 - Intent-to-Treat Population
Table 6.8
Summary of Percentage of Patient Responding
50% Reduction from Baseline in Number of Full Panic Attacks
Randomization Phase

	10 MG**				20 MG**				40 MG**			
	PLACEBO	%	PAROXETINE	%	PLACEBO	%	PAROXETINE	%	PLACEBO	%	PAROXETINE	%
End of Maintenance	15 /15	100.0	11 /11	100.0	13 /13	100.0	13 /13	100.0	15 /15	100.0	18 /18	100.0
7th 2 weeks	8 /10	80.0	10 /10	100.0	9 /10	90.0	8 /8	100.0	10 /11	90.9	14 /15	93.3
8th 2 weeks	9 /9	100.0	11 /11	100.0	9 /10	90.0	9 /10	90.0	7 /8	87.5	17 /17	100.0
10th 2 weeks	8 /9	88.9	7 /7	100.0	8 /8	100.0	9 /10	90.0	7 /9	77.8	15 /15	100.0
12th 2 weeks	8 /8	100.0	9 /9	100.0	6 /6	100.0	9 /9	100.0	6 /6	100.0	15 /15	100.0
Endpoint	10 /12	83.3	12 /12	100.0	10 /12	83.3	12 /13	92.3	10 /13	76.9	17 /18	94.4

Data Source: Appendix 8

End of Maintenance = Last maintenance value prior to entering randomization phase.
** Maintenance phase treatment groups.
7th 2-week interval also includes patients falling in the 6th 2-week interval visit window.
Excludes run-out phase data

Paroxetine Protocol 222 - Intent-to-Treat Population
Table 6B
Summary of Percentage of Patients Responding
50% Reduction from Baseline in Number of Full Panic Attacks
Randomization Phase

	PLACEBO->PLACEBO	%	PAROXETINE->PLACEBO	%	PAROXETINE TOTAL	%	Treatment P-value Par vs Pla
End of Maintenance	18 /19	94.7	43 /43	100.0	42 /42	100.0	-
7th 2 weeks	18 /19	94.7	27 /31	87.1	32 /33	97.0	0.190
8th 2 weeks	14 /15	93.3	25 /27	92.6	37 /38	97.4	0.565
10th 2 weeks	13 /13	100.0	23 /26	88.5	31 /32	96.9	0.316
12th 2 weeks	14 /14	100.0	20 /20	100.0	33 /33	100.0	-
Endpoint	18 /18	100.0	30 /37	81.1	41 /43	95.3	0.073

Data Source: Appendix 8

End of Maintenance = Last maintenance value prior to entering randomization phase.
7th 2-week interval also includes patients falling in the 6th 2-week interval visit window.

Excludes run-out phase data

Treatment p-value comparing Paroxetine->Placebo vs Paroxetine Total from Fisher's Exact test.
* significant for alpha=0.05

Paroxetine Protocol 222 - Intent-to-Treat Population
Table 7 A
Summary of Baseline Mean and Mean Change from Baseline
Number of Full Panic Attacks
Maintenance Phase

	PLACEBO			PAROXETINE 10 MG			PAROXETINE 20 MG			PAROXETINE 40 MG			PAROXETINE TOTAL		
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)
Baseline (PAR120)	29	6.48	(0.98)	31	6.61	(1.52)	32	6.75	(1.09)	39	8.74	(1.96)	102	7.47	(0.94)
Endpoint (PAR120)	29	-5.86	(0.90)	31	-6.23	(1.50)	32	-6.19	(1.03)	39	-8.18	(1.81)	102	-6.96	(0.89)
2nd 2 weeks	29	-5.03	(1.25)	31	-5.55	(1.52)	32	-5.59	(1.08)	39	-8.09	(1.71)	102	-6.53	(0.87)
4th 2 weeks	26	-5.80	(0.90)	28	-6.07	(1.66)	28	-5..3	(1.15)	39	-8.29	(1.92)	95	-6.96	(0.98)
6th 2 weeks	20	-5.93	(1.06)	27	-4.65	(0.70)	21	-6.21	(1.49)	32	-7.92	(2.19)	80	-6.37	(0.99)
7th 2 weeks	3	12.00	(13.50)	2	-5.00	(3.00)	5	-4.60	(1.02)	4	-4.75	(0.85)	11	-4.73	(0.66)
8th 2 weeks	.	.	.	.	.	.	1	-4. 0	.	.	.	.	1	-4.00	.

Data Source: Appendix 8

Paroxetine Protocol 222 - Intent-to-Treat Population
Table 7.#
Summary of End of Maintenance Phase and Mean Change from End of Maintenance Phase
Number of Full Panic Attacks
Randomization Phase

	10 MG**				20 MG**				40 MG**			
	PLACEBO		PAROXETINE		PLACEBO		PAROXETINE		PLACEBO		PAROXETINE	
	n	mean (s.e.)	n	mean (s.e.)	n	mean (s.e.)	n	mean (s.e.)	n	mean (s.e.)	n	mean (s.e.)
End of Maintenance	12	0.13 (0.13)	11	0.00 (0.00)	12	0.25 (0.13)	13	0.04 (0.04)	13	0.08 (0.05)	18	0.83 (0.58)
7th 2 weeks	10	1.20 (0.61)	10	0.00 (0.00)	10	0.55 (0.30)	8	0.00 (0.00)	11	0.91 (0.74)	15	0.97 (0.92)
8th 2 weeks	9	0.06 (0.24)	10	0.10 (0.10)	10	1.35 (1.20)	10	0.45 (0.5[illegible])	8	0.88 (0.69)	17	-0.15 (0.13)
10th 2 weeks	9	0.28 (0.22)	7	0.00 (0.00)	8	-0.06 (0.20)	10	0.55 (0.50)	9	6.33 (3.98)	15	-0.07 (0.13)
12th 2 weeks	8	-0.19 (0.19)	8	0.00 (0.00)	6	0.08 (0.45)	9	-0.06 (0.06)	7	-0.14 (0.09)	15	-0.13 (0.13)
Endpoint	12	0.79 (0.72)	11	0.00 (0.00)	12	1.33 (1.04)	13	0.35 (0.39)	13	3.73 (2.77)	18	0.64 (0.76)

Data Source: Appendix 8

End of Maintenance = Last maintenance value prior to entering randomization phase.
** Maintenance phase treatment groups.
Week 14 (7th 2-week) interval also includes patients falling in the week 12 (6th 2-week) interval visit window of the randomization
Excludes run-out phase data.

Paroxetine Protocol 222 - Intent-to-Treat Population
Table
Summary of End of Maintenance Phase and Mean Change from End of Maintenance Phase
CGI Severity of Illness
Randomization Phase

	10 MG**				20 MG**				40 MG**			
	PLACEBO		PAROXETINE		PLACEBO		PAROXETINE		PLACEBO		PAROXETINE	
	n	mean (s.e.)	n	mean (s.e.)	n	mean (s.e.)	n	mean (s.e.)	n	mean (s.e.)	n	mean (s.e.)
End of Maintenance	12	1.83 (0.32)	12	2.00 (0.25)	12	2.17 (0.24)	13	2.46 (0.27)	13	1.69 (0.40)	18	2.17 (0.22)
Week 14	10	0.50 (0.45)	11	0.00 (0.13)	10	0.20 (0.25)	8	-0.25 (0.25)	10	1.20 (0.44)	15	0.20 (0.10)
Week 16	9	-0.11 (0.11)	10	0.10 (0.18)	9	0.56 (0.34)	10	-0.20 (0.20)	9	0.33 (0.50)	18	0.06 (0.15)
Week 20	9	0.11 (0.11)	7	0.14 (0.26)	8	0.25 (0.25)	10	-0.20 (0.29)	9	0.56 (0.50)	15	0.07 (0.15)
Week 24	8	-0.13 (0.30)	9	0.00 (0.24)	6	0.17 (0.31)	9	-0.44 (0.18)	7	-0.14 (0.26)	15	-0.13 (0.19)
Endpoint	12	0.25 (0.39)	12	0.00 (0.17)	12	0.67 (0.31)	13	-0.15 (0.25)	13	1.15 (0.45)	18	0.00 (0.20)
Treatment P-value at Endpoint		0.581				0.068				0.005*		

Data Source: Appendix 9

End of Maintenance = Last maintenance value prior to entering randomization phase.
** Maintenance phase treatment groups.
Week 14 (7th 2-week) interval also includes patients falling in the week 12 (6th 2-week) interval visit window of the randomization
Excludes run-out phase data.

Treatment P-value comparing Paroxetine vs Placebo within maintenance phase treatment group from CONTRAST statement of analysis of variance general linear model procedure in SAS.
* significant for overall alpha=0.05 (p<0.017)

Paroxetine Protocol 222 - Intent-to-Treat Population
Table 9
Summary of End of Maintenance Phase and Mean Change from End of Maintenance Phase
Intensity of Anticipatory Anxiety
Randomization Phase

	PAROXETINE->PLACEBO				ETINE 20 MG			PAROXETINE 40 MG			PAROXETINE TOTAL			Treatment
	n	mean (s.e.)			an (s.e.)		n	mean (s.e.)		n	mean (s.e.)		P-value mean (s.e.)	Par vs Pla
End of Maintenance	37	0.74	(0.21		0.55	(0.25)	13	0.62	(0.21)	28	1.40	(0.40)	42	0.93	(0.20)	0.135
Week 14	31	0.31	(0.21.		0.10	(0.10)	8	-0.10	(0.30)	19	-0.03	(0.14)	33	-0.01	(0.10)	0.172
Week 16	27	0.12	(0.23)	10	0.20	(0.13)	10	0.29	(0.15)	17	-0.27	(0.16)	37	0.01	(0.10)	0.752
Week 20	26	0.41	(0.24)	7	0.14	(0.14)	10	0.79	(0.32)	15	0.07	(0.26)	32	0.31	(0.17)	0.768
Week 24	21	0.05	(0.13)	8	0.13	(0.13)	9	0.00	(0.17)	15	-0.18	(0.17)	32	-0.05	(0.10)	0.331
Endpoint	37	0.45	(0.27)	11	0.18	(0.12)	13	-0.02	(0.22)	18	-0.14	(0.16)	42	-0.02	(0 10)	0.254

Data Source: Appendix 8

End of Maintenance = Last maintenance value prior to entering randomization phase.
This tables excludes those patients who were randomized to placebo throughout the entire study.
Week 14 (7th 2-week) interval also includes patients falling in the week 12 (6th 2-week) interval visit window of the randomization
Excludes run-out phase data.

Treatment p-value comparing Paroxetine->Placebo vs Paroxetine Total from nonparametric Mann-Whitney U test.
* significant for alpha=0.05

Paroxetine Protocol 222 - Intent-to-Treat Population
Table 10
Summary of End of Maintenance Phase and Mean Change from End of Maintenance Phase
Overall MSPS Fear Score
Randomization Phase

	PAROXETINE->PLACEBO			PAROXETINE 10 MG			PAROXETINE 20 MG			PAROXETINE 40 MG			PAROXETINE TOTAL			Treatment P-value
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla
End of Maintenance	28	1.96	(0.47)	10	2.30	(1.02)	11	3.19	(0.75)	16	2.27	(0.60)	37	2.55	(0.43)	0.501
Week 14	23	1.16	(0.59)	9	0.22	(0.64)	7	-0.12	(0.43)	13	-0.05	(0.22)	29	0.02	(0.24)	0.058
Week 16	20	1.18	(0.63)	8	1.33	(0.56)	8	0.19	(0.44)	16	0.40	(0.31)	32	0.58	(0.24)	0.310
Week 20	18	0.99	(0.58)	6	0.50	(0.34)	9	-0.14	(0.49)	13	0.54	(0.33)	28	0.32	(0.23)	0.224
Week 24	12	0.38	(0.54)	7	0.93	(0.52)	7	-0.43	(0.52)	14	0.01	(0.40)	28	0.13	(0.28)	0.646
Endpoint	28	1.69	(0.56)	10	0.42	(0.62)	11	0.09	(0.43)	16	-0.16	(0.36)	37	0.07	(0.26)	0.006*

Data Source: Appendix 10

End of Maintenance = Last maintenance value prior to entering randomization phase.
This tables excludes those patients who were randomized to placebo throughout the entire study.
Week 14 (7th 2-week) interval also includes patients falling in the week 12 (6th 2-week) interval visit window of the randomization
Excludes run-out phase data.

Treatment p-value comparing Paroxetine->Placebo vs Paroxetine Total from analysis of variance using general linear model procedure in SAS with model including effect for treatment.
* significant for alpha=0.05

Paroxetine Protocol 222 - Intent-to-Treat Population
Table 11
Summary of End of Maintenance Phase and Mean Change from End of Maintenance Phase
Overall MSPS Avoidance Score
Randomization Phase

	PAROXETINE->PLACEBO			PAROXETINE 10 MG			PAROXETINE 20 MG			PAROXETINE 40 MG			PAROXETINE TOTAL			Treatment P-value
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla
End of Maintenance	28	0.93	(0.23)	10	0.77	(0.41)	11	1.30	(0.28)	16	1.10	(0.30)	37	1.07	(0.19)	0.538
Week 14	23	0.39	(0.27)	9	0.11	(0.35)	7	0.15	(0.26)	13	-0.06	(0.09)	29	0.04	(0.13)	0.226
Week 16	20	0.36	(0.28)	8	0.46	(0.32)	8	0.24	(0.26)	16	0.08	(0.09)	32	0.21	(0.11)	0.566
Week 20	18	0.52	(0.31)	6	0.06	(0.22)	9	0.10	(0.27)	13	0.15	(0.17)	28	0.11	(0.12)	0.160
Week 24	12	0.28	(0.29)	7	0.48	(0.46)	7	0.07	(0.28)	14	-0.08	(0.13)	28	0.10	(0.15)	0.781
Endpoint	28	0.60	(0.35)	10	0.20	(0.40)	11	0.36	(0.25)	16	-0.07	(0.12)	37	0.13	(0.14)	0.090

Data Source: Appendix 10

End of Maintenance = Last maintenance value prior to entering randomization phase.
This tables excludes those patients who were randomized to placebo throughout the entire study.
Week 14 (7th 2-week) interval also includes patients falling in the week 12 (6th 2-week) interval visit window of the randomization
Excludes run-out phase data.

Treatment p-value comparing Paroxetine->Placebo vs Paroxetine Total from analysis of variance using general linear model procedure in SAS with model including effect for treatment.
* significant for alpha=0.05

Paroxetine Protocol 222 - Intent-to-Treat Population
Table 12
Summary of End of Maintenance Phase and Mean Change from End of Maintenance Phase
SDS Work
Randomization Phase

	PAROXETINE->PLACEBO			PAROXETINE 10 MG			PAROXETINE 20 MG			PAROXETINE 40 MG			PAROXETINE TOTAL			Treatment P-value
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla
End of Maintenance	35	0.77	(0.29)	12	0.50	(0.36)	13	1.54	(0.85)	18	0.89	(0.50)	43	0.98	(0.34)	0.759
Week 14	30	0.70	(0.37)	11	-0.09	(0.09)	7	0.71	(0.47)	15	0.20	(0.11)	33	0.21	(0.12)	0.197
Week 16	26	0.35	(0.39)	10	0.10	(0.10)	9	0.33	(0.47)	18	-0.33	(0.24)	37	-0.05	(0.17)	0.299
Week 20	24	0.50	(0.37)	7	0.00	(0.00)	9	-0.67	(1.30)	15	0.00	(0.26)	31	-0.19	(0.39)	0.211
Week 24	19	-0.11	(0.17)	9	0.00	(0.00)	9	0.67	(0.83)	15	-0.20	(0.20)	33	0.09	(0.24)	0.574
Endpoint	35	0.91	(0.36)	12	0.00	(0.00)	13	1.23	(0.68)	18	-0.33	(0.23)	43	0.23	(0.24)	0.122

Data Source: Appendix 12

End of Maintenance = Last maintenance value prior to entering randomization phase.
This tables excludes those patients who were randomized to placebo throughout the entire study.
Week 14 (7th 2-week) interval also includes patients falling in the week 12 (6th 2-week) interval visit window of the randomization
Excludes run-out phase data.

Treatment p-value comparing Paroxetine->Placebo vs Paroxetine Total from analysis of variance using general linear model procedure in SAS with model including effect for treatment.
* significant for alpha=0.05

APPENDIX 8.1

SAFETY DATA

Table 13

Response at Study Endpoint for Paroxetine (n/N and %)
Studies 108, 187 and 223

	Paroxetine dose											
	10mg		20mg		30mg		40mg		50mg		60mg	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Study 108												
Zero or One Panic Attacks			9/20	45%			3/19	16%			4/19	21%
≥50% Reduction in No. of Full Panic Attacks			17/20	85%			13/18	72%			14/18	78%
≥50% Reduction in HAMA Total			18/20	90%			14/19	74%			14/19	74%
CGI Severity of Illness ≤ 2 with baseline ≥3			15/21	71%			11/19	58%			13/19	68%
Study 187												
Zero Panic Attacks			17/28	61%			23/44	52%			16/38	42%
≥50% Reduction in No. of Full Panic Attacks			20/27	74%			39/44	89%			28/38	74%
≥50% Reduction in HAMA Total	0/4	0%	19/31	61%			29/45	64%			24/39	62%
CGI Severity of Illness ≤ 2 with baseline ≥3	0/5	0%	16/30	53%			27/45	60%			18/38	47%
Study 223												
Zero Panic Attacks	0/2	0%	6/10	60%	17/28	61%	8/12	67%	6/8	75%	3/8	38%
≥50% Reduction in No. of Full Panic Attacks	0/2	0%	8/10	80%	22/28	79%	10/12	83%	7/8	88%	7/8	88%
≥50% Reduction in HAMA Total	0/1	0%	3/8	38%	14/24	58%	6/12	50%	3/8	38%	2/8	25%
CGI Severity of Illness ≤ 2 with baseline ≥3	0/5	0%	4/12	33%	20/28	71%	7/12	58%	3/8	38%	1/8	13%

N = number of patients at that dose n = number of patients who responded

Data Source: Volume 60, p. 176, Table 5.2e

Appendix 8.1

As a component of our review of the NDA, we audited the following CRF's, identified by patient ID number:

The following volumes were submitted on August 1, 1995 and contain the CRFs requested for audit purposes.

Volume	PID	Volume	PID
1		6	
2		7	
3		8	
4		9	
5		10	

Appendix 8.5.1.1
Events Occurring at a Rate of 1% or Greater in Paroxetine-Treated Patient

	PAROXETINE N=469 (%)	ALPRAZOLAM N=77 (%)	CLOMIPRAMINE N=121 (%)	PLACEBO N=324 (%)
BODY AS A WHOLE				
Headache	25	18	17	25
Asthenia	14	18	14	5
Infection	5	5	2	7
Trauma	4	9	0	4
Abdominal Pain	4	4	3	3
Back Pain	3	4	1.0	2
Chills	2	3	4	1.0
Chest Pain	2	1.0	2	3
Flu Syndrome	2	0	0	2
Pain	2	1.0	1.0	2
Allergic Reaction	1.0	0	1.0	0
Fever	1.0	3	1.0	1.0
CARDIOVASCULAR SYSTEM				
Migraine	2	0	0	1.0
Palpitation	2	1.0	7	3
Vasodilatation	2	0	4	3
Hypertension	1.0	0	1.0	1.0
Hypotension	1.0	0	1.0	1.0
Postural Hypotension	1.0	0	7	2
Syncope	1.0	0	0	0
Tachycardia	1.0	0	2	1.0

Appendix 8.5.1.1 (continued)
Events Occurring At A Rate of 1% or Greater in Paroxetine-Treated Patients

	PAROXETINE N=469 (%)	ALPRAZOLAM N=77 (%)	CLOMIPRAMINE N=121 (%)	PLACEBO N=324 (%)
DIGESTIVE SYSTEM				
Nausea	23	13	31	17
Dry Mouth	18	9	50	11
Diarrhea	12	7	3	7
Constipation	8	7	17	5
Decreased Appetite	7	3	3	3
Dyspepsia	4	4	4	7
Bruxism	2	0	0	0
Flatulence	2	3	1.0	3
Increased Appetite	2	1.0	1.0	1.0
Tooth Disorder	2	1.0	0	1.0
Vomiting	2	1.0	2	2
Dysphagia	1.0	1.0	3	0
Gastrointestinal Disorder	1.0	3	1.0	0
HEMIC / LYMPHATIC				
Purpura	1.0	0	0	0
METABOLIC / NUTRITIONAL				
Weight Loss	2	1.0	1.0	0
Thirst	1.0	1.0	0	1.0
Weight Gain	1.0	4	1.0	1.0
MUSCULOSKELETAL				
Arthralgia	2	1.0	0	1.0
Myalgia	2	4	3	3

Appendix 8.5.1.1 (continued)
Events Occurring at a Rate of 1% or Greater in Paroxetine-Treated Patients

	PAROXETINE N=469 (%)	ALPRAZOLAM N=77 (%)	CLOMIPRAMINE N=121 (%)	PLACEBO N=324 (%)
NERVOUS SYSTEM				
Somnolence	19	49	11	11
Insomnia	18	21	10	10
Dizziness	14	13	18	10
Libido Decreased	9	5	8	1
Tremor	9	9	25	1.0
Nervousness	8	23	5	8
Agitation	5	9	3	4
Anxiety	5	12	3	4
Depression	4	14	3	5
Abnormal Dreams	3	8	0	3
Myoclonus	3	4	4	2
Paresthesia	3	1.0	6	4
Depersonalization	2	0	0	2
Hypertonia	2	1.0	3	0
Amnesia	1.0	4	0	0
Concentration Impaired	1.0	4	3	1.0
Dystonia	1.0	0	1.0	0
Emotional Lability	1.0	3	1.0	1.0
Hyperkinesia	1.0	4	0	1.0
Hypesthesia	1.0	0	0	1.0
Lack of Emotion	1.0	0	0	1.0
Manic Reaction	1.0	0	1.0	0
Vertigo	1.0	1.0	3	1.0

Appendix 8.5.1.1 (continued)
Events Occurring at a Rate of 1% or Greater in Paroxetine-Treated Patients

	PAROXETINE N=469 (%)	ALPRAZOLAM N=77 (%)	CLOMIPRAMINE N=121 (%)	PLACEBO N=324 (%)
RESPIRATORY SYSTEM				
Respiratory Disorder	8	22	2	9
Sinusitis	6	5	0	5
Pharyngitis	3	3	1.0	3
Rhinitis	3	1.0	0	0
Cough Increased	2	0	3	2
Yawn	2	1.0	2	0
Bronchitis	1.0	0	1.0	0
Dyspnea	1.0	1.0	1.0	1.0
Hyperventilation	1.0	0	0	0
Pneumonia	1.0	0	0	0
SKIN / APPENDAGES				
Sweating	14	0	30	6
Rash	2	3	3	2
Herpes Simplex	1.0	0	0	0
Pruritus	1.0	3	1.0	1.0
SPECIAL SENSES				
Abnormal Vision	3	4	4	3
Abnormality of Accommodation	1.0	0	3	0
Conjunctivitis	1.0	0	1.0	0
Ear Disorder	1.0	0	0	1.0
Otitis Media	1.0	0	0	0
Taste Perversion	1.0	0	3	1.0
Tinnitus	1.0	3	2	3

Appendix 8.5.1.1 (continued)
Events Occurring at a Rate of 1% or Greater in Paroxetine-Treated Patients

	PAROXETINE N=469 (%)	ALPRAZOLAM N=77 (%)	CLOMIPRAMINE N=121 (%)	PLACEBO N=324 (%)
UROGENITAL SYSTEM				
*Abnormal Ejaculation	21	7	24	1.0
*Female Genital Disorders	9	0	4	1.0
*Impotence	5	3	15	0
*Dysmenorrhea	2	2	0	2
Urinary Frequency	2	3	0	0
Urinary Tract Infection	2	1	1.0	1.0
Cystitis	1.0	1.0	0	1.0
Dysuria	1.0	0	2	0
*Menorrhagia	1.0	0	1.0	1.0
*Menstrual Disorder	1.0	2	1.0	0
*Prostate Disorder	1.0	0	0	0

Source: Adapted from Appendix Table 6.2.1, Vol., 63, P. 181. Pooled Data

* Percentage corrected for gender

Appendix 8.5.1.2

Summary of Emergent Adverse Events (≥5.0% Patients) Regardless of Relationship

Study 120

Body System / Preferred term	Placebo N=69 n	%	Paroxetine 10mg N=67 n	%	Paroxetine 20mg N=70 n	%	Paroxetine 40mg N=72 n	%
Body as a Whole								
Abdominal pain	4	(6)	4	(6)	6	(9)	2	(3)
Asthenia	3	(4)	7	(10)	9	(13)	13	(18)
Back pain	1	(1)	3	(5)	2	(3)	4	(6)
Chest pain	5	(7)	2	(3)	4	(6)	0	(0)
Headache	30	(44)	19	(28)	27	(39)	19	(26)
Infection	10	(15)	9	(13)	2	(3)	3	(4)
Trauma	3	(4)	2	(3)	6	(9)	5	(7)
Cardiovascular Syst.								
Palpitation	4	(6)	1	(2)	0	(0)	1	(1)
Digestive System								
Bruxism	0	(0)	2	(3)	4	(6)	1	(1)
Constipation	5	(7)	5	(8)	3	(4)	9	(13)
Decreased appetite	3	(4)	2	(3)	7	(10)	4	(6)
Diarrhea	3	(4)	8	(12)	7	(10)	16	(22)
Dry mouth	8	(12)	6	(9)	8	(11)	25	(35)
Dyspepsia	10	(15)	4	(6)	3	(4)	0	(0)
Nausea	18	(26)	16	(24)	17	(24)	23	(32)
Musculoskeletal								
Myalgia	6	(9)	2	(3)	1	(1)	1	(1)
Nervous System								
Abnormal dreams	5	(7)	3	(5)	4	(6)	0	(0)
Agitation	6	(9)	4	(6)	4	(6)	3	(4)
Anxiety	2	(3)	2	(3)	3	(4)	5	(7)
Depression	5	(7)	1	(2)	6	(9)	2	(3)
Dizziness	11	(16)	8	(12)	8	(11)	9	(13)
Insomnia	14	(20)	17	(25)	12	(17)	21	(29)
Libido decreased	1	(1)	2	(3)	5	(7)	6	(8)
Nervousness	12	(17)	6	(9)	7	(10)	6	(8)
Paresthesia	4	(6)	1	(2)	0	(0)	3	(4)
Somnolence	12	(17)	16	(24)	14	(20)	23	(32)
Tremor	2	(3)	3	(5)	6	(9)	12	(17)

Data Source: ISS, Appendix 6.2.2A

Appendix 8.5.1.2 (continued)

Body System Preferred term	Placebo N=69 n	%	Paroxetine 10mg N=67 n	%	Paroxetine 20mg N=70 n	%	Paroxetine 40mg N=72 n	%
Respiratory System								
Cough increased	3	(4)	3	(5)	1	(1)	4	(6)
Pharyngitis	5	(7)	1	(2)	0	(0)	2	(3)
Respiratory disorder	10	(15)	8	(12)	6	(9)	8	(11)
Rhinitis	0	(0)	4	(6)	0	(0)	2	(3)
Sinusitis	5	(7)	12	(18)	1	(1)	6	(8)
Skin/Appendages								
Rash	1	(1)	1	(2)	1	(1)	5	(7)
Sweating	1	(1)	6	(9)	5	(7)	7	(10)
Special Senses								
Tinnitus	4	(6)	1	(2)	1	(1)	1	(1)
Urogenital System								
Abnormal ejaculation*	0	(0)	2	(10)	4	(17)	8	(28)
Dysmenorrhea*	5	(11)	3	(6)	1	(2)	1	(2)
Female genital disorder*	0	(0)	4	(9)	5	(11)	4	(9)
Prostate disorder*	0	(0)	1	(5)	0	(0)	0	(0)
Urinary frequency	1	(1)	2	(3)	4	(6)	2	(3)
Urinary Tract Infection	2	(3)	1	(2)	4	(5)	1	(1)

* Percentage corrected for gender.
Data Source: ISS, Appendix 6.2.2A

Appendix Table 8.5.2

Extended Ranges for Laboratory Values of Potential Clinical Concern

Hematology	
Hemoglobin	Males ≤11.5 g/dl
	Females ≤9.5 g/dl
Hematocrit	Males ≤37%
	Females ≤32%
White Blood Cells (WBC)	≤2.8 or ≥16 x 10^9/L
Red Blood Cells (RBC)	Males ≥8 x 10^{12}/L
	Females ≥10 x 10^{12}/L
Neutrophils	≤15%
Lymphocytes	≥75%
Monocytes	≥15%
Basophils	≥10%
Eosinophils	≥10%
Bands	≥10%
Platelets	≤75 or ≥700 x 10^9/L
Segmented Neutrophils	≤15%
Blood Chemistry	
Urea	≥10.71 mmol/L
Blood Urea Nitrogen	≥30 mg/dL
Serum Creatinine	≥2 mg/dL
Total Bilirubin	≥2 mg/dL
SGOT (AST)	≥150 U/L
SGPT (ALT)	≥165 U/L
Alkaline Phosphate	≥390 U/L
Total Protein	≥10 g/dl
	≤4.5 g/dl
Albumin	≤2.5 g/dl
Sodium	≥156 mEq/L
	≤126 mEq/L
Potassium	≥6 mEq/L
	≤3 mEq/L
Chloride	≥118 mEq/L
	≤90 mEq/L
Total Triiothyronine (T3)	≥4.62 nmol/L
Total Thyroxine (T4)	≥193.05 nmol/L
	≤38.61 nmol/L

Urinalysis

The criteria for identifying patients with change from baseline of potential clinical significance with respect to urinalysis analytes were as follows: protein, a value of 4 or above; glucose, a value of 4+ or above; red blood cells> 10/hpf, WBC> 10/hpf.

Appendix 8.5.2.1

Number of Patients with Blood Chemistry Values of Potential Clinical Concern by Parameter, All Studies Combined

	Paroxetine			Alprazolam			Clomipramine			Placebo		
Parameter	N Tested	n	%	N Tested	n	%	N Tested	n	%	N Tested	n	%
Urea	75	0	0	0			63	0	0	63	0	0
Blood Urea Nitrogen	222	0	0	67	0	0	0			111	0	0
Serum Creatinine	347	0	0	67	0	0	74	0	0	219	0	0
Total Bilirubin	348	0	0	67	0	0	73	0	0	218	0	0
AST (SGOT)	333	0	0	67	0	0	71	1	1	206	1	<1
ALT (SGPT)	323	0	0	67	0	0	74	1	1	192	0	0
Alkaline Phosphatase	350	0	0	67	0	0	74	0	0	219	0	0
Total Protein	15	0	0	0			0			13	0	0
Albumin	32	0	0	0			0			29	0	0
Sodium	223	0	0	67	1	1	0			111	0	0
Potassium	223	0	0	67	1	1	0			111	3	3
Chloride	223	0	0	67	0	0	0			111	0	0
Triiodothyronine (T3)	12	0	0	4	0	0	4	0	0	10	0	0
Thyroxine (T4)	10	0	0	4	0	0	5	0	0	11	0	0

Data Source: Appendix 10.1

Appendix 8.5.2.1 (continued)

Mean Change from Baseline for Blood Chemistry Parameters
All Studies Combined[a]

	Albumin (g/dL)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Serum Urates (mcmol/L)	Triidothyronine (T3) (nmol/L)	Thyroxine (T4) (nmol/L)
	(n) mean	(n) mean	(n) mean	(n) mean	(n) mean	(n) mean	(n) mean
Paroxetine	(31) -0.1	(187) -0.9	(187) <0.1	(187) 0.9	(9) 20.2	(2) 0.1	(2) -13.5
Alprazolam		(60) -0.2	(60) 0.7	(60) 1.3		(2) 0.2	(2) -1.9
Clomipramine					(11) -25.9	(2) -0.3	(3) -16.3
Placebo	(25) -0.2	(94) -0.8	(94) 0.3	(94) 0.8	(5) 8.6	(5) -0.1	(5) -6.8
Pairwise Comparisons[1]							
Par vs Pla	0.478	0.760	0.320	0.905	0.750	0.639	0.605
Par vs Alp		0.151	0.357	0.504		0.885	0.585
Par vs Clo					0.087	0.527	0.846

[a] Mean change is shown for week 10 (Studies 120, 223) and week 12 (Studies 108, 187) for patients yielding data at these visits

[1] Pairwise comparisons made using T-test

NOTE: Sample sizes (N) shown in table 10.5 are number of patients at baseline. Samples sizes (n) is this table are number of patients with lab assessment at baseline and at week 10 or week 12.

Appendix 8.5.2.1

Mean Change from Baseline for Blood Chemistry Parameters
All Studies Combined[a]

	Urea (mmol/L)	Blood Urea Nitrogen (mg/dL)	Serum Creatinine (mg/dL)	Total Bilirubin (mg/dL)	AST (SGOT) (U/L)	ALT (SGPT) (U/L)	Alkaline Phosphatase (U/L)	Total Protein (g/dL)
	(n) mean	(n) mean	(n) mean	(n) mean	(n) mean	(n) mean	(n) mean	(n) mean
Paroxetine	(72) 0.3	(187) 0.7	(308) <0.1	(309) -0.1	(293) 1.1	(284) 1.7	(310) 5.1	(11) -0.1
Alprazolam		(60) 0.3	(60) <0.1	(60) -0.1	(60) 1.7	(60) 1.0	(60) -4.4	
Clomipramine	(60) <-0.1		(72) <0.1	(71) 0.1	(69) 6.2	(71) 4.4	(72) 6.9	
Placebo	(59) <0.1	(94) -0.2	(194) <0.1	(192) <-0.1	(183) 1.4	(170) 1.4	(195) -3.1	(9) 0.1
Pairwise Comparisons[1]								
Par vs Pla	0.239	0.015	0.375	0.090	0.804	0.807	<0.001	0.411
Par vs Alp		0.350	0.926	0.484	0.552	0.645	<0.001	
Par vs Clo	0.167		0.938	0.893	0.100	0.407	0.490	

[a] Mean change is shown for week 10 (Studies 120, 223) and week 12 (Studies 108, 187) for patients yielding data at these visits

[1] Pairwise comparisons made using T-test

NOTE: Sample sizes (N) shown in table 10.5 are number of patients at baseline. Samples sizes (n) is this table are number of patients with lab assessment at baseline and at week 10 or week 12.

Appendix Table 8.5.2.2

Number of Patients with Hematological Values of Potential Clinical Concern by Parameter, All Studies Combined

Parameter	Paroxetine			Alprazolam			Clomipramine			Placebo		
	N Tested	n	%	N Tested	n	%	N Tested	n	%	N Tested	n	%
Hemoglobin	345	1	<1	66	0	0	74	0	0	216	1	<1
Hematocrit	296	3	1	66	0	0	70	1	1	171	0	0
White Blood Cells	344	4	1	66	1	2	74	0	0	218	2	1
Red Blood Cells	46	0	0	0			3	0	0	44	0	0
Neutrophils	90	0	0	0			67	0	0	72	0	0
Lymphocytes	345	1	<1	65	0	0	74	1	1	216	1	<1
Monocytes	345	1	<1	65	0	0	74	1	1	215	0	0
Basophils	334	0	0	65	0	0	74	0	0	202	0	0
Eosinophils	339	4	1	65	0	0	74	0	0	208	1	<1
Bands	241	2	1	64	0	0	6	0	0	128	1	1
Segmental Neutrophils	251	0	0	64	0	0	7	0	0	139	0	0
Platelets	301	2	1	66	0	0	73	0	0	173	0	0

Data Source: Appendix 10.1

Appendix 8.5.2.2

Mean Change from Baseline for Hematological Parameters, All Studies Combined[a]

	Hemoglobin (g/dL)	Hematocrit (%)	White Blood Cell (10^9/L)	Red Blood Cell (10^{12}/L)	Neutrophils (%)	Lymphocytes (%)
	(n) mean	(n) mean	(n) mean	(n) mean	(n) mean	(n) mean
Paroxetine	(302) -0.3	(253) -1.0	(301) 0.1	(46) <0.1	(83) -2.1	(297) -0.7
Alprazolam	(59) -0.2	(59) -0.6	(59) -0.7			(57) 1.2
Clomipramine	(71) <0.1	(69) <0.1	(72) -0.5	(2) -0.1	(63) -1.7	(70) 1.7
Placebo	(191) <-0.1	(150) -0.3	(192) -0.2	(40) <-0.1	(61) -2.6	(188) 0.7
Pairwise Comparisons[1]						
Par vs Pla	0.006	0.019	0.054	0.470	0.812	0.147
Par vs Alp	0.632	0.223	0.005			0.155
Par vs Clo	0.014	0.010	0.033	0.503	0.859	0.134

[a] Mean change is shown for week 10 (Studies 120, 223) and week 12 (Studies 108, 187) for patients yielding data at these visits

[1] Pairwise comparisons made using T-test

NOTE: Sample sizes (N) shown in table 10.4 are number of patients at baseline. Samples sizes (n) is this table are number of patients with lab assessment at baseline and at week 10 or week 12.

Appendix 8.5.2.2 (continued)

Mean Change from Baseline for Hematological Parameters, All Studies Combined[a]

	Monocytes (%)	Basophils (%)	Eosinophils (%)	Granulocytes (%)	Bands (%)	Segmental Neutrophils (%)	Platelets (10^9/L)
	(n) mean	(n) mean	(n) mean	(n) mean	(n) mean	(n) mean	(n) mean
Paroxetine	(297) 0.6	(284) -0.1	(289) 0.6	(4) 1.8	(197) <-0.1	(208) 0.3	(255) <0.1
Alprazolam	(57) 0.8	(57) <-0.1	(57) 0.2		(56) 0.0	(56) -2.4	(59) -15.0
Clomipramine	(70) 0.1	(69) 0.1	(70) 0.2		(6) -0.1	(7) -3.1	(69) 9.4
Placebo	(186) 0.2	(173) -0.1	(180) 0.2	(3) 15.7	(108) 0.1	(120) -1.1	(151) -8.0
Pairwise Comparisons[1]							
Par vs Pla	0.119	0.727	0.067	0.061	0.590	0.236	0.050
Par vs Alp	0.687	0.644	0.257		0.970	0.073	0.007
Par vs Clo	0.115	0.042	0.172		0.921	0.391	0.114

[a] Mean change is shown for week 10 (Studies 120, 223) and week 12 (Studies 108, 187) for patients yielding data at these visits

[1] Pairwise comparisons made using T-test

NOTE: Sample sizes (N) shown in table 10.4 are number of patients at baseline. Samples sizes (n) is this table are number of patients with lab assessment at baseline and at week 10 or week 12.

8.5.2.3.

Summary of Clinically Significant Abnormal Urinalysis Values
Protocol 120 and 223 Combined (Including Run-Out Phase)

PARAMETER		PAROXETINE N = 286 n (%)	ALPRAZOLAM N = 77 n (%)	PLACEBO N = 141 n (%)
Urinalysis - glucose	Above	0 (0.0%)	0 (0.0%)	0 (0.0%)
Urinalysis - protein	Above	0 (0.0%)	0 (0.0%)	0 (0.0%)
Urinalysis - red blood cells	Above	7 (2.4%)	0 (0.0%)	2 (1.4%)
Urinalysis - white blood cells	Above	4 (1.4%)	1 (1.3%)	4 (2.8%)

Appendix 8.5.3.

Number of Patients with Vital Sign Measurements Outside Predetermined Limits or With a Change From Baseline of Potential Clinical Concern, All Studies Combined

	Paroxetine			Alprazolam			Clomipramine			Placebo		
	N Tested	n	%	N Tested	n	%	N Tested	n	%	N Tested	n	%
Diastolic BP Sitting												
Low/Decreased	419	0	0	73	0	0	85	0	0	278	2	1
High/Increased	419	0	0	73	0	0	85	0	0	278	2	1
Diastolic BP Standing												
Low/Decreased	271	0	0	72	0	0	0			138	0	0
High/Increased	271	0	0	72	0	0	0			138	2	1
Systolic BP Sitting												
Low/Decreased	419	0	0	73	0	0	85	0	0	278	0	0
High/Increased	419	0	0	73	0	0	85	0	0	278	2	1
Systolic BP Standing												
Low/Decreased	271	0	0	72	0	0	0			138	0	0
High/Increased	271	0	0	72	0	0	0			138	1	1
Pulse Sitting												
Low/Decreased	418	0	0	73	0	0	85	1	1	277	1	<1
High/Increased	418	1	<	73	0	0	85	0	0	277	1	<1
Pulse Standing												
Low/Decreased	271	0	0	72	0	0	0			137	0	0
High/Increased	271	1	<1	72	0	0	0			137	0	0
Weight												
Decreased	418	11	3	71	6	9	86	6	7	276	4	1
Increased	418	18	4	71	2	3	86	4	5	276	7	3

NB: patients could have more than one variable flagged

Data Source: Appendix 11.1.1

Appendix 8.5.3.2

Mean Change from Baseline for Vital Signs
All Studies Combined[a]

	--- Diastolic BP (mmHg) ----		---- Systolic BP (mmHg) ----		------- Pulse (bpm) --------		
	Sitting	Standing	Sitting	Standing	Sitting	Standing	Weight (kg)
	(n) mean	(n) mean	(n) mean	(n) mean	(n) mean	(n) mean	(n) mean
Paroxetine	(333) 0.6	(190) -0.4	(333) 0.1	(190) 0.9	(332) 1.2	(189) 0.1	(331) 0.6
Alprazolam	(61) -0.4	(61) 0.6	(61) -0.1	(61) -0.5	(61) 1.9	(61) 2.3	(59) -1.0
Clomipramine	(85) 2.0		(85) 0.1		(85) 5.5		(85) <-0.1
Placebo	(230) -0.6	(96) -1.2	(230) -0.7	(96) -0.7	(229) -0.7	(96) 1.6	(228) 0.1
Pairwise Comparisons[1]							
Par vs Pla	0.124	0.532	0.483	0.355	0.025	0.296	0.013
Par vs Alp	0.435	0.467	0.923	0.396	0.624	0.197	<0.001
Par vs Clo	0.206		0.991		0.001		0.059

[a] Mean change is shown for week 10 (Studies 120, 223) and week 12 (Studies 108, 187) for patients yielding data at these visits

[1] Pairwise comparisons made using T-test

NOTE: Sample sizes (N) shown in table 11.3 are number of patients at baseline. Samples sizes (n) is this table are number of patients with lab assessment at baseline and at week 10 or week 12.

Appendix 8.7
Summary of Serious Adverse Events Occurring in Paroxetine-Treated Patients and Considered Unlikely Drug Related

Treatment: Paroxetine

Patient Identifier (PID)	Serious Adverse Experience (Verbatim term)	Day of Onset (from first dose of study medication)	Dose at Onset	Investigator Determined Relationship to Study Medication	Outcome
108.001.0060					
108.002.0038					
120.005.0257					

Appendix 8.7 (continued)

Treatment: Paroxetine

Patient Identifier (PIT)	Serious Adverse Experience (Verbatim term)	Day of Onset (from first dose of study medication)	Dose at Onset	Investigator Determined Relationship to Study Medication	Outcome
120.011.0065					
120.013.016					
120.001.0176					
187.029.0587					
223.016.0261					

Summary of Serious Adverse Events Occurring in Comparator Drug-Treated Patients and Considered Unlikely to be Drug-Related
Appendix 8.7 (continued)

Treatment: Comparator*

Patient Identifier (PID)	Serious Adverse Experience (Verbatim term)	Day of Onset (from first dose of study medication)	Dose at Onset	Investigator Determined Relationship to Study Medication	Outcome
187.009.0062					
187.038.0384					
223.007.(					

* Comparator in Study 187 = Clomipramine

Comparator in Study 223 = Alprazolam

Summary of Serious Adverse Events Occuring in Placebo-Treated Patients and Considered Unlikely to be Placebo Related 8.7 (continued)

Treatment: Placebo

Patient Identifier (PID)	Serious Adverse Experience (Verbatim term)	Day of Onset (from first dose of study medication)	Dose at Onset	Investigator Determined Relationship to Study Medication	Outcome
108.002.0039					
108.005.0010					
108.006.0014					
120.004.0006					
120.009.0116					

8.7 (continued)

Treatment: Placebo

Patient Identifier (PID)	Serious Adverse Experience (Verbatim term)	Day of Onset (from first dose of study medication)	Dose at Onset	Investigator Determined Relationship to Study Medication	Outcome
120.013.0214					
187.002.0007					
187.004.0020					
187.009.0064					
187.011.0531					
187.027.0227					
187.031.0297					
187.035.0510					

8.7 (continued)

Treatment: Placebo Run-In

Patient Identifier (PID)	Serious Adverse Experience (Verbatim term)	Day of Onset	Dose at Onset	Investigator Determined Relationship to Study Medication	Outcome
120.004.9010					
120.005.9006					
223.005.9008					

8.7 (continued)

Treatment: Placebo Run-In

Patient Identifier (PID)	Serious Adverse Experience (Verbatim term)	Day of Onset	Dose at Onset	Investigator Determined Relationship to Study Medication	Outcome
223.006.9001					
223.006.9006	I				

Appendix 8.8.1

Paroxetine Panic Disorder Integrated Summary of Safety
Summary of Treatment Emergent Adverse Experiences Regardless of Relationship
Where the Percentage is ≥ 5 % of Paroxetine and ≥ 2 Times the Percentage of Placebo
by ADECS Body System and Preferred Term
Protocol 108, 120, 187, and 223
Intent-to-Treat Population
Table 1 - Relative Risk and Confidence Intervals for Selected Adverse Events

Adverse Event	MALES				FEMALES			
	Paroxetine (n = 166) N* (%)	Placebo (n = 111) N (%)	RRm[1]	95% C.I.	Paroxetine (n = 303) N (%)	Placebo (n = 213) N (%)	RRf[2]	95% C.I.
Asthenia	26 (15.7)	7 (6.3)	2.484	(1.117, 5.523)	37 (12.2)	7 (3.3)	3.716	(1.689, 8.176)
Decreased Appetite	18 (10.8)	3 (2.7)	4.012	(1.210, 13.299)	15 (5.0)	6 (2.8)	1.757	(0.693, 4.456)
Libido Decreased	16 (9.6)	1 (0.9)	10.699	(1.439, 79.525)	24 (7.9)	3 (1.4)	5.624	(1.715, 18.437)
Tremor	8 (4.8)	1 (0.9)	5.349	(0.678, 42.178)	31 (10.2)	3 (1.4)	7.264	(2.250, 23.453)
Sweating	23 (13.9)	8 (7.2)	1.922	(0.892, 4.143)	43 (14.2)	11 (5.2)	2.748	(1.451, 5.204)
Abnormal Ejaculation	34 (20.5)	1 (0.9)	22.735	(3.158, 163.679)				
Impotence	9 (5.4)	0 (0.0)						
Female Genital Disorders					27 (8.9)	1 (0.5)	18.980	(2.599, 138.603)

* N = number of patients with the event

1 Rkm = relative risk for male patients

2 RRf = relative risk for female patients

Paroxetine Panic Disorder Integrated Summary of Safety
Summary of Treatment Emergent Adverse Experiences Regardless of Relationship
Where the Percentage is ≥ 5 % of Paroxetine and ≥ 2 Times the Percentage of Placebo
by ADECS Body System and Preferred Term
Protocol 108, 120, 187, and 223
Intent-to-Treat Population
Table 2 - Odds Ratios by Gender for Selected Adverse Events

Adverse Event	Odds Ratios[1]		Common Odds Ratio[2]	95% C.I.	Breslow-Day[3]	
	Males	Females			$X^2(1)$	p-value
Asthenia	2.759	4.093	3.433	(1.942, 6.068)	0.416	0.519
Decreased Appetite	4.378	1.797	2.635	(1.274, 5.441)	1.462	0.261
Libido Decreased	11.733	6.022	7.451	(3.046, 18.226)	0.313	0.576
Tremor	5.570	7.978	7.340	(2.993, 18.000)	0.086	0.770
Sweating	2.071	3.037	2.624	(1.567, 4.397)	0.478	0.489
Abnormal Ejaculation	28.333			(7.228, 111.058)#		
Impotence						
Female Genital Disorders		20.739		(4.976, 86.436)@		

1 Odds ratios computed with reference to placebo patients

2 Common Odds Ratios computed using the Mantel-Haenszel method

3 Breslow-Day test for homogeneity of the odds ratios

= for males only

@ = for females only

Paroxetine Panic Disorder Integrated Summary of Safety
Summary of Treatment Emergent Adverse Experiences Regardless of Relationship
Where the Percentage is ≥ 5 % of Paroxetine and ≥ 2 Times the Percentage of Placebo
by ADECS Body System and Preferred Term
Protocol 108, 120, 187, and 223
Intent-to-Treat Population
Table 1 - Relative Risk and Confidence Intervals for Selected Adverse Events

Adverse Event	< 55 YEARS				≥ 55 YEARS				RR = RRf/RRm
	Paroxetine (n = 446) N* (%)	Placebo (n = 307) N (%)	RRm[1]	95% C.I.	Paroxetine (n = 23) N (%)	Placebo (n = 17) N (%)	RRf[2]	95% C.I.	
Asthenia	55 (12.3)	13 (4.2)	2.912	(1.620, 5.236)	8 (34.8)	1 (5.9)	5.913	(0.815, 42.916)	2.03
Decreased Appetite	31 (7.0)	9 (2.9)	2.371	(1.145, 4.909)	2 (8.7)	0 (0.0)			
Libido Decreased	39 (8.7)	4 (1.3)	6.711	(2.423, 18.588)	1 (4.4)	0 (0.0)			
Tremor	36 (8.1)	3 (1.0)	8.260	(2.567, 26.582)	3 (13.0)	1 (5.9)	2.217	(0.252, 19.510)	0.27
Sweating	63 (14.1)	19 (6.2)	2.282	(1.396, 3.733)	3 (13.0)	0 (0.0)			
Abnormal Ejaculation+	32 (20.3)	1 (0.9)	21.468	(2.979, 154.727)	2 (25.0)	0 (0.0)			
Impotence+	9 (5.7)	0 (0.0)			0 (0.0)	0 (0.0)			
Female Genital Disorders+	26 (9.0)	1 (0.5)	18.146	(2.483, 132.635)	1 (6.7)	0 (0.0)			

* N = number of patients with the event

1 RRm = relative risk for patients < 55

2 RRf = relative risk for patients ≥ 55

+ = percentage corrected for gender

Paroxetine Panic Disorder Integrated Summary of Safety
Summary of Treatment Emergent Adverse Experiences Regardless of Relationship
Where the Percentage is ≥ 5 % of Paroxetine and ≥ 2 Times the Percentage of Placebo
by ADECS Body System and Preferred Term
Protocol 108, 120, 187, and 223
Intent-to-Treat Population
Table 2 - Odds Ratios by Age Group for Selected Adverse Events

Adverse Event	Odds Ratios[1]		Common Odds Ratio[2]	95% C.I.	Breslow-Day[3]	
	< 55 Years	≥ 55 Years			$X^2(1)$	p-value
Asthenia	3.181	8.533	3.463	(1.964, 6.105)	0.755	0.385
Decreased Appetite	2.473		2.645	(1.281, 5.462)	0.635	0.425
Libido Decreased	7.259		7.455	(3.048, 18.233)	0.106	0.745
Tremor	8.898	2.400	7.375	(2.988, 18.201)	1.054	0.305
Sweating	2.493		2.625	(1.567, 4.399)	0.989	0.320
Abnormal Ejaculation Impotence	27.667		28.278	(7.196, 111.127)	0.062	0.803
Female Genital Disorders	19.847		20.677	(4.956, 86.272)	0.043	0.836

1 Odds ratios computed with reference to placebo patients

2 Common Odds Ratios computed using the Mantel-Haenszel method

3 Breslow-Day test for homogeneity of the odds ratios

Paroxetine Panic Disorder Integrated Summary of Safety
Summary of Treatment Emergent Adverse Experiences Regardless of Relationship
Where the Percentage is ≥ 5 % of Paroxetine and ≥ 2 Times the Percentage of Placebo
by ADECS Body System and Preferred Term
Protocol 120, 187, and 223
Intent-to-Treat Population
Table 1 - Relative Risk and Confidence Intervals for Selected Adverse Events

Adverse Event	CAUCASIAN				NON-CAUCASIAN				RR = RRf/RRm
	Paroxetine (n = 364) N* (%)	Placebo (n = 247) N (%)	RRm[1]	95% C.I.	Paroxetine (n = 45) N (%)	Placebo (n = 17) N (%)	RRf[2]	95% C.I.	
Asthenia	50 (13.7)	12 (4.9)	2.827	(1.538, 5.198)	4 (8.9)	0 (0.0)			
Decreased Appetite	25 (6.9)	9 (3.6)	1.885	(0.895, 3.969)	5 (11.1)	0 (0.0)			
Libido Decreased	30 (8.2)	3 (1.2)	6.786	(2.094, 21.990)	3 (6.7)	0 (0.0)			
Tremor	32 (8.8)	4 (1.6)	5.429	(1.944, 15.157)	2 (4.4)	0 (0.0)			
Sweating	51 (14.0)	16 (6.5)	2.163	(1.263, 3.704)	1 (2.2)	0 (0.0)			
Abnormal Ejaculation+	32 (23.4)	1 (1.1)	21.489	(2.989, 154.514)	1 (5.9)	0 (0.0)			
Impotence+	8 (5.8)	0 (0.0)			1 (5.9)	0 (0.0)			
Female Genital Disorders+	23 (10.1)	1 (0.7)	15.705	(2.143, 115.082)	2 (7.1)	0 (0.0)			

* N = number of patients with the event

1 RRm = relative risk for caucasian patients

2 RRf = relative risk for non-caucasian patients

\+ = percentage corrected for gender

Paroxetine Panic Disorder Integrated Summary of Safety
Summary of Treatment Emergent Adverse Experiences Regardless of Relationship
Where the Percentage is ≥ 5 % of Paroxetine and ≥ 2 Times the Percentage of Placebo
by ADECS Body System and Preferred Term
Protocol 120, 187, and 223
Intent-to-Treat Population
Table 2 - Odds Ratios by Race for Selected Adverse Events

Adverse Event	Odds Ratio[1]		Common Odds Ratio[2]	95% C.I.	Breslow-Day[3]	
	Caucasian	Non-Caucasian			$X^2(1)$	p-value
Asthenia	3.118		3.296	(1.770, 6.140)	0.529	0.467
Decreased Appetite	1.950		2.225	(1.046, 4.732)	1.055	0.304
Libido Decreased	7.305		7.807	(2.794, 21.811)	0.167	0.683
Tremor	5.855		6.108	(2.398, 15.556)	0.136	0.713
Sweating	2.352		2.386	(1.345, 4.232)	0.164	0.686
Abnormal Ejaculation Impotence	27.733		27.963	(6.976, 112.083)	0.005	0.946
Female Genital Disorders	17.363		18.669	(4.274, 81.549)	0.067	0.796

1 Odds ratios computed with reference to placebo patients

2 Common Odds Ratios computed using the Mantel-Haenszel method

3 Breslow-Day test for homogeneity of the odds ratios

Date: DEC 21 1995

Statistical Review and Evaluation

DETIRN

DEC 21 1995

NDA #: 20-031/SE1-009

Applicant: SmithKline Beecham

Name of the Drug: Paxil® (paroxetine hydrochloride) Tablets

Indication: Panic Disorder

Documents Reviewed: Volumes 51.001, 51.067 to 101, amendment dated July 7, 1995 (Received Aug.16, 95)

Clinical Reviewer: James Knudsen, M.D., Ph.D. (HFD-120)

The issues in this review have been discussed with the reviewing medical officer, James Knudsen, M.D., Ph.D. (HFD-120).

Various Sections of this review are:

I. Background/Introduction

This efficacy supplement for the treatment of Panic Disorder comprises four principal studies (double-blind, randomized, parallel group). Summary design aspects of these studies are

attached as Table 0.1.1.[1] One study (protocol 120) was conducted in the US and Canada, one (protocol 223) in the US alone, and two studies (protocols 108 and 187) were conducted in centers in Europe and Israel.

Study 120 was a placebo-controlled, fixed dose study (10, 20, or 40 mg). Study 223 was a placebo-controlled flexible dose study (10-60 mg) with an active treatment arm (alprazolam, 1-6 mg). Both studies were divided into a 2-week, single-blind placebo run-in phase, and a 10-week double-blind medication phase. Each study concluded with a 4-6 week single-blind, down-titration phase.

The double-blind medication phase of each of the European studies (Protocols 108 and 187) was of 12 weeks duration and was preceded by a 3-week, single-blind placebo run-in phase. Study 187 was of a placebo-controlled, flexible dose design (10-60 mg) with an active treatment arm (clomipramine, 10-150 mg) which was followed by a 3-week down titration phase. Study 108 was also a placebo-controlled, flexible dose design (10-60 mg) study, with both groups receiving standardized psychotherapy in the form of cognitive-behavioral therapy. In this study, all patients discontinued medication abruptly at the end of the treatment phase.

The US flexible dose Study 223 has not demonstrated the efficacy of paroxetine and, therefore, will not be reviewed in detail. The sponsor stated, "In Study 223, ..., neither paroxetine nor alprazolam were found to be significantly different from placebo. High response rates were seen for all three treatment groups, the placebo response being exceptionally high. However the results of this study can be considered to be supportive of the results of the other studies, in that numerical superiority was evident for paroxetine and alprazolam over placebo in the majority of the parameters."

Also included in the submission are two long-term studies. Study 228 allowed 180 patients who had satisfactorily completed the short-term Study 187 to continue double-blind treatment with either paroxetine, clomipramine, or placebo for a further 9

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[1] In the Table (or Appendix or Figure; no separate numbering systems have been created for these) number i.j.k, i stands for the serial number of the study in the list of studies above (except that 0 indicates overall or "common to all"), j stands for the Section or Group number for the tables in a particular study, and k stands for the Table number in that Section.

months. Patients were not re-randomized.

Study 222 allowed 138 patients who had satisfactorily completed the short-term Study 120 to continue double-blind treatment with either paroxetine 10, 20, or 40 mg daily or placebo for a further 3 months, in the first phase of the Study (222). In the second phase (3 months) of the study, patients were re-randomized to either their previous treatment regimen or to placebo. This phase assessed the efficacy of paroxetine in the prevention of relapse and recurrence of panic disorder symptoms.

II. Clinical Studies

All analyses referred to in this report are the sponsor's analyses, except where specifically mentioned to be done by this reviewer.

By discussion with Dr. Dubitsky (HFD-120), this reviewer has the idea that "Number of Full Panic Attacks Reduced to zero," "Change from Baseline in Number of Full Panic Attacks," and "Change from Baseline in CGI Severity of Illness" are the three most important efficacy variables.

1. Study MY 1047/BRL-029060/1/CPMS-120

Essential features of the study, including Objectives, Design, (Patient) Population, Dosage and Administration, Evaluation Criteria, Statistical Methodology, Patient Disposition, Patient Characteristics, Results on Efficacy, etc. may be seen in the synopsis provided by the sponsor in the NDA pages 21 to 30 of Statistical Volume 51.068. In addition, the Clinical Reviewer's report contains essential features of the study.

This reviewer will discuss only the efficacy results and a few other items as needed below and provide all other criticisms under the "Reviewer's Comments".

A. Objectives

Primary
To assess the safety and efficacy (in terms of number of full

panic attacks and Clinical Global Impression) of 3 dose levels of paroxetine in the treatment of panic disorder.

Secondary
To assess the effect on anticipatory anxiety and phobic avoidance. To assess the relationship of plasma paroxetine levels with clinical outcome.

C. Efficacy Results (Sponsor's Analyses)

In this multi-dose study, the sponsor applied the Dunnett's test, as mentioned in the protocol, for the multiple comparison adjustment and declared a p-value smaller than or equal to .019 as significant. [This reviewer thinks that the multiple comparison adjustment method mentioned in the protocol should be adhered to.]

Statements about the OC results (while comparing with the LO results) below are based on the difference between paroxetine results and placebo results. The alternative analysis, suggested by this reviewer, based on the average number of full panic attacks per week considered the whole period the patient was on the study, instead of considering time intervals separately.

Primary Efficacy Variables

Number of Full Panic Attacks

Summary of Number of Full Panic Attacks at Baseline and Change from Baseline is attached as Table 1.3.1a and the p-values are in Table 1.3.1b, for the intent-to-treat population (both LOCF and OC). Results for the Per-Protocol Population are similar (may be even better).

According to the protocol defined primary result (last 2-week interval), efficacy of 40 mg paroxetine has been shown statistically (p-value= .010) with respect to the change from baseline in Number of Full Panic attacks but not of any other dose at the Dunnett's Test level of .019. By the Extender (LOCF) Data Set, the mean (median) reduction in the Number of Full Panic

Attacks from baseline to 5th (last) 2 weeks is 8.23 (4) for 40 mg paroxetine and 5.53 (3) for placebo. For the Visit-Wise dataset, the results are slightly better.

Results in other 2-week intervals except the 1st are also, generally, statistically significant. Also, by an alternative analysis based on the average number of full panic attacks per week, the results are statistically significant (p-value = .004, for Change from Baseline) for 40 mg paroxetine.

The test for a linear relationship of a dose to efficacy, which was of secondary interest by the protocol, was statistically significant (i.e. data indicated linear relationship) at these intervals (i.e., except the 1st interval).

Percentage of Patients with Zero Full Panic Attacks

Summary of results on the percentage of patients having Zero Full Panic Attacks is attached as Table 1.4.1 for the Intent-to-Treat Population. Results for the Per-Protocol Population were, generally, worse but showed statistical efficacy at the primary time interval (5th 2 weeks).

According to the protocol defined primary result (from the Extender Data Set for the Intent-to-Treat Population at the last 2-week interval), efficacy of paroxetine has not been shown statistically (p-value= .025 for 40 mg, which is non-significant at the Dunnett's Test level of .019 for this study) with respect to the Percentage of Patients Having Zero Full Panic attacks. The percentages from the protocol-defined primary results are 43.9%, 55.9%, 57.4%, and 75.8% respectively for the placebo, and paroxetine 10, 20, and 40 mg groups. Results in other 2-week intervals except the 2nd are also, generally, statistically non-significant. OC results are slightly stronger and statistically significant also at the last 2-week interval.

The test for a linear relationship of a dose to efficacy, which was of secondary interest by the protocol, was statistically significant (i.e. data indicated linear relationship) at the 2nd and 5th 2-week intervals.

Percentage of Patients With 50% or More Reduction From Baseline

in the Number of full Panic Attacks

Summary of results on percentage of patients with 50% reduction from baseline in Number of Full Panic Attacks is attached as Table 1.5.1 for the Intent-to-Treat Population. Results for the Per-Protocol Population are similar.

According to the protocol defined primary result (from the Extender Data Set for the Intent-to-Treat Population at the last 2-week interval), efficacy of paroxetine has not been shown statistically (p-value= .136 for 40 mg) with respect to the Percentage of Patients Having 50% or more reduction in the number of Full Panic attacks. The percentages (with 50% or more reduction) from the protocol-defined primary results are 74.2%, 81.4%, 85.2%, and 88.7% respectively for the placebo, and paroxetine 10, 20, and 40 mg groups. OC results with respect to the efficacy of paroxetine are about the same.

The test for a linear relationship of a dose to efficacy, which was of secondary interest by the protocol, was statistically significant (i.e. data indicated linear relationship) at the 2nd (3rd in the per-protocol population) 2-week interval.

CGI Severity of Illness Item

Summary of CGI Severity of Illness at Baseline and Change from Baseline is attached as Table 1.6.1 for the Intent-to-Treat Population. There was confusion in this Table and others in that there are 62 patients in the 10 mg group at Week 1 even in the OC dataset; whereas, only 58 patients have been reported to have completed Week 1. The sponsor explained that a patient was considered to have completed Week 1 only when the patient was in the study for at least 10 days; whereas, the patient might have Week 1 data and then drop out before Day 10. This appears awkward to this reviewer. Also, the sponsor explained that, in the intent-to-treat dataset of the 10 mg group, the one extra patient shown at Week 8 is according to what was written in the CRF. Otherwise, the patient dropped out much earlier after only one visit.

According to the protocol defined primary result (from the Extender Data Set for the Intent-to-Treat Population), efficacy

of paroxetine has not been shown statistically (p-value= .022 for 40 mg, which is not significant at the Dunnett's Test level of .019) with respect to the change from baseline in CGI Severity of Illness. By the Extender Data Set, the mean reduction in CGI Severity of Illness Item from baseline is 1.33, 1.26, 1.47, and 1.81 respectively for placebo and 10, 20, and 40 mg paroxetine groups.

Results for visit-wise dataset provided significant p-value (.007) at Week 10.

The test for a linear relationship of a dose to efficacy, which was of secondary interest by the protocol, was statistically significant (i.e. data indicated linear relationship) at Weeks 8 and 10.

Secondary Efficacy Variables

According to the protocol, the per-protocol analyses were to be done only for the primary efficacy variables. Therefore, per-protocol analyses for the secondary efficacy variables have not been provided by the sponsor.

Anticipatory Anxiety: Percent of Time Worrying

Summary of Baseline and Change from Baseline on "Anticipatory Anxiety: Percent of Time Worrying" is attached as Table 1.7.1a and the p-values are in Table 1.7.1b, for the intent-to-treat population.

Efficacy of paroxetine has not been shown statistically (p-value= .089 for 40 mg) with respect to the change from baseline in Percentage of Time Engaged in Anticiparory Attacks. By the Extender Data Set, the mear (median) reduction in "Anticipatiry Anxiety: Percent of Time Worrying" from baseline to 5th 2-weeks period is 4.44(3.6), 6.01 (6.00), 8.67 (7.00), and 10.35 (9.50), respectively, for placebo, and paroxetine 10, 20, and 40 mg groups.

OC results are about the same with respect to statistical significance.

The test for a linear relationship of a dose to efficacy, which was of secondary interest by the protocol, was statistically significant (i.e. data indicated linear relationship) only at the 1st (also 3rd by visit-wise dataset) 2-week interval.

Marks Sheehan Phobia Scale (MSPS) Avoidance Score

Summary of Baseline and Change from Baseline on "MSPS Avoidance Score" is attached as Table 1.8.1, for the intent-to-treat population.

By the primary analysis, efficacy of paroxetine has not been shown statistically (p-value= .048 for 40 mg, which is not significant by the multiple comparison adjustment) with respect to the change from baseline in the Avoidance Score. By the Extender Data Set, the mean reduction in the "Avoidance Score" from baseline to Week 10 visit is 0.75, 0.90, 1.01, and 1.22, respectively, for placebo, and paroxetine 10, 20, and 40 mg groups. OC results are about the same (negligibly worse).

The test for a linear relationship of a dose to efficacy, which was of secondary interest by the protocol, was statistically significant (i.e. data indicated linear relationship) at the Week 10 visit (not by visit-wise dataset).

Marks Sheehan Phobia Scale (MSPS) Fear Score

Summary of Baseline and Change from Baseline on "MSPS Fear Score" is attached as Table 1.9.1, for the intent-to-treat population.

Efficacy of both 20 and 40 mg paroxetine has been shown statistically by the extender dataset with respect to the change from baseline to Weeks 4 and 10 visits (there are results only at these two time points) in the Fear Score. By the Extender Data Set, the mean reduction in the "Fear Score" from baseline to Week 10 visit is 1.80, 2.56, 3.19, and 3.59, respectively, for placebo, and paroxetine 10, 20, and 40 mg groups. OC results are statistically significant only at the Week 10 evaluation and not at Week 4 evaluation (p-value = .029, which is not significant by the multiple comparison adjustment).

The test for a linear relationship of a dose to efficacy, which was of secondary interest by the protocol, was statistically

significant (i.e. data indicated linear relationship) at both the the Weeks 4 and 10 visits.

Sheehan Disability Scale (SDS) Work

Summary of Baseline and Change from Baseline on "SDS (Work) Score" is attached as Table 1.10.1, for the intent-to-treat population.

Efficacy of paroxetine has not been shown statistically (p-value= .034 for 40 mg, which is not significant at the Dunnett's Test level of .019) with respect to the change from baseline in the Work Score. By the Extender Data Set, the mean reduction in the "SDS (Work) Score" from baseline to Week 10 visit is 1.86, 2.30, 3.05, and 3.14, respectively, for placebo, and paroxetine 10, 20, and 40 mg groups. OC results are weaker.

The test for a linear relationship of a dose to efficacy, which was of secondary interest by the protocol, was statistically significant (i.e. data indicated linear relationship) at the Week 10 visit (not by the visit-wise dataset).

Sheehan Disability Scale (SDS) Social Life

Summary of Baseline and Change from Baseline on "SDS (Social Life) Score" is attached as Table 1.11.1, for the intent-to-treat population.

Efficacy of paroxetine has not been shown statistically (p-value .102 for 40 mg) with respect to the change from baseline in the Social Life Score. By the Extender Data Set, the mean reduction in the "SDS (Social Life) Score" from baseline to Week 10 visit is 2.27, 2.87, 3.29, and 3.22, respectively, for placebo, and paroxetine 10, 20, and 40 mg groups. OC results are slightly better.

The test for a linear relationship of a dose to efficacy, which was of secondary interest by the protocol, was not statistically significant.

Sheehan Disability Scale (SDS) Family Life

Summary of Baseline and Change from Baseline on "SDS (Family

Life) Score" is attached as Table 1.12.1, for the intent-to-treat population.

Efficacy of paroxetine has not been shown statistically (p-value= .122 for 40 mg) with respect to the change from baseline in the Family Life Score. By the Extender Data Set, the mean reduction in the "SDS (Family Life) Score" from baseline to Week 10 visit is 1.56, 2.13, 2.64, and 2.43, respectively, for placebo, and paroxetine 10, 20, and 40 mg groups. OC results are about the same.

The test for a linear relationship of a dose to efficacy, which was of secondary interest by the protocol, was not statistically significant.

Comments and Conclusions on Study 120

1. Of the 4 primary efficacy variables, only wrt one, Change From Baseline in Number of Full Panic Attacks, there was clear statistical evidence in favor of the 40 mg paroxetine, at the Dunnett's Test level of .019.

The test for a linear relationship of a dose to efficacy, which was of secondary interest by the protocol, was statistically significant (i.e. data indicated linear relationship) at one or more time points wrt all primary efficacy variables.

Of the 6 secondary efficacy variables considered above, only wrt one, Marks Sheehan Phobia Scale- Fear Score, there was clear statistical evidence in favor of the efficacy of 20 or 40 mg paroxetine.

Therefore, we cannot claim that this study clearly provides statistical evidence for the efficacy of paroxetine; however, because of the numerical superiority (or trends), this study may be accepted as supportive of other studies providing undebatable statistical evidence in favor of the efficacy of paroxetine. Results for 20 mg paroxetine are far less impressive.

2. The protocol stated, "The number of patients completing the study period and valid for inclusion in the analysis, required under the given assumptions is 55 per treatment group, i.e., 220 patients for the entire study. Allowing for a 30% attrition rate

it will be necessary to recruit 316 patients in total."

In reality, from the per-protocol, visit-wise analyses, we see that there were only 44, 41, 44, and 47 patients in the different treatment groups instead of 55 per treatment group, during the 5th 2 weeks. Total randomized patients also were only 278 in number.

3. There was slight inconsistency in sites in the sense that two sites had non-overlapping 95% confidence intervals for the difference between paroxetine and placebo (see attached Figure 1.3.2, Sites 013 and 012).

2. Study MY 1002/BRI-029060/1/CPMS-108 (Denmark)

Essential features of the study, including Objectives, Study Design, Study (Patient) Population, Diagnosis and Criteria for Inclusion, Test Product and Mode of Administration, Duration of Therapy, Evaluation Criteria, and Results may be seen in the Study Synopsis provided by the sponsor in the NDA pages 16 to 19 of Statistical Volume 51.086. In addition, the Clinical Reviewer's report contains essential features of the study.

This reviewer will discuss only the efficacy results and a few other items as needed below and provide all other criticisms under the "Reviewer's Comments".

A. Objectives

Primary
To compare the reduction in the number of panic attacks in patients treated with paroxetine and those treated with placebo.

Secondary
To compare the efficacy and tolerance of paroxetine and placebo by means of various rating scales.

There was a concomitant standardized psychotherapy for all patients, although it was not specifically mentioned in these objectives written in the protocol.

C. Efficacy Results (Sponsor's Analyses)

This protocol is unsatisfactory with respect to specifics. It did not specify which variables were to be primary and which ones secondary.

In the protocol, under "Statistical Considerations," the sponsor indicated the per-protocol analysis as the main analysis. However, per-protocol analyses have not been provided except for panic attacks.

This reviewer's comments on the OC results are based on the difference between paroxetine results and placebo results.

Why some of the things have been done the way they have been is not clear from the protocol. For example, nowhere in the protocol was it mentioned that summary statistics would be provided for certain weeks and p-values would be provided for only some of those weeks, or that p-values for response rates would be provided for weeks 1, 6, and 12 but p-values for change from baseline would be provided for these weeks and also for end-point. Under a. of "6.2.5. Efficacy Evaluation" of the protocol, "each time point" was mentioned and under b. of that section "end-point" was mentioned.

Also, the response rates based on (1) Panic Attacks Reduced to 1 or less and (2) CGI, was not spelled out in the protocol. However, under "Sample Size Calculation," it was stated, "Response is determined by a 50% reduction from baseline in the number of panic attacks over a 3 week period, and by only suffering 0 or 1 panic attacks over a 3 week period."

In this study, only the End-point results are based on the extender dataset. All other results are visit-wise or OC, except that in Tables 2.3.1 to 2.3.3 and 2.5.2 both LOCF and OC results are available.

The alternative analysis based on the average number of full panic attacks per week considered the whole period the patient was on the study, instead of considering time intervals separately.

Panic Attacks (Diary)

Summary of the response rates and the corresponding p-values for (1) 50% reduction in total and (2) Reduced to 1 or less are attached as Tables 2.3.1 and 2.3.2. With respect to these response rates, this study has provided statistical evidence of the efficacy of paroxetine at the 4th (last) 3-weeks time interval (visit-wise and also end-point). With respect to 50% or more Reduction (but not wrt Reduced to 1 or less), statistical evidence of the efficacy is present also at the 2nd and 3rd 3-weeks intervals. Results for the Per-Protocol Population are similar.

At end-point, the percentages for the above two efficacy variables were, respectively, (1) 78.6% and (2) 32.8% for paroxetine, and (1) 47.3% and (2) 14.3% for placebo.

Results on Number of Panic Attacks at Baseline and Change from Baseline are in Table 2.3.3. Efficacy of paroxetine has not been shown statistically (p-value= .12) with respect to the change from baseline in Number of Panic attacks. The mean (median) reduction in the Number of Full Panic Attacks from baseline to end-point is 15.0 (10.9) for paroxetine and 10.0 (6.6) for placebo. Results for the OC dataset are slightly better.

Also, by an alternative analysis based on the average number of full panic attacks per week, the results are statistically significant (p-value = .034, for Change from Baseline), when the first interval of time is excluded but not otherwise (p-value=.105, for the whole period of the study).

Hamilton Anxiety Rating Scale (HAM-A)

Summary results of HAM-A Response Rates (50% reduction in total score) and Changes in Total Score from Baseline are attached as Tables 2.4.1 and 2.4.2. The p-values (also for CGI and Zung Score) are in Table 2.4.3. All these are for the intent-to-treat population. Protocol-correct analyses have not been provided for these variables.

Most of the p-values provided (specifically for HAM-A) were statistically significant, indicating the superiority of paroxetine plus psychotherapy over psychotherapy with respect to HAM-A. At end-point, wrt HAM-A Total Score, the percentage of patients with 50% reduction was 79.3% for paroxetine and 44.6% for placebo (p-value not provided for end-point), and the mean (median) change (reduction) from baseline was 14.9 (16.0) for paroxetine and 10.0 (11.0) for placebo (p-value < .001).

CGI Severity of Illness Item

Summary of CGI Severity of Illness Response Rates and summary of CGI Severity of Illness at Baseline and Change from Baseline are attached as Tables 2.5.1 and 2.5.2 for the Intent-to-Treat Population. Results for the Per-Protocol Population have not been provided.

Efficacy of paroxetine has been shown statistically with respect to the change from baseline in CGI Severity of Illness. At end-point, the mean (median) change (reduction) from baseline was 2.1 (2.0) for paroxetine and 1.4 (1.0) for placebo (p-value= .002). OC results are about the same.

At end-point, the percentage of patients with 50% reduction in CGI Severity of Illness Score was 66.1% for paroxetine and 33.9% for placebo. End-point p-values have not been provided for the response rates; the p-value at week 12 (<.001) for the response rate is highly significant.

CGI Improvement Score

Summary of CGI Improvement Score is attached as Table 2.5.3 for the Intent-to-Treat Population. Results for the Per-Protocol Population have not been provided.

As can be seen from Table 2.4.3, efficacy of paroxetine has been shown statistically with respect to the CGI Improvement Score.

At end-point, for CGI Improvement Score, the mean (median) was 1.7 (1.0) for paroxetine and 2.1 (2.0) for placebo (p-value= .014).

Zung's Self-Rating Anxiety Scale (Zung)

Summary of Zung's Self-Rating Anxiety Scale Total Score and summary of this Total Score at Baseline and Change from Baseline are attached as Tables 2.6.1 and 2.6.2 for the Intent-to-Treat Population. Results for the Per-Protocol Population have not been provided.

As can be seen from Table 2.4.3, efficacy of paroxetine has been shown statistically with respect to the change from baseline in Zung Total Score at Weeks 6 and 12 but not at End-point (p-value= .058). At end-point, the mean (median)change (reduction) from baseline in Zung's Total Score was 6.1 (5.5) for paroxetine and 3.9 (4.0) for placebo.

Comments and Conclusions on Study 108

This study provided reasonable statistical evidence in favor of the superiority of paroxetine plus psychotherapy over placebo plus psychotherapy, with respect to all the efficacy variables considered above, except Change From Baseline in the Total Number of Full Panic Attacks (the most or one of the few most important efficacy variables).

In the protocol, under "Statistical Considerations," the sponsor indicated the per-protocol analysis as the main analysis. However, per-protocol analyses have not been provided except for panic attacks. Why some of the things have been done the way they have been is not clear from the protocol (details in the beginning of the Section, "Efficacy Results").

3. Study MY 1036/BRL-029060/1/CPMS-187

Essential features of the study, including Objectives, Methodology, various Design and Study Conduct matters, Duration of Treatment, Evaluation Criteria, and Results may be seen in the Study Synopsis provided by the sponsor in the NDA pages 16 to 19 of Statistical Volume 51.086. In addition, the Clinical Reviewer's report contains essential features of the study.

This reviewer will discuss only the efficacy results and a few

other items as needed below and provide all other criticisms under the "Reviewer's Comments".

A. Objectives

To compare the effect of paroxetine, clomipramine, and placebo on efficacy and safety in the treatment of patients with panic disorder.

B. Disposition of Patients

Attached Figure 3.2.1 compares the 3 treatment arms with respect to Percent of Patients Continuing over time. The numbers of patients withdrawn at Week 1 were 10, 9, and 1 respectively for the paroxetine, clomipramine, and placebo. Of these withdrawals, there were 3 patients in each of the paroxetine and clomipramine group, who withdrew due to significant adverse events. After Week 1 there was aproximately a linear trend, slope for the placebo group being steeper.

From the reasons for withdrawal over time on pages 31 to 33 of the statistical volume 51.091, no trend is clear. The numbers of patients withdrawn due to significant adverse events were 5, 10, and 11 respectively for the paroxetine, clomipramine, and placebo groups, and due to lack of efficacy/relapse were 5, 5, and 17 respectively. Of these 17 withdrawals from the placebo group due to lack of efficacy, 9 withdrew at Week 6.

C. Efficacy Results (Sponsor's Analyses)

It was mentioned in the protocol, "The 'intention to treat' extender data set will be considered as the primary data set." Comments on the OC results are based on the difference between paroxetine results and placebo results. Per-protocol dataset (occassionally, also referred to as efficacy dataset) was mentioned in the protocol; it was not mentioned in the protocol for this study that the per-protocol analysis would be done only for the primary efficacy variables. However, per-protocol analyses have been provided only for the primary efficacy variables.

The alternative analysis based on the average number of full panic attacks per week considered the whole period the patient was on the study, instead of considering time intervals separately.

Primary Efficacy Variables

Number of Full Panic Attacks

Results on Mean Change from Baseline in Number of Full Panic Attacks is attached as Table 3.3.1. Only the p-value at the 4th (last) 3-weeks for the paroxetine vs placebo comparison was significant (p-value= .035). Placebo was, generally, better than clomipramine. Efficacy of paroxetine has been shown statistically at the 4th 3-weeks time interval, with respect to the change from baseline in Number of Full Panic attacks. At this time interval, the mean reduction in the Number of Full Panic Attacks from baseline was 12.2 for paroxetine, 8.7 for clomipramine, and 8.5 for placebo. None of the p-values from the OC analyses were significant (see Reviewer's Comments and Conclusions on Study 187).

Results for the Per-Protocol Population were worse.

By an alternative analysis based on the average number of full panic attacks per week, the results are statistically significant (p-value = .041) when the first time interval is excluded but not significant (p-value = .116) when the whole period of the study is considered.

Percentage of Patients with Zero Full Panic Attacks

Results on the percentage of patients having Zero Full Panic Attacks is attached as Table 3.4.1, for the Intent-to-Treat Population. Results for the Per-Protocol Population were worse and none of the p-values were significant.

Efficacy of paroxetine has been shown statistically with respect to the Percentage of Patients Having Zero Full Panic attacks, at the 2nd, 3rd, and 4th 3-week periods by the intent-to-treat analysis (none by the per-protocol analysis). Paroxetine was

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7.1 Metabolism

Drug metabolism studies and identification of the major metabolites of paroxetine [1] indicate that the compound is eliminated from the body by oxidative metabolism. Metabolism is initiated by oxidation at the methylenedioxyphenyl carbon atom by the liver, a well know metabolic process for compounds containing this moiety. Identification of metabolic end products in the urine of mice, Rhesus monkeys, and man indicated that this is the primary metabolic process for all species. The catechol intermediate resulting from the initial oxidation was too unstable to isolate. It is further metabolized, in part, by methylation at the meta-position (BRL 36610A), followed by conjugation of the free phenolic group with glucuronic acid or sulfate to produce the major metabolites in plasma, urine, and bile. Some methylation at the para position and cleavage of the ether linkage also occurs. The proposed metabolic pathway is illustrated in Scheme 1 below.

All of the species studied utilized the metabolic pathway depicted in Scheme 1. In human subjects, 68% of the urine radioactivity (equivalent to 40% of the dose) was identified as the metabolites shown. The very low percentage of dose excreted unchanged in the urine and feces of rats, monkeys and humans indicated that metabolism was the major determinant in the elimination of paroxetine hydrochloride. Because of its high lipophilicity, paroxetine is not excreted by the kidneys in significant amounts. Rather, the compound is eliminated by metabolism to a range of polar analogs and conjugates. The routes of excretion of metabolites depended upon the species studied; urine and feces were the predominant routes in man.

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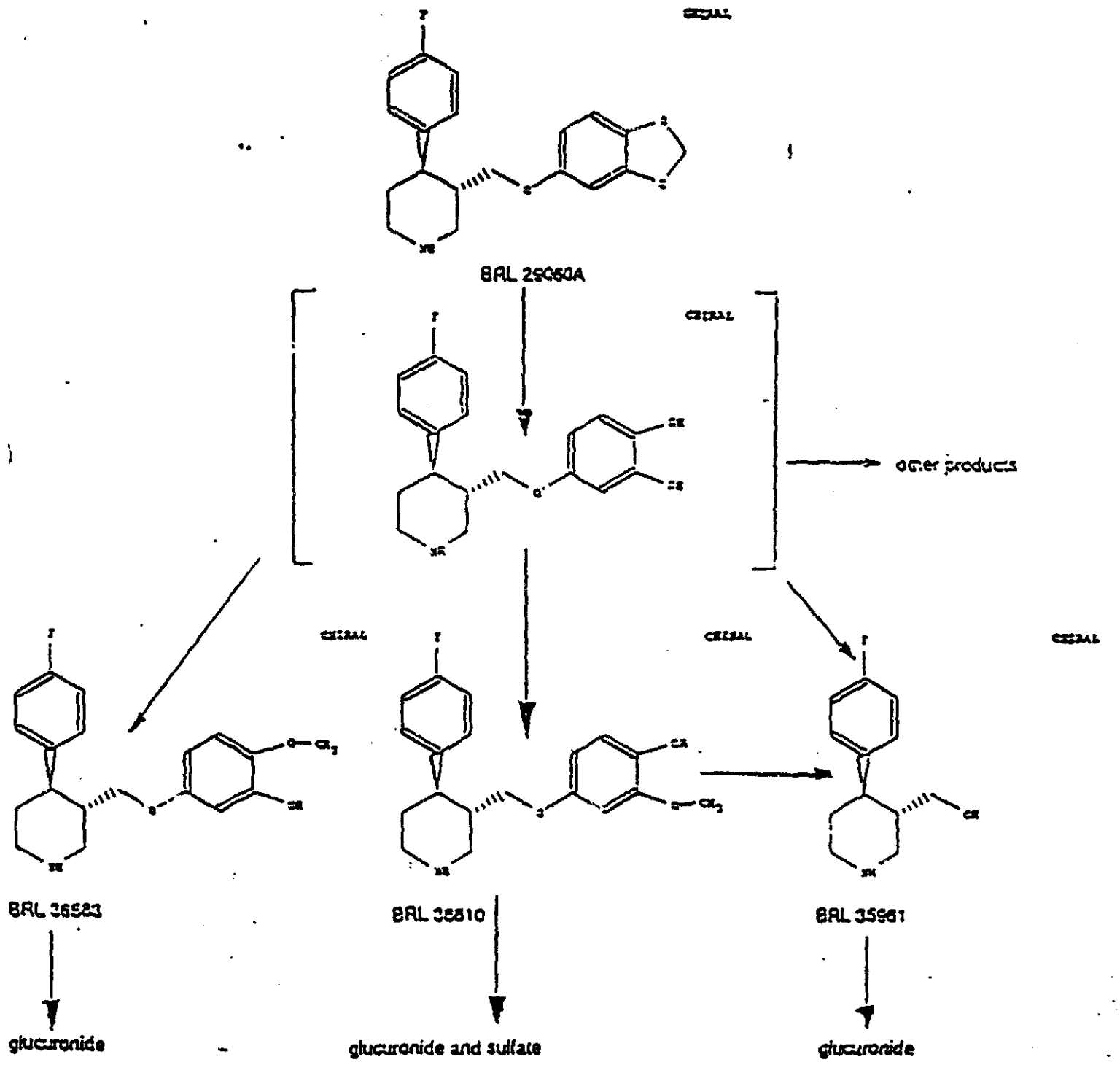
Scheme 1: Proposed Metabolic Pathway for BRL 29060A



Given that glucuronide and sulfate conjugates would undergo rapid cleavage back to BRL 36610A in a waste water treatment plant environment, this compound was considered the major metabolite of paroxetine from an environmental prospective. BRL 36583, the minor metabolite, would be expected to behave in the environment in a manner similar to BRL 36610A. Therefore, no studies were carried out on BRL 36583. Rather, environmental fate and effects predictions are based on data on paroxetine parent and on paroxetine major metabolite, BRL 36610A.

7.2 Physical Properties of Paroxetine Hydrochloride

Physical properties were determined for paroxetine hydrochloride or its free base as appropriate. The data are summarized below for selected determinations. The details of each test follow. The analytical method and validation studies are listed as references [2,3 and 4]. All concentrations are reported in terms of the free base of paroxetine.

Property	Value	Comment
H_2O Solubility	1165 ± 22.6 mg/L (pH 7)	See 7.2.1
pK_a	9.6	See 7.2.2
Log K_{ow}	1.30 (pH 7)	See 7.2.3
Vapor Pressure (estimate)	<8.25E-6 torr (free base)	See 7.2.4
UV/Vis	Sign. abs. > 290 nm	See 7.2.5
Log $K_{biomass}$	2.94	See 7.2.6

7.2.1 Water Solubility

The water solubility of paroxetine hydrochloride as a function of pH was determined using the under- and oversaturation method [5]. An anomaly was observed in the deionized water and pH 5 buffer systems, where the undersaturated and oversaturated solutions did not come within 5% of each other (indicating equilibrium), but rather differed by 22-29% and 24-37%, respectively. The pH 7 buffer system gave satisfactorily close results from both undersaturation and oversaturation studies; however, the pH 9 studies showed varying degrees of spread between results from the two procedures, as well as evidence of degradation of the paroxetine[6]. See Item 7.4.1 for discussion of paroxetine hydrolysis. For use in fate prediction, the water solubility at pH 7 is used as the least subject to experimental anomalies and the

most meaningful in environmental terms. The equilibrium value for paroxetine hydrochloride hemihydrate in pH 7 buffer is 1165 ± 22.6 mg/L. BRL 36610A would be expected to be somewhat more soluble.

7.2.2 Dissociation Constant

Previous determinations of the paroxetine pK_a were carried out by SmithKline Beecham R&D in 50% aqueous dimethylsulfoxide (DMSO) and gave a pK_a of 9.9 [7]. Definitive determination of the pK_a for paroxetine in deionized water by SmithKline Beecham Environmental Research Laboratory gave a value of 9.6 [8]. An abnormality observed with the results is the non-symmetric behavior of the titration curve at pH levels greater than the pK_a. While the compound started to precipitate out at pH levels >9, this should not have caused the non-symmetric behavior, although the pK_a values calculated from data points above pH 9 cannot be used. In a saturated solution, the concentration of free base is no longer free to vary but is constant at the solubility limit, thus invalidating the pK_a calculation.

It is more likely that the non-symmetry is due to the hydrolysis of the compound that starts to appear at pH levels around 9, and the reaction rate is increased by the increase in base concentration brought about by the titration of the solution with NaOH. This is consistent with the observations during the water solubility studies discussed above, suggesting hydrolysis of paroxetine in the pH 9 buffer system. The failure of the system pH to rise once an equivalent of NaOH was added suggests that the hydroxide ion is being consumed by the hydrolysis reaction.

The above factors are thought to explain why preliminary determinations of the paroxetine pK_a gave a value of 7.3, previously reported in an earlier version of the environmental assessment. The real pK_a was missed because of the lack of a symmetric curve above pH 9.

The pK_a of BRL 36610A would be expected to be almost exactly the same as paroxetine parent, as the ionizable group and its chemical structural environment in the molecule is the same in both parent and metabolite.

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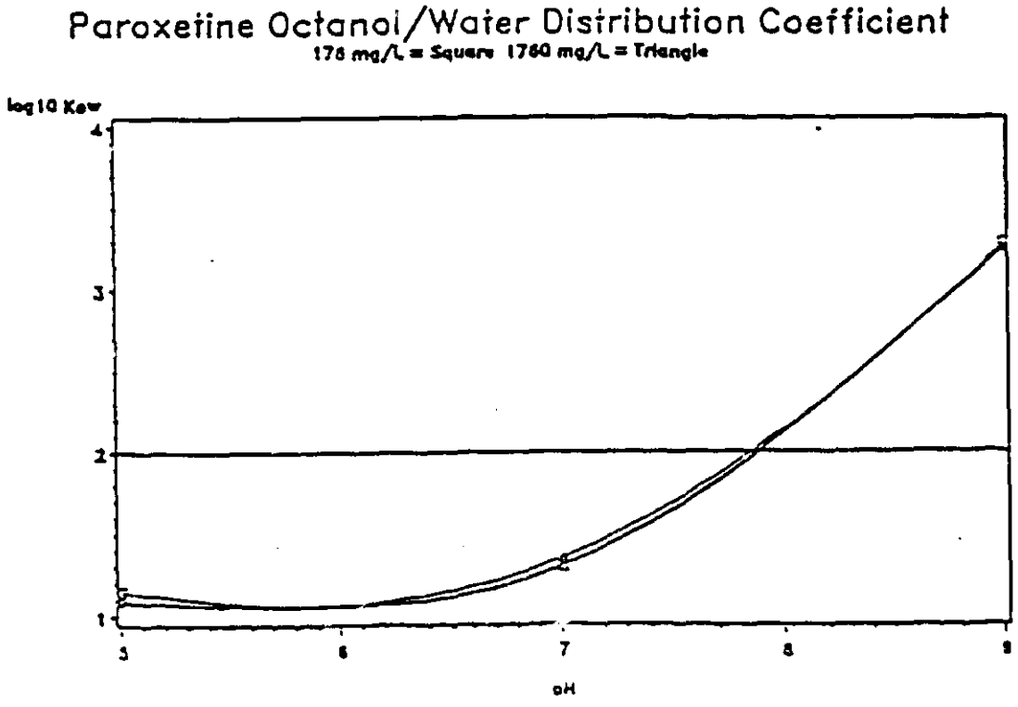
7.2.3 Octanol/Water Distribution Coefficient

The octanol/water distribution coefficients (K_{ow}) for paroxetine were determined in triplicate at 25°C at three pH levels: 5, 7 and 9, and at two concentrations [9]. The results are summarized below.

	Concentration 1 (176 mg/L)		Concentration 2 (1769 mg/L)	
pH	K_{ow} (%RSD)	$\log_{10}K_{ow}$	K_{ow} (%RSD)	$\log_{10}K_{ow}$
5	14.1 (3.5)	1.15	12.2 (3.3)	1.09
7	20.0 (1.8)	1.30	22.2 (1.2)	1.35
9	1930 (14.2)	3.29	1800 (4.2)	3.26

A plot of these results, shown in Figure 1, indicates that the log K_{ow} should not exceed 2 until a pH of about 7.9. Consequently, at typical environmental pH levels, the log K_{ow} will be such that no significant bioconcentration should occur. For the purposes of fate evaluations, a log K_{ow} of 1.32 will be used. Given its structural similarity to paroxetine, a similar value may be used for BRL 36610A.

Figure 1



7.2.4 Vapor Pressure

Because it is a relatively high molecular weight salt, paroxetine hydrochloride would be expected to have an extremely low vapor pressure. However, both the cationic protonated form and the neutral free base form will exist in the environment. Although the latter form will be at very low concentrations at environmental pH levels, it would be expected to be more volatile than the cationic form. Since the cationic form and the free base form are in equilibrium, the loss of the free base form by volatilization will cause the generation of more free base form by conversion of cationic form in order to restore the equilibrium. Thus, significant losses could occur, especially during aeration processes in wastewater treatment plants, were paroxetine free base to have an appreciable vapor pressure. In light of its low water solubility, the vapor pressure would not need to be very high to yield a relatively high Henry's constant. The vapor pressure of the free base of paroxetine was estimated using a volatility limit test [10], which represents a "worst case" scenario since all loss of compound is attributed to volatilization losses.

The vapor pressure was estimated to be less than 8.25×10^{-6} torr. This estimated vapor pressure, when coupled with the water solubility determinations, gives an estimated Henry's constant of $<10^{-8}$ to $<10^{-10}$ atm-m^3/mol. Based on these estimates, volatilization will not be a significant transport process in the environment for paroxetine. BRL 36610A would be expected to exhibit similar behavior.

7.2.5 UV/Vis Spectrum

The UV/Vis spectra of aqueous solutions of paroxetine hydrochloride were determined at pH 5, 7 and 9 [11]. Absorbance maxima of 234 and 292 nm were observed for all three pH values; another maximum at 210 nm was observed at pH 7 and 9, but not at pH 5. The molar extinction coefficients(e) of 3736, 3827, and 3811 in L mol^{-1} cm^{-1} were calculated for pH 5, 7, and 9, respectively. The absorbance spectrum did not appear to be affected by the pH of the aqueous solution, and the significant absorption of light above 290 nm suggests that paroxetine hydrochloride may undergo direct photochemical degradation in the environment (see Item 7.4.3).

7.2.6 Soil Sorption/Desorption (K_{OC})

No soil sorption/desorption isotherm study to generate a K_{OC} value for BRL 36610A (the major metabolite of paroxetine) was performed. A preliminary estimate of the K_{OC} value for BRL 36610A may be made, however, based on data obtained on the adsorption of paroxetine itself to biomass. That some adsorption would occur was apparent from early studies on paroxetine biodegradability, where rapid depletion of some of the

paroxetine from solution occurred over the first day of the studies, followed by no further depletion despite culture acclimations, enrichments, etc. [12] A controlled paroxetine biomass adsorption study was then carried out [13], monitoring depletion of paroxetine as a function of initial biomass concentration (as measured by total suspended solids (TSS)) and of time. The data were fit to a Freundlich equation

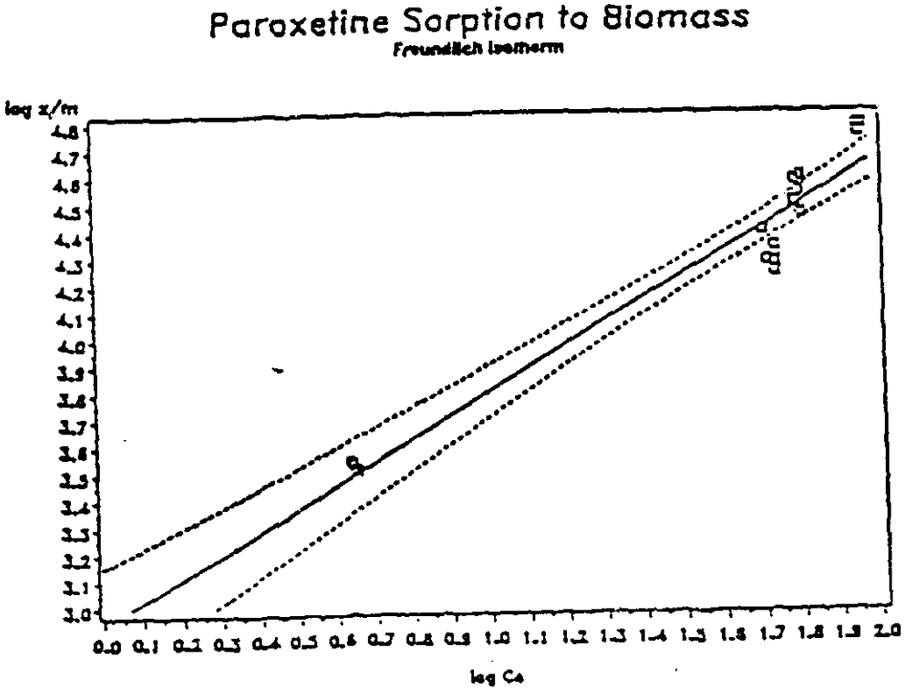
$$\text{Log } x/m = \log K + (1/n) \log C_e$$

where

Log x/m	=	logarithm of the amount of chemical sorbed per amount of adsorbent at equilibrium;
Log C_e		logarithm of the amount of chemical in solution at equilibrium;
K	=	Freundlich adsorption coefficient;
n	=	a constant describing the degree of nonlinearity of the isotherm. When n ≅ 1, the K_f Freundlich constant can be used as an adsorption distribution coefficient, K_d.

If a plot of Log x/m vs Log C_e gives a straight line, the slope of the line is the (1/n) linearity term and the intercept is the log K. The plot for paroxetine is given in Figure 2.

Figure 2



The data were subjected to the SAS General Linear Models Procedure [14] to give the linear regression results shown below:

PAROXETINE SORPTION TO BIOMASS

GENERAL LINEAR MODELS PROCEDURE

DEPENDENT VARIABLE: LOGCSORB

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE
MODEL	1	2.56453608	2.56453608	199.81
ERROR	13	0.20536048	0.01283503	PR > F
CORRECTED TOTAL		14	2.76989656	0.0001

R-SQUARE	C.V.	ROOT MSE	LOGCSORB MEAN
0.925860	2.6200	0.11329179	4.32404502

SOURCE	DF	TYPE I SS	F VALUE	PR > F
LOGCSOLN	1	2.56453608	199.81	0.0001

SOURCE	DF	TYPE III SS	F VALUE	PR > F
LOGCSOLN	1	2.56453608	199.81	0.0001

PARAMETER	ESTIMATE	T FOR H0: PARAMETER=0	PR > |T|	STD ERROR OF ESTIMATE
INTERCEPT	2.94109574	29.00	0.0001	0.10141504
LOGCSOLN	0.86121117	14.14	0.0001	0.06092614

The intercept term above shows that the estimated log $K_{biomass}$ for paroxetine is 2.94. See discussion on paroxetine metabolite and bioadsorption in Item 7.6.

7.3 Environmental Partitioning Estimates for Paroxetine Hydrochloride

Based on the physical property data generated for paroxetine hydrochloride and/or its free base, predictions of environmental distribution in the air, water, ground, and hydrosoil can be made. For this assessment, a simple fugacity equilibrium model is used to estimate the percent of the compound which would be expected to distribute in each compartment at steady-state, assuming no depletion mechanisms. For this evaluation, the QSAR system supplied by Technical Database Services was used (reference [15]).

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This model appears to apply reasonably well to the paroxetine chemical structure. A comparison of the predicted physical properties with those actually determined for the free base (pH 9) is shown below.

Property	Predicted Value	Actual Value
Water Solubility- mg/L	203	318-485
Log P	3.25	3.27
pK_a	9.66	9.6

Used in the QSAR Environmental Partitioning Model, the actual data at pH 9 yielded the following prediction:

<<<< QSAR >>>>
Institute for Process Analysis
Montana State University

Name: Paroxetine Free Base

Smiles: O(-c(c(-O1)ccc2-OCC(C(-c(ccc(-F)c3)c3)CCN4)C4)c2)C1

QSAR Estimates for Exposure Assessment

LOG(Water Solubility) = -2.83 Mol/L
Log(BCF) = 2.19 BCF = 155.31
Absorption Coef. Log(Koc) = 3.12 (See Lyman et al. 1990) [16]
Hydrolysis Half Life = 1000 Days
Hydrolysis is not likely to be an important transformation mechanism for this chemical.

Henrys law Constant and Environmental Partitioning

Log10 (Henrys Constant) = -10.15 atm-m**3/mole
Lyman et al. 1990. [16] would conclude that a chemical with these properties is non-volatile. See p15-15.

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NEELY 100 Day Partitioning Pattern

Air	=	0.00 %
Water	=	70.11 %
Ground	=	15.46 %
Hydrosoil	=	14.43 %

However, the pH 9 data represent the lower limit of water solubility and the upper limit of log P. Using the actual physical property data generated in-house at pH 7, the environmental partitioning is as follows:

<<<< QSAR >>>>
Institute for Process Analysis
Montana State University

Name: Paroxetine Hydrochloride
Smiles: O(-c(c(-O1)ccc2-OCC(C(-c(ccc(-F)c3)c3)CCN4)C4)c2)C1

QSAR Estimates for Exposure Assessment

LOG(Water Solubility) = -2.51 Mol/L
Log(BCF) = 0.65 BCF = 4.47
Absorption Coef. Log(Koc) = 2.06 (See Lyman et al. 1990) [16]
Hydrolysis Half Life = 1000 Days
Hydrolysis is not likely to be an important transformation mechanism for this chemical.

Henrys law Constant and Environmental Partitioning

Log10 (Henrys Constant) = -9.47 atm-m**3/mole

Lyman et al. 1990. [16] would conclude that a chemical with these properties is non-volatile. See p15-15.

NEELY 100 Day Partitioning Pattern

Air	=	0.00 %
Water	=	99.52 %
Ground	=	0.25 %
Hydrosoil	=	0.23 %

Therefore, based on this model using data generated at pH 7, any paroxetine hydrochloride emitted into the environment from production or accident is predicted to partition predominantly in the aquatic (water) compartment. No losses to atmosphere are anticipated, and only a small percentage of material is expected to enter the ground or hydrosoil compartments [17]. At pH levels greater than 7, as more paroxetine free base is present, more partitioning into ground and hydrosoil would be expected. However, even at pH 9, predominant partitioning is to the aquatic compartment.

7.4 Transformation and Depletion Mechanisms of Paroxetine Hydrochloride

7.4.1 Hydrolysis

The hydrolytic stability of paroxetine hydrochloride was determined at 50°C in deionized water and aqueous buffer solutions at pH 5, 7, and 9 over a five day period [18]. No appreciable hydrolysis was found to occur in deionized water or at pH levels of 5 and 7; for pH 9, a 6.95% loss was determined after 5 days. No rate determination was carried out since less than 10% of the initial concentration hydrolyzed over the 5 day period. However, as discussed above, even this slow rate of hydrolysis was significant enough to interfere with water solubility studies and pK_a studies at pH ≥ 9. In the environment, there is little potential for paroxetine to experience pH levels > 9, and no evidence of hydrolysis was observed in any tests at pH levels < 9. Hydrolysis per se is therefore unlikely to be a significant transformation or depletion process for paroxetine in the environment.

7.4.2 Aerobic Biodegradation

Extensive aerobic biodegradability studies were carried out using paroxetine hydrochloride and a variety of microorganisms sources. These included seed from both domestic and industrial biotreatment plants and soils. Extensive work was carried out in attempts to acclimate, adapt, and enrich cultures for organisms with a propensity to degrade paroxetine as both a sole carbon source and as a co-metabolic substrate[19]. None of these studies was successful. After some decrease in paroxetine concentration

due to bioadsorption [20], the concentration of paroxetine in all studies remained essentially constant and no by-products were observed in the HPLC chromatograms used to monitor the studies. One in-house definitive study is listed as reference [21]. A contract laboratory study which followed the aerobic biodegradation by both CO_2 evolution and HPLC assays for parent was also unsuccessful in demonstrating biodegradability [22].

7.4.3 Aqueous Photolysis

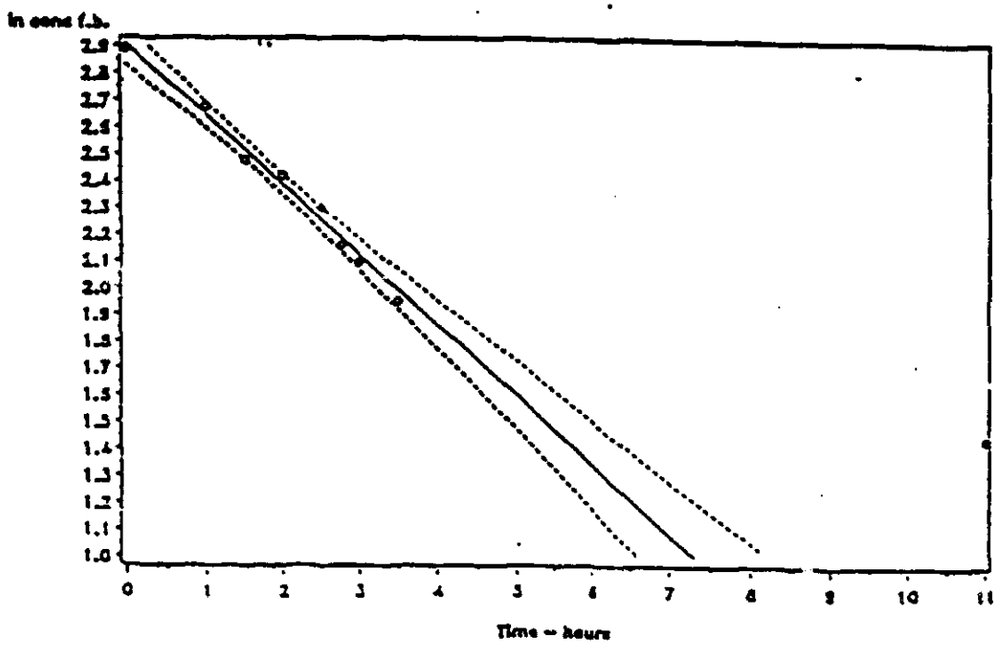
Given the recalcitrance of paroxetine to microbial biodegradation, and its significant absorption of light at wavelengths >290 nm, an evaluation was made of the potential of aquatic photolysis as a degradative pathway for paroxetine in the environment. The maximum direct aqueous photoreaction rate constant and minimum half-life were estimated using standard methods based on UV/visible spectra and solar irradiance data [23].

The results indicate estimated half-lives for paroxetine in natural sunlight of 0.01 days to 0.004 days depending on season and latitude. Because of this favorable preliminary estimate, an aquatic photolysis study was carried out to determine definitive experimental values.

Studies were carried out in deionized water and in pH 7 buffer in natural sunlight. The results gave initial first order photolysis rate constants for paroxetine of 0.29 hr^{-1} and 0.27 hr^{-1} respectively [24]. The rate constants were derived from linear regressions of initial data, as illustrated in Figure 3 for the reaction in pH 7 buffer.

Figure 3

Aqueous Photolysis of Paroxetine in pH 7 Buffer



The rate constant corresponds to a half-life of 2.4 hours. HPLC analysis of the photolyzed solution, which contained no residual paroxetine, did not show any major UV active degradants. See Item 8.2.2 for a discussion of the toxicity of the photolysis by-products.

7.5 Physical Property Determinations for Paroxetine Metabolite (BRL 36610A)

No physical property determinations were carried out for paroxetine metabolite (BRL 36610A). However, its very close similarity to paroxetine itself makes the use of paroxetine physical property data adequate for evaluation of the fate of metabolite.

7.6 Environmental Partitioning Estimates for Paroxetine Metabolite (BRL 36610A)

Since paroxetine metabolite (BRL 36610A) is the predominant species resulting from use of the product, its fate in conventional wastewater treatment plants is first considered. Based on its structural similarity to paroxetine parent, BRL 36610A would be expected to have similar physical properties and to partition in similar ways. Thus the $K_{biomass}$ determined for paroxetine is relevant to estimating the sorption of BRL 36610A to the sludge during waste treatment. The implications of this sorption to biomass can be assessed using a distribution calculation based on a "worst case" situation:

The recommended dose of paroxetine for Panic Disorder will be 40 mg per day for most patients. Assuming that the average person discharged 600 L/day into a wastewater treatment plant, this corresponds to a maximum emitted concentration (C_T) of

$$\frac{40\text{ mg} \times 331\text{ (MW metabolite)}}{600\text{ L} \times 374\text{ (MW parent)}} = 5.90\text{E-}02\text{ mg/L/day}$$

$$C_T = C_{sorbed} + C_{soln}$$

$$C_{sorbed} = C_T - C_{soln}$$

$$K_{biomass} = \frac{C_{sorb}\text{(mg/L)/biomass(mg/L)}}{C_{soln} \times 10^{-6}\text{ (mg/mg)}}$$

$$8.71\text{E}02 = \frac{(5.90\text{E-}02 - C_{soln})/2500}{C_{soln} \times 10^{-6}\text{ (mg/mg)}}$$

$$8.71\text{E}02 \times C_{soln} \times 10^{-6} = 2.36\text{E-}05 - 4.00\text{E-}04 C_{soln}$$

$$1.27\text{E-}03 \times C_{soln} = 2.36\text{E-}05$$

$$C_{soln} = 1.86\text{E-}02\ (31.5\%)$$

$$C_{sorb} = 5.90\text{E-}02 - 1.86\text{E-}02$$

$$= 4.04\text{E-}02\ (68.5\%)$$

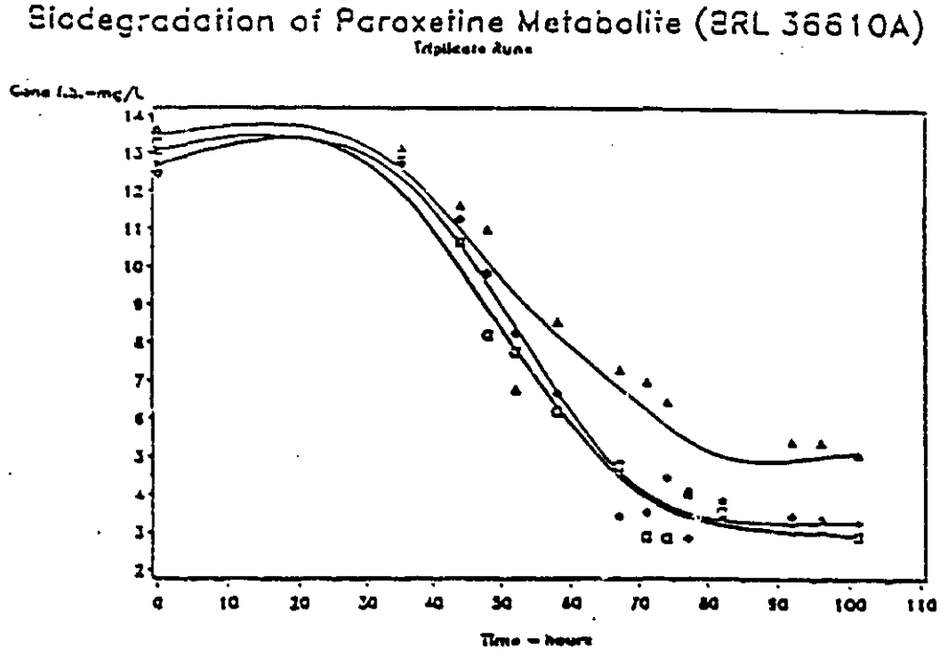
Thus, in a wastewater treatment plant, 68.5% of the compound should sorb to the biomass, with 31.5% remaining in solution.

7.7 Transformation and Depletion Mechanisms of Paroxetine Metabolite (BRL 36610A)

7.7.1 Aerobic Biodegradation

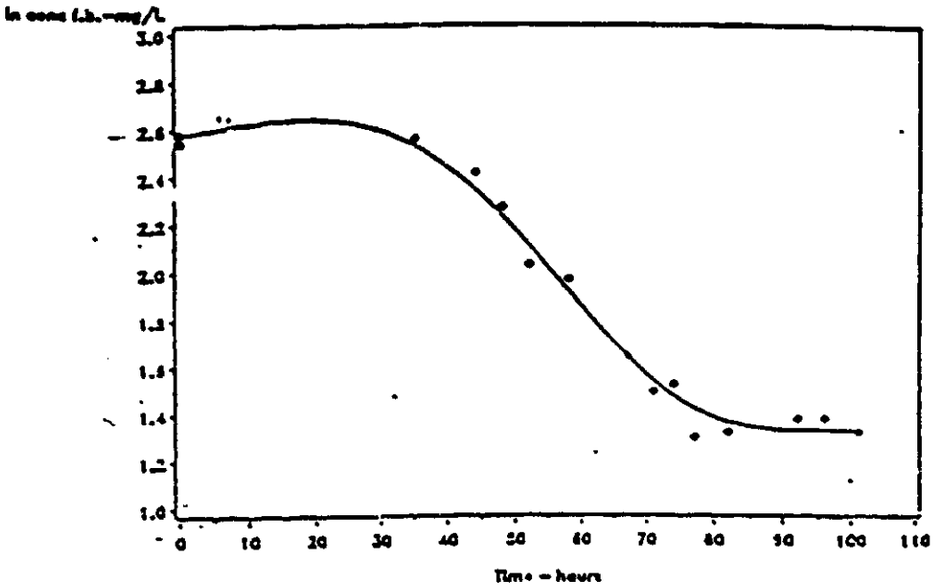
Aerobic biodegradation studies were carried out on paroxetine metabolite (BRL 36610A) since it is the major compound excreted into the environment from use. BRL 36610A was found to degrade to less than detectable levels within 5 days. Although adsorption to biomass occurs, the compound should still be available for degradation, since the adsorption is reversible. As the compound is biodegraded, more will desorb from the biomass until complete degradation is accomplished. The results of preliminary and definitive in-house studies are given in references [25] and [26]. A contract laboratory aerobic biodegradation study was also completed, but has not been included in this assessment due to non-compliance issues. For reference, a memo describing the preliminary results of that study was prepared [27]. A plot of the data from the definitive in-house study is shown in Figure 4.

Figure 4



A natural log transformation of the averaged data gave the results shown in Figure 5. Here, the early lag, the active biodegradation, and the die-off portions of the study are clearly apparent.

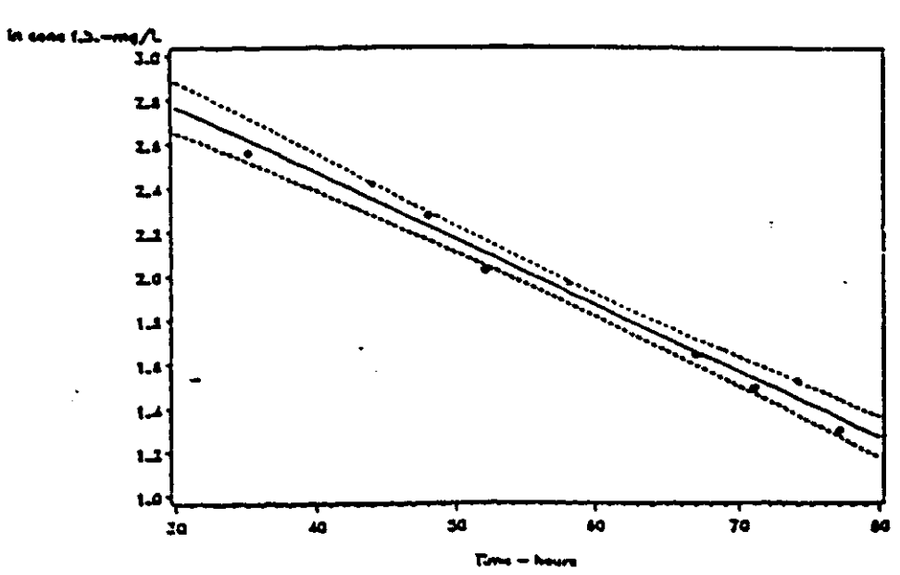
Figure 5
Biodegradation of Paroxetine Metabolite (BRL 36610A)



The linear regression and 95% confidence limits for the data from hours 35-77 are shown in Figure 6.

Figure 6

Biodegradation of Paroxetine Metabolite (BRL 36610A)



The data were subjected to the SAS General Linear Models Procedure [14] to give the linear regression results shown below:

BIODEGRADATION OF PAROXETINE METABOLITE (BRL 36610A)

GENERAL LINEAR MODELS PROCEDURE

DEPENDENT VARIABLE: LNCAV

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE
MODEL	1	1.56088461	1.56088461	380.24
ERROR	7	0.02873512	0.00410502	
CORRECTED TOTAL	8	1.58961973		

R-SQUARE	C.V.	ROOT MSE	LNCAV MEAN
0.981923	3.3549	0.06407041	1.90972871

SOURCE	DF	TYPE I SS	F VALUE	PR > F
TIME	1	1.56088461	380.24	0.0001

SOURCE	DF	TYPE III SS	F VALUE	PR > F
TIME	1	1.56088461	380.24	0.0001

PARAMETER	ESTIMATE	T FOR H0: PARAMETER=0	PR > |T|	STD ERROR OF ESTIMATE
INTERCEPT	3.66716780	39.59	0.0001	0.09262232
TIME	-0.03007025	-19.50	0.0001	0.00154209

The intercept term above shows that the ln K, the first order rate constant for biodegradation of paroxetine metabolite (BRL 36610A), is 0.03 hr^{-1}.

7.8 Environmental Transport Issues

In addition to estimation of the distribution and transformation of a chemical in the environment, Item 7 of the Environmental Assessment requires some evaluation of the likely mobility of the chemical in the environment by means of air, water, and other environmental transport mechanisms. However, given data supporting the distribution of paroxetine and paroxetine metabolite (BRL 36610A) essentially completely in the aquatic compartment, and the rapid depletion of paroxetine parent by photolysis and paroxetine

metabolite (BRL 36610A) by biodegradation at expected environmental discharge concentrations, further consideration of environmental transport issues is not considered necessary. Both compounds should not persist in the environment long enough for significant transport to occur.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

8.1 Human and Mammalian Health Effects Summary

8.1.1 Acute Toxicity Studies

8.1.1.1 Oral Toxicity [28]

The oral and intravenous acute toxicity of paroxetine free base has been examined in the mouse and in the rat. The approximate oral LD_{50} was similar for both species (mouse 341 and rat 374 mg/kg pfb). Intravenously, the compound was approximately ten times as toxic as by the oral route. In both species, the central nervous system (CNS) was apparently the target organ as physical signs of CNS stimulation were evident. Paroxetine hydrochloride was found to be less toxic, with acute oral LD_{50} values of >630 mg/kg pfb in both male and female rats.

8.1.1.2 Skin Irritation [29]

Paroxetine hydrochloride was classified as a non-irritant to rabbit skin based on studies that showed no signs of irritation up to 3 days after direct application for 4 hours in rabbits.

8.1.1.3 Eye Irritation [29]

Paroxetine hydrochloride was classified as a very severe to extremely severe irritant to rabbit eyes. Severe irritation occurred immediately after direct application and animals were immediately destroyed.

8.1.1.4 Sensitization [29]

Paroxetine hydrochloride was classified as a non-sensitizer to guinea pig skin. No irritation or adverse skin reactions occurred in guinea pigs used to test for sensitization or allergic skin reaction (modified Maguire/Split Adjuvant Test).

8.1.2 Chronic Toxicity Studies [28]

8.1.2.1 Carcinogenicity

Studies were carried out in Sprague-Dawley rats and an outbred CD1 strain of mice from the same suppliers. The conclusions reached were that paroxetine has no apparent carcinogenic potential. The predicted carcinogenic risk for man following long term administration of paroxetine is therefore very low.

8.1.2.2 Reproduction toxicology

The rat and rabbit were used to assess the potential of paroxetine to cause embryo toxicity. These studies did not indicate any adverse effect on the embryo or fetus, and in neither species was there any teratogenicity. In addition, the effects of paroxetine on fertility were assessed in the rat and there were no indications from the general toxicity studies that the female reproductive system has been adversely affected.

8.1.2.3 Mutagenicity studies

The tests carried out for examining the effects on the gene were the bacterial Ames and mouse lymphoma tests, both of which are *in vitro* tests. In neither system (with and without a metabolic activating system) were significant increases in mutation frequency observed. The potential to cause chromosomal aberrations was studied by examining the bone marrow cells for micronuclei following the administration of paroxetine to mice at the very high doses of 75 and 150 mg/kg. There was no evidence for any chromosomal damage. Human lymphocytes were also studied *in vitro* with and without a metabolic activating system, and again no damage to the chromosomes of these cells was observed.

8.2 Aquatic Toxicity Studies

8.2.1 Acute Aquatic Toxicities of Paroxetine Hydrochloride and its Major Metabolite (BRL 36610A)

Acute aquatic toxicity studies were carried out on microorganisms (Microtox® [30] and [31] and Microbial Respiration Inhibition [32]), *Daphnia magna*, [33], [35] and bluegill sunfish (*Lepomis macrochirus*) [34], [36] for paroxetine parent and on microorganisms [39] and *Daphnia magna* [37], [38] for paroxetine metabolite BRL 36610A.

The results are summarized below, and in the summary sheet (Appendix V).

Toxicity Test	Paroxetine HCl (mg/L)	BRL 36610A (mg/L)
Microtox® - EC_{50}	8.2	29
Respiration Inhibition - EC_{50}	25 to 26	80 to 83
Daphnia magna - LC_{50}	2.5	35
Bluegill Sunfish - LC_{50}	1.6	No study performed

From the data above, paroxetine metabolite appears to be less toxic to aquatic organisms than paroxetine itself. This, coupled with its ready biodegradability, indicates that paroxetine metabolite will not have an adverse impact on the environment.

8.2.2 Acute Aquatic Toxicity of Paroxetine Photolysis By-Products

Paroxetine itself, although more toxic, is rapidly degraded in the presence of sunlight to simpler by-products. These by-products can be assumed to be less toxic than paroxetine based on the results of a Microtox® test carried out on samples of paroxetine solutions that had been exposed to sunlight [40]. No EC_{50} could be determined for the degraded solutions as compared to the control solutions which showed an EC_{50} of 9.1 mg fb/L, comparable to the independently determined EC_{50} of paroxetine hydrochloride of 8.2 mg fb/L shown. Any paroxetine which might enter the environment from production or accident will rapidly photodegrade into innocuous polar by-products.

8.2.3 Acute Aquatic Toxicity of BRL 36610A Biodegradation By-Products

BRL 36610A, the major metabolite of paroxetine, will be readily biodegraded in municipal wastewater treatment plants. Although the compound is not mineralized, it does appear to be transformed into simpler, more polar by-products. These by-products can be assumed to be less toxic than BRL 36610A itself based on the results of a Microtox® test carried out on samples of BRL 36610A solutions after laboratory biodegradation experiments. No EC_{50} could be determined for the degraded solutions [41]. Any compounds entering the environment after biotreatment of paroxetine metabolite should be innocuous polar by-product which should not exert any toxic effects.

Thus, the production and use of paroxetine will not have any adverse impacts on the environment.

9. USE OF RESOURCES AND ENERGY

9.1 Use of Resources And Energy At Cork

The following table summarizes the percent of total plant resources utilized at the Cork facility to produce the paroxetine drug substance required for the Panic Disorder product, at estimated fifth year production levels (in 1999).

	Electricity (kw-hour)	Fuel (gas therms)	Water (m^3)
Percent Consumption (1999)	26%	27%	27%

The effects on the use of resources and land for the production of paroxetine drug substance are minimal because of the relatively low production volumes and associated wastes, and the existing treatment units that will be used.

9.1.1 Effect Upon Endangered Species And Historic Places

The production of paroxetine substance and the disposal of associated wastes should have no impact on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by paroxetine

substance production or waste disposal activities since the production is taking place outside of the United States.

9.2 Use of Resources And Energy At Irvine

To produce the drug substance required for the paroxetine Panic Disorder product at estimated fifth year production levels (in 1999), it is estimated that the following percentages of the total Irvine site usage of resources will be used.

	Electricity (kw-hours)	Fuel (gas therms)	Water (m^3)
Percent Consumption	0.077%	0.16%	0.22%

9.2.1 Effect Upon Endangered Species And Historic Places

The production of paroxetine substance and the disposal of associated wastes should have no impact on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by paroxetine substance production or waste disposal activities since the production is taking place outside of the United States.

9.3 Use of Resources And Energy At Cidra

The drug product will be produced in the SmithKline Beecham Pharmaceuticals' facility in Cidra, Puerto Rico, which also produces other pharmaceutical products. The facility is located on a 52 acre site. The effects on the use of resources and land for the production of paroxetine drug product are minimal because of the relatively low production volumes and associated wastes, and the existing treatments units which will be used. Manufacture of this product uses only a small percentage of the resources and energy available at this site and of resources and energy required for transport.

To produce Paxil ™ Panic Disorder tablets at estimated fifth year production levels (in 1999), it is estimated that 3% of total plant usage of fuel and water will be used at Cidra.

9.3.1 Effect Upon Endangered Species And Historic Places

The production of paroxetine [redacted] and the disposal of associated wastes should have no effect on threatened or endangered species. Details on the environmental characteristics of the Cidra community are given in Appendix V. Property listed in or

eligible for listing in the National Register of Historic Places will also not be impacted by paroxetine product production or waste disposal activities.

10. MITIGATION MEASURES

10.1 Mitigation At Cork

Plans to minimize waste output were considered and implemented at the outset of paroxetine development, as well as during substance production. The Integrated Pollution Control (IPC) license contains guidelines for the establishment of an Environment Management Programme to assess all operations for the use of cleaner technology and the minimization of waste. Potential environmental impacts associated with production at Cork are also minimized by the following:

Most waste streams are incinerated, and the gases scrubbed before being discharged. Scrubber liquors are biotreated in the on-site wastewater treatment facility before discharge.

Biotreated effluent streams are checked before discharge, with ample capacity for emergency storage in the event that effluent criteria are not met.

Airstreams from the process buildings are filtered prior to venting to the atmosphere.

10.2 Mitigation At Irvine

Plans to minimize waste output were considered and implemented at the outset of paroxetine development, as well as during substance production. A nitrogen generating plant was built at the facility to meet the plant's nitrogen requirements, thus eliminating the need for external sources of nitrogen.

10.2.1 Energy

Approximately 10% of steam energy is saved, through the use of boiler economisers and spray recuperations.

10.2.2 Effluents

The amounts of regulated components discharged in effluent is regularly monitored by the Irvine facility's QA department and the local water authority of Irvine, to ensure compliance with established consent levels. Additional details on the mitigation and disposal of aqueous wastes are provided in Item 6 of this assessment.

10.2.3 Resource Recovery

Components discharged to effluent are monitored by the Irvine facility's QA department and the local water authority of Irvine, to ensure compliance with established consent levels. Additional details on the mitigation and disposal of aqueous wastes are provided in Item 6 of this report.

10.2.4 Spill Control

The SmithKline Beecham Pharmaceutical's facility at Irvine, Scotland (U.K.), has established adequate spill control and clean up procedures, as described in Item 6 of this assessment.

10.3 Mitigation At Cidra

Potential adverse environmental impacts associated with the proposed action are minimized at the Cidra facility by the following:

No waste or exhaust streams are directly discharged. All streams are directed to major treatment units. Treated effluent streams are checked before discharge, with ample capacity for emergency storage in the event that effluent criteria are not met;

Airstreams from the process are small and directed to dust collectors, which minimize the effects of the emissions by at least 99.9%;

Storage facilities are designed to allow for the capture and treatment of any spills or oil contaminated water before any major environmental effects could result. Also, the adopted spills prevention, control and contingency plans have been demonstrated to be effective in the prevention of such emergencies.

11. ALTERNATIVE TO THE PROPOSED ACTION:

No potential adverse environmental impacts have been identified for the proposed action. The only alternative to the proposed action is that of no action, thus depriving patients an important therapy. The approval of paroxetine tablets for the treatment of Panic Disorder will provide an important benefit to patients requiring its administration with no known adverse environmental risk.

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ENVIRONMENTAL ASSESSMENT
***Paxil*™ Panic**
July 28, 1995

REDACTIONS MADE BY APPLICANT

13. CERTIFICATION:

The undersigned official certifies that the information presented is true, accurate, and complete to the best knowledge of the SmithKline Beecham Corporate Environmental Research Laboratory.

Date: August 1, 1995

Signature: James Hagan

James R. Hagan, P.E.
Vice President & Director
Corporate Environment & Safety
SmithKline Beecham

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15. APPENDICES

ENVIRONMENTAL ASSESSMENT
Paxil ™ Panic
July 28, 1995

ITEM **PAGE**

SmithKline Beecham
Pharmaceuticals

REDACTIONS MADE BY APPLICANT

Penn Chemicals B.V. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Paroxetine at its facilities in Currabinny, Carrigaline, Co. Cork, Ireland.

Declan Ryan 14/10/91

NAME: DATE:

TITLE: Manager Engineering / Environmental

Finbar Whyte 14/10/91

NAME: DATE:

TITLE: Director of Manufacturing

PENN CHEMICALS B.V., Currabinny, Carrigaline, Co. Cork, Ireland.
Tel. 021-371291, Fax 021-372362, Telex 75668 Intl Dialing +353-21-371291

Reg. No. 4 Schedule 1 (i)

Emissions to Atmosphere

Emission point Reference No. V1 Incinerator No. 1

Location : Incinerator compound

Volume to be emitted : Maximum in any one day 264,000 m^3
: Maximum rate per hour 11,000 m^3

Minimum efflux velocity : 24 $m.sec^{-1}$
Minimum discharge height: 30 m

Incinerator operating temperature : 1100 °C minimum
Residence time : 2 seconds minimum

Parameter	Emission limit values	
	30 min mean mg/m^3	Daily mean mg/m^3
Volatile organic compounds (excluding particulate matter) (expressed as total organic carbon).	20	10
Total Particulate matter	100	30
Hydrogen Chloride	60	10
Hydrogen Fluoride	4	1
Sulphur Dioxide	200	50
Hydrogen Bromide	10	-

Dioxin (as TEQ) *-see page 26*	6-8 hour sample	0.1 ng/m^3

Parameter	The concentration of carbon monoxide after the last injection of combustion air shall not exceed the following levels
Carbon monoxide	50 mg/m^3 daily average 100 mg/m^3 hourly average 95% of all 10 minute average values over any 24 hour period shall be less than 150 mg/m^3.

Source: Integrated Pollution Control (IPC) licence
Oct. 94 - Environmental Protection Act, 1992

Reg. No. 4 Schedule 1 (i)

Emission point Reference No. V3 Incinerator No. 3

Location : Incinerator compound

Volume to be emitted : Maximum in any one day 407,952 m^3
: Maximum rate per hour 17,000 m^3

Minimum efflux velocity : 24 $m.sec^{-1}$
Minimum discharge height: 24.4 m

Incinerator operating temperature : 900 °C minimum
Residence time : 0.65 second minimum

Parameter	Emission limit values	
	30 min mean mg/m^3	Daily mean mg/m^3
Volatile organic compounds (excluding particulate matter) (expressed as total organic carbon)	20	10
Total Particulate matter	30	10
Hydrogen Chloride	60	10
Hydrogen Fluoride	4	1
Sulphur Dioxide	200	50

Dioxin (as TEQ) - *see page 26*	6-8 hour sample	0.1 ng/Nm^3

Parameter	The concentration of carbon monoxide after the last injection of combustion air shall not exceed the following levels
Carbon monoxide	50 mg/m^3 daily average 100 mg/m^3 hourly average 95% of all 10 minute average values over any 24 hour period shall be less than 150 mg/m^3.

Reg. No. 4 Schedule 1 (i)

Emission point Reference No. V2 Incinerator No.4

Location : Incinerator compound

Volume to be emitted : Maximum in any one day 37,320 m^3
: Maximum rate per hour 1,555 m^3

Minimum efflux velocity : 17 $m.sec^{-1}$
Minimum discharge height: 24.4 m

Incinerator operating temperature : 1100 °C minimum
Residence time : 2 seconds minimum

Parameter	Emission limit values	
	30 min mean mg/m^3	Daily mean mg/m^3
Volatile organic compounds (excluding particulate matter) (expressed as total organic carbon)	20	10
Total Particulate matter	30	10
Hydrogen Chloride	60	10
Hydrogen Fluoride	4	1
Sulphur Dioxide	200	50
Hydrogen Bromide	10	-

Dioxin (as TEQ) - *see page 26*	6 - 8 hour sample	0.1 ng/Nm^3

Parameter	The concentration of carbon monoxide after the last injection of combustion air shall not exceed the following levels
Carbon monoxide	50 mg/m^3 daily average 100 mg/m^3 hourly average 95% of all 10 minute average values over any 24 hour period shall be less than 150 mg/m^3.

Reg. No. 4 Schedule 1 (i)

Emission point Reference No. V7 Scrubber fan exhaust

Location : Process Building 120, Scrubber fan exhaust.

Volume to be emitted : Maximum in any one day 12,000 m^3
: Maximum rate per hour 500 m^3

Minimum efflux velocity : 4.33 $m.sec^{-1}$
Minimum discharge height: 17.7 m above ground

Parameter	Emission limit values mg/m^3
Total Mercaptan	2
Dimethyl Disulphide	2
Carbon disulphide	5
Dimethyl Sulphate	2
Chlorine	10
Hydrogen Chloride	30
Methanol	600 (at < 3 kg/hr mass flow)

Reg. No. 4 Schedule 1 (i)

Emission point Reference No. V8 - Production building 101, scrubber

Location : Production building 101

Volume to be emitted : Maximum in any one day 2,477,700 m^3
: Maximum rate per hour 102,000 m^3

Minimum efflux velocity : 36 $m.sec^{-1}$
Minimum discharge height: 14.7 m

Parameter	Emission limit values mg/m^3 (*see note* [1])
Hydrogen Chloride	30
T.A. Luft Class II Organics	100
T.A. Luft Class III Organics	150
Chlorine	10

Note[1] Where organic substances of several classes are emitted simultaneously, in addition to the above individual limits the sum of the concentrations of Classes II & III shall not exceed the Class III limit. (T.A. Luft 1986)

Emission point Reference Nos. : V9 - V13 Production Building 101

V14 Production Building 104

Emissions of Pharmaceutical dust from drying, filtering, milling and packing operations :

Vent Ref No	Location	Max daily discharge (m^3)	Max hourly discharge (m^3)	Minimum efflux velocity ($m.sec^{-1}$)	Minimum discharge height (m)	Emission limit value mg/m^3
V9	Building 101	300,000	12,477	13.9	1.4	1
V10	Building 101	30,000	1,232	6.7	0.65	1
V11	Building 101	30,000	1,232	6.7	0.65	1
V12	Building 101	144,000	6,000	5.5	1.25	1
V13	Building 101	120,960	5,040	20.3	1.1	1
V14	Building 104	67,200	2,800	1.62	1.1	1

Reg. No. 4 Schedule 1 (i)

Emission point Reference No. V102 - Hydrogenation vent from process building 120 (P)

Location : Adjacent to production building 120

Volume to be emitted : Maximum in any one day 350 m^3
: Maximum rate per hour 150 m^3

Minimum efflux velocity : 20.5 $m.sec^{-1}$
Minimum discharge height: 19.5

Parameter	Emission limit values
	mg/m^3
Methylene Dichloride	150
Methanol	150

Emission point Reference No. V118

Location : Boiler Room in proposed extension to building 105.

Volume to be emitted : Maximum in any one day 541,296 m^3
: Maximum rate per hour 22,554 m^3

Minimum efflux velocity : 19.8 $m.sec^{-1}$
Minimum discharge height: 11.6 m above ground

Parameter	Emission limit values	
	Routine	Alternative Fuel
	mg/m^3	mg/m^3
Particulate	5	100
Sulphur Dioxide	35	1700
NO_X (as NO_2)	200	450
Carbon Monoxide	100	100

Reg. No. 4 Schedule 2 (i)

Emission to Waters

Emission point Reference No. Process Effluent Diffuser.

Emission to : Mouth of Lough Beg Bay, into Cork Harbour

Volume to be emitted : Maximum in any one day 600 m^3

: Maximum rate per hour 151.2 m^3

Emission limits up to and including 30th September 1995

Parameter	Emission limit values	
	mg/l	kg/ day
Total Ammonia (as N)	400	240
Suspended Solids	750	450
Zinc (as Zn)	1.0	0.6
Copper (as Cu)	0.5	0.3
C.O.D.	5000	3000
B.O.D.	600	360
Nitrates (as N)	100	60
Phosphate (as P)	24.0	15

Parameter	As Discharged emission limits	Sampling period
pH	6 - 9	Continuous
Organohalogens	see note 2	Monthly mean
Number of Toxicity Units (Note 1)	10	Weekly composite

[1] The Toxicity of the effluent shall be determined on an appropriate aquatic species. The number of toxic units (TU) = 100/ 96 hour LC50 in percentage vol/vol so that higher TU values reflect greater levels of toxicity.

[2] Screening for a priority pollutant list is required (such as CPL 40 , US EPA volatile and/or semi-volatile)

Reg. No. 4 Schedule 2 (i)

Emission to Waters

Emission point Reference No. Process Effluent Diffuser

Emission to : Mouth of Lough Beg Bay, into Cork Harbour

Volume to be emitted : Maximum in any one day 600 m^3

: Maximum rate per hour 151.2 m^3

Emission limits from 1st October 1995

Parameter	Emission limit values	
	mg/l	kg/day
Total Ammonia (as N)	50	30
Suspended Solids	250	150
Zinc (as Zn)	1.0	0.6
Copper (as Cu)	0.5	0.3
C.O.D.	4000	2400
B.O.D.	500	300
Nitrates (as N)	15	9
Phosphate (as P)	24	15

Parameter	As Discharged emission limits	Sampling period
pH	6 - 9	Continuous
Organohalogens	see note 2	Monthly mean
Number of Toxicity Units (Note 1)	10	Weekly composite

[1] The Toxicity of the effluent shall be determined on an appropriate aquatic species. The number of toxic units (TU) = 100/96hour LC50 in percentage vol/vol so that higher TU values reflect greater levels of toxicity.

[2] Screening for a priority pollutant list. (such as CPL 40 , US EPA volatile and/or semi-volatile)

Reg. No. 4 Schedule 1 (i)

Emission point Reference No. V4 - Bay 5 Scrubber in building 101

Location : Bay 5 Scrubber in building 101

Volume to be emitted : Maximum in any one day 28,800 m^3
: Maximum rate per hour 1,200 m^3

Minimum efflux velocity : 35 $m.sec^{-1}$
Minimum discharge height: 14.2 m

Parameter	Emission limit values
	mg/m^3
Hydrogen Chloride	30
Chlorine	15
Ammonia	75
Epichlorohydrin	5

Emission point Reference No. V5

Location : At the Boiler House - Adjacent to Building 105.

Volume to be emitted : Maximum in any one day 195,610 m^3
: Maximum rate per hour 8,150 m^3

Minimum efflux velocity : 15.6 $m.sec^{-1}$
Minimum discharge height: 11.6 m above ground

Parameter	Emission limit values	
	Routine mg/m^3	Alternative Fuel mg/m^3
Particulate	5	100
Sulphur Dioxide	35	1700
NO_x (as NO_2)	200	450
Carbon Monoxide	100	100

ENVIRONMENTAL ASSESSMENT
Paxil ™ Panic
July 28, 1995

SmithKline Beecham
Pharmaceuticals

PAROXETINE ENVIRONMENTAL ASSESSMENT

GENERAL COMPLIANCE STATEMENT

SMITHKLINE BEECHAM states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of PAROXETINE HYDROCHLORIDE at its facilities in IRVINE, SCOTLAND, U.K. as currently interpreted and applied by the relevant environmental enforcing authorities.

D McCurry 15/10/91

NAME: Mr. D. McCurry DATE:
TITLE: Plant Manager

R H Leckie 11.10.91

NAME: Dr. R.H. Leckie DATE:
TITLE: Safety and Environmental Manager

Shewalton Road, Irvine, Ayrshire, KA11 5AP, Scotland. Telephone: 0294-74200. Telex: 779171. Fax: 0294-73738

EFFLUENT CONSENT LEVELS AT IRVINE, SCOTLAND

CONSTITUENT	PARAMETER (mg/L)
BOD_5	7000
Suspended Solids	5000
Methyl isobutyl ketone	700
Isopropyl alcohol	350
Acetone	300
Methanol	500
Methylene dichloride	80
Phenol	30
Ethanol	200
Triethylamine	5
Toluene	60
Butanol	100
Tertiary butyl amine	40
Dimethylformamide	20
Tetrahydrofuran	20
Pyridine	5
Zinc	2
Copper	1.5
Ammonia (as NH_3-N)	200
pH	4 - 12

The volume of the discharge in any one day shall not exceed 6000 m^3 and the rate of discharge shall not exceed 400 m^3 per hour.

Reference: Clyde River Purification Board
Glasgow, Scotland
Consent No.: CP8750 (N2)

ENVIRONMENTAL ASSESSMENT
Paxil ™ Panic
July 28, 1995

SB

SmithKline Beecham

Environmental Research Laboratory

22/October/1991

TO: Dr. Virginia Cunningham

cc: ERL Files
D&C Files

FROM: W. Tirado

SUBJECT: Summary of the Environmental Characteristics of the Cidra Community

Attached you will find an abstract and translation of the following Environmental Evaluation Reports from the Cidra community in Puerto Rico:

Environmental Evaluation Report for the Residential Project Sabanera Estates & Country Club

Environmental Evaluation Report for the Expanded Operations of SKF Lab Co (Actually SB Pharmaceuticals)

Environmental Evaluation of the Proposed Cidra Industrial Park

The abstract provides a description of the physical and biotic characteristics of the Cidra community.

Abstract

The Cidra community is located within the subtropical humid forest zone, more specifically within a transition zone between the Humid Coastal Forest and the Lower Mountain Forest. The area has been extensively deforested due to farming activities and for this reason the natural vegetation was reported as being in an extinction phase by 1926 (See Table I). By 1988 there were few representatives of the tree species common to this climatic zone. Within this area is also found grasslands associations and small secondary vegetation associations (See Table II for dominant species reported by 1988).

SB Cidra plant is specifically located in a 50.4 acre lot owned by SmithKline Beecham (Road 172 Km 9.1) and it is surrounded by Cidra Lake (North), by Road 172 (South) and by two semi-urban developments projects (east and west). The area is located at 425 meters above the sea level. The annual average precipitation recorded during a twenty (20) year period, and reported in 1969, was 68.96 inches. The average temperature for the same period of time was 72.6 F. Wind direction is from east to west at an average speed of 10 knots.

There are three types of soils reported for this area:

a) "Arcilla Aceituna"
b) "Arcilla Humatas"
c) "Arcilla Daguey"

All these soils have good drain characteristics and moderate permeability.

Cidra is not included in the inventory of areas with potential to exceed the air limits for sulfur oxides and particulate matter. This is mainly due to the fact that Puerto Rico is located within a permanent air current which maintains a constant renovation of the atmospheric air. Persistent progressive accumulation of atmospheric contaminants are not observed.

The fauna that it is present in Cidra is usually restricted to the tree zones where adequate humidity and temperature conditions for the fauna are found. Table III presents a list of the species reported in our reference report from 1988.

No endangered species were reported in our reference reports for Cidra. Nevertheless, it has been reported in other references that the Cidra Lake is a protected area for the endangered specie known as Columbi inornata wetmorei ("Paloma Sabanera"). This specie gets its food mainly from fruits and seeds. It breeds in trees such as Bambusa vulgaris, Syzygium jambos, Spathodea campulata, and Didimopanax morototonis (See Table IV). It's breed peak period is between winter and spring and its characteristic habitat is tree zones associated with water bodies.

The main factors contributing to its extinction are the destruction of their habitat and the uncontrolled intervention of man mainly through hunting. The recent increase in their number within the Cidra area may be associated to the decrease in agricultural activities.

Abstract (Continued)

The total population of Cidra was estimated to be 28,365 by 1980 Census. The projection for year 2000 is an increase of 7736 habitants (See Table V).

References:

Evaluacion Ambiental Sabanera Estates and Country Club, Barrio Bayamon, Cidra, Puerto Rico, 1988

Evaluacion Ambiental Para La Expansion de SKF Lab. Co., Cidra, Puerto Rico. Proyecto UNIPRO num. 88093, 1989

Evaluacion Ambiental Para Proyecto Parque Industrial de Cidra, Barrio Bayamon, Cidra, Puerto Rico, 1991

TABLE I

Natural Tree Species From the Transition Zone Between The Coastal Forest Zone and The Lower Mountain Forest Zone.*

	Common Name	Scientific Name
I. Humid Coastal Forest		
1.	Corozo	Acrocomia media
2.	Mago	Hernandia sonora
3.	Moca	Andira inermis
4.	Tortugo Amadillo	Sideroxilum sp.
5.	Maria	Calophyllum brasiliense
6.	Asubo	Manilkara bidentata
7.	Roble Blanco	Tabebuia heterophylla
II. Lower Mountain Forest		
1.	Yagrumo Hembra	Cecropia peltata
2.	Laurel Geo	Ocotea leucoxylon
3.	Nuez Moscada	Ocotea moschata
4.	Guama	Inga laurina
5.	Moca	Andira inermis
6.	Taboruco	Dacryodes excelsa
7.	Capa Prieto	Cordia alliodora
8.	Yagrumo Macho	Didimopanax Morototoni

* No source for an English translation was available for the common name of these species.

TABLE II

Dominant Vegetation Species From Cidra Reported By 1968.*

	Common Name	Scientific Name
I. Grasslands		
1.	Yerba Pangola	Digitaria decumbes
2.	Morivivi	Mimosa pudica
3.	La Escobilla	Vernonia sericea
4.	Bejuco de Puerco	Ipomea setifera
5.	Cohitre Falso	Ichnanthus pallens
II. Secondary Vegetation Associations		
1.	Tulipan Africano	Spathodea campanulata
2.	Pomarrosa	Syzygium jambos
3.	Guaba	Inga vera
4.	Yagrumo Macho	Didimopanax morototoni
5.	Yagrumo Hembra	Cecropia peltata
6.	Guaraguao	Guarea guidonia
7.	Teca	Tectonia grandis
8.	Palma real	Roystonea borinquena
9.	Bambu	Bambusa vulgaris

* No source for an English translation was available for the common name of these species.

TABLE III

Fauna From Bo. Bayamon, Cidra Reported By 1988

A. Birds

	Common Name Spanish	Common Name English	Scientific Name	Family
1.	Guaraguao	Red-tailed hawk	Buteo jamaicensis	Accipitridae
2.	Garza ganadera	Cattle egret	Bubulcus ibis	Ardeidae
3.	Martinete	Green heron	Butorides striatus	Ardeidae
4.	Reinita comun	Bananquit	Coereba flaveola	Coerebidae
5.	Paloma turca	Scaly-naped pigeon	Columba squamosa	Columbidae
6.	Tortola cardosantera	Zenaida dove	Zenaida aurita	Columbidae
7.	Pajaro bobo menor	Mangrove cuckoo	Coccyzus minor	Cuculidae
8.	Diablito	Bronze manniquin	Lonchura cucullata	Estrildidae
9.	Gorrion barba amarilla	Yello-faced grassquit	Tiaris olivacea	Fringillidae
10.	Golondrina de cuevas	Cave swallow	Petrochelidon fulva	Hirundinidae
11.	Chango	Greater Antillean grackle	Quiscalus niger	Icteridae
12.	Ruisenor	Mockingbird	Mimus poly[illegible]los	Mimidae
13.	Gallinazo americano	American coot	Fulica americana	Rallidae
14.	Gallareta comun	Common gallinule	Gallinula chloropus	Rallidae
15.	San Pedrito	Puerto Rican tody	Todus mexicanus	Todidae

TABLE III (Continued)

16.	Zumbadorcito de Puerto Rico	Puerto Rican emerald	Chlorostilbon maugeus	Trochilidae
17.	Zorzal de patas coloradas coloradas	Red-legged thrush	Mimocichla plumbea	Turdidae
18.	Pitirre	Gray kingbird	Tyrannus dominicensis	Tyrannidae

B. Gastropods

	Scientific Name	Family
1.	Caracolus caracolla	Camaenidae
2.	Polydontes acutangula	Camaenidae
3.	Nenia tridens	Clausiliidae
4.	Megalomastoma croceum	Cyclophoridae
5.	Austrosolenites alticola	Haplotrematidae
6.	Alcadia striata	Helicinidae
7.	Alcadia alta	Helicinidae
8.	Varicella terebraiformis	Oleacinidae
9.	Subulina octona	Subulinidae
10.	Obeliscus terebraster	Subulinidae

TABLE III (Continued)

C. Amphibians*

	Common Name	Scientific Name	Family
1.	Sapo Comun	Bufo marinus	Bufonidae
2.	Coqui	Eleutherodactylus coqui	Leptodactylidae
3.	Coqui Antillensis	Eleutherodactylus antillensis	Leptodactylidae
4.	Coqui Grillus	Eleutherodactylus grillus	Leptodactylidae
5.	Rana Leptodactila	Leptodactylus albilabris	Leptodactylidae
6.	Sapo Yure	Rana catesbeiana	Ranidae

* No source for an English translation was available for the common name of these species.

D. Reptiles*

	Common Name	Scientific Name	Family
1.	Lagartija Comun	Anolis cristatellus	Iguanidae
2.	Lagartija de las Yerbas	Anolis pulchellus	Iguanidae
3.	Lagartija de los Arboles	Anolis stratulus	Iguanidae
4.	Gekko	Sphaerodactylus klauberi	Gekkonidae
5.	Iguana	Ameiva exsul	Teiidae

* No source for an English translation was available for the common name of these species.

TABLE IV

Vegetation Used for Feeding Purposes by Genus Columba and Other Related genus.*

	Common Name	Scientific Name	Family	Columba species
1.	Achiotillo	Alchornea latifolia	Euphorbiaceae	Zenaida aurita
2.	Adelia	Bernaldia dichotoma	Euphorbiaceae	Columba leucocephala
3.	Adormidera	Croton rigidus	Euphorbiaceae	Columbina passerina
4.	Arroz	Oryza sativa	Gramineae	Columba squamosa Zenaida aurita
5.	Bejuco de Puerco	Ipomoea tiliacea	Convolvulaceae	Zenaida aurita
6.	Berenjena Cimarrona	Solanum torvum	Solanaceae	Columba squamosa C. inornata wetmorei
7.	Bledo	Amaranthus dubius	Amaranthaceae	Columbina passerina Zenaida aurita
8.	Bretonica Prieta	Melochia nodiflora	Sterculiaceae	Columbina passerina
9.	Cadillo	Urena lobata	Malvaceae	Zenaida aurita
10.	Camasey	Miconia prasina	Melostomataceae	Geotrygon montana
11.	Cardo Santo	Argemone mexicana	Papaveraceae	Columbina passerina Zenaida aurita
12.	Carrucillo	Oryza latifolia	Gramineae	Columbina passerina Geotrygon montana Zenaida aurita
13.	China	Citrus sinensis	Rutaceae	Columbina passerina Geotrygon montana Zenaida aurita
14.	Cohitre Azul	Gibasys geniculata	Commelinaceae	Columbina passerina
15.	Coqui	Hypoxis decumbens	Hypoxidaceae	Columbina passerina

TABLE IV (Continued)

Common Name	Scientific Name	Family	Columba species
16. Coqui Blanco	Rhynchospora miliacea	Gramineae	Columbina passerina
17. Cortadora	Paspalum milegrans	Gramineae	Columbina passerina
18. Cortadora de Altura	Scleira secans	Cyperaceae	Columbina passerina Zenaida aurita
19. Escoba	Sida acuta	Malvaceae	Columbina passerina Zenaida aurita
20. Espino Rubial	Zanthoxylum caribaeum	Rutaceae	Zenaida aurita
21. Fresa	Rubus rosaefolius	Rosaceae	Columbina passerina
22. Guaraguao	Trichilia hirta	Meliaceae	Columba squamosa
23. Habichuela Para	Macroptilium lathyroides	Papilionoideae	Columbina passerina Zenaida aurita
24. Hedionda	Cassia occidentalis	Caesalpinioideae	Zenaida aurita
25. Hicaco	Chrysobalanus icaco	Chrysobalanaceae	Columba leucocephala
26. Higuillo	Piper aduncum	Piperaceae	Zenaida macroura
27. Jacana	Pouteria multiflora	Sapotaceae	Zenaida macroura
28. Jaguey Blanco	Ficus citrifolia	Moraceae	Columbina passerina Columba squamosa
29. Junquito	Fimbristylis dichotoma	Cyperaceae	Columbina passerina
30. Laurel de Paloma	Ocotea portoricensis	Lauraceae	Columba squamosa
31. Laurel Geo	Ocotea leucoxylon	Lauraceae	Zenaida macroura
32. Leche Vana	Euphorbia heterophylla	Euphorbiaceae	Columbina passerina Zenaida aurita

TABLE IV (Continued)

Common Name	Scientific Name	Family	Columba species
33. Lechecilla	Chamaesyce hirta	Euphorbiaceae	Columbina passerina Geotrygon montana
34. Llantén	Plantago major	Plantaginaceae	Columbina passerina Zenaida aurita
35. Maiz	Zea mays	Gramineae	Columba squamosa
36. Manzanillo	Hippomane mancinella	Euphorbiaceae	Geotrygon montana
37. Maricao	Byrsonima spicata	Malpighiaceae	Zenaida macroura
38. Matagallina	Solanum americanum	Solanaceae	Columba squamosa Zenaida aurita
39. Moral	Cordia sulcata	Boraginaceae	Geotrygon montana Columba squamosa Columba leucocephia Zenaida aurita
40. Morivivi Bobo	Aeschynomene americana	L.-Papilionoideae	Zenaida aurita
41. Naranja	Citrus aurantium	Rutaceae	Geotrygon montana
42. Palma de Abanico	Coccothrinax argentea	Palmaceae	Columba leucocephala Columba squamosa
43. Palma de Sierra	Prestoea montana	Palmaceae	Columba squamosa
44. Palma Real	Roystonea boringuena	Palmaceae	Columba squamosa Columba leucocephala
45. Palo Blanco	Drypetes glauca	Euphorbiaceae	Columba leucocephala
46. Palo de Jazmin	Styrax portoricensis	Styracaceae	Columba squamosa
47. Pata de Gallina	Eleusine indica	Gramineae	Columbina passerina

TABLE IV (Continued)

	Common Name	Scientific Name	Family	Columba species
48.	Pazote	Chenopodium ambrosioides	Chenopodiaceae	Zenaida aurita Columbina passerina
49.	Penduta	Citharexylum fruticosum	Verbenaceae	Columba livia
50.	Pomarrosa	Syzygium jambos	Myrtaceae	Columba inornata wetmorei
51.	Tagua-Tagua	Passiflora foetida	Passifloraceae	Zenaida aurita
52.	Toronja	Citrus maxima	Rutaceae	Geotrygon montana
53.	Tua-Tua	Jatropha gossypiifolia	Euphorbiaceae	Zenaida aurita Columbina passerina
54.	Verdolaga	Portulaca oleracea	Portulacaceae	Zenaida aurita Columbina passerina
55.	Verdolaga de Abrojo	Kallstroemia maxima	Zygophyllaceae	Zenaida aurita Columbina passerina
56.	Verdolaguilla	Talinum triangulare	Portulacaceae	Columbina passerina
57.	Vinagrillo	Oxalis corniculata	Oxalidaceae	Columbina passerina
58.	Yagrumo Macho	Didymopanax morototoni	Araliaceae	Zenaida macroura Columba inornata wetmorei
59.	Yerba de Hicotea	Polygonum glabrum	Polygonaceae	Zenaida aurita Columbina passerina
60.	Yuca	Manihot esculenta	Euphorbiaceae	Zenaida aurita

* No source for an English translation was available for the common name of these species.

TABLE V

Projected Population per Municipality

MUNICIPIO	1990	1995	1998	1995	2000	2005
ADJUNTAS	18784.	18144.	17604.	17154.	16821.	16617.
AGUADA	41567.	37221.	34967.	35679.	37262.	38674.
AGUADILLA	54606.	54934.	55555.	56325.	57322.	57975.
AGUAS BUENAS	22429.	22659.	23089.	23556.	24103.	24538.
AIBONITO	22167.	22251.	22620.	23134.	23767.	24182.
ARASCO	23274.	23952.	24693.	25457.	26333.	27072.
ARECIBO	88766.	89101.	91449.	91905.	96832.	[illegible]246.
ARROYO	17014.	18128.	20014.	22072.	24534.	16.
BARCELONETA	18742.	19729.	20540.	21585.	22[illegible].	32[illegible]
BARRANQUITAS	21639.	20908.	20358.	19923.	19[illegible]	20[illegible]
BAYAMON	196206.	207629.	219780.	232567.	24[illegible]	[illegible]
CABO ROJO	36055.	35805.	37681.	[illegible].	[illegible]	[illegible]
CAGUAS	117959.	121595.	129251.	135603.	142[illegible]	[illegible]
CAMUY	23922.	27668.	29488.	31500.	[illegible]	[illegible]254.
CANOVANAS	31850.	34287.	37187.	40387.	[illegible]093.	47175.
CAROLINA	165956.	171112.	178196.	181561.	187582.	192122.
CATAÑO	26283.	26316.	26691.	27177.	27806.	28313.
CAYEY	41079.	42060.	44157.	46700.	49418.	51841.
CEIBA	16966.	16517.	18177.	20567.	23086.	25073.
CIALES	16211.	16652.	16888.	17406.	18001.	18486.
CIDRA	28365.	29251.	30530.	31912.	33451.	34813.
COAMO	30822.	31587.	32209.	33071.	33642.	34100.
COMERIO	15212.	15567.	15923.	16367.	16138.	15634.
CONCEPCION	28221.	28737.	29670.	30718.	31807.	32716.
CULEBRA	1265.	1417.	1598.	1806.	2064.	2348.
DORADO	25511.	28826.	32661.	36965.	41992.	47376.
FAJARDO	32057.	33697.	35182.	37192.	39565.	41683.
FLORIDA	7232.	8004.	8916.	9967.	11153.	12606.
GUANICA	18799.	19652.	20079.	20625.	21301.	22065.
GUAYAMA	40183.	39988.	40013.	40150.	40531.	40717.
GUAYANILLA	21050.	20703.	20367.	19953.	19598.	19223.
GUAYNABO	80742.	85152.	90229.	95154.	100289.	104665.
GURABO	25574.	27260.	27196.	29284.	31609.	33849.
HATILLO	28958.	30637.	32117.	34020.	36223.	38315.
HORMIGUEROS	14030.	15141.	16287.	17503.	18870.	20158.
HUMACAO	46154.	48931.	52174.	55851.	60117.	64220.
ISABELA	37435.	38629.	39978.	41459.	43175.	44686.
JAYUYA	14722.	14459.	14321.	14261.	14229.	14163.
JUANA DIAZ	43505.	43363.	43515.	43646.	43976.	44184.
JUNCOS	25397.	25757.	26160.	26566.	27046.	27386.
LAJAS	21236.	22798.	24611.	26041.	27920.	29790.
LARES	26743.	26265.	25903.	25624.	25462.	25159.
LAS MARIAS	8747.	8896.	9071.	9263.	9493.	9681.
LAS PIEDRAS	22612.	23518.	24754.	25987.	27337.	28621.
LOIZA	20867.	22367.	24162.	26188.	28516.	30820.

REDACTIONS MADE BY APPLICANT

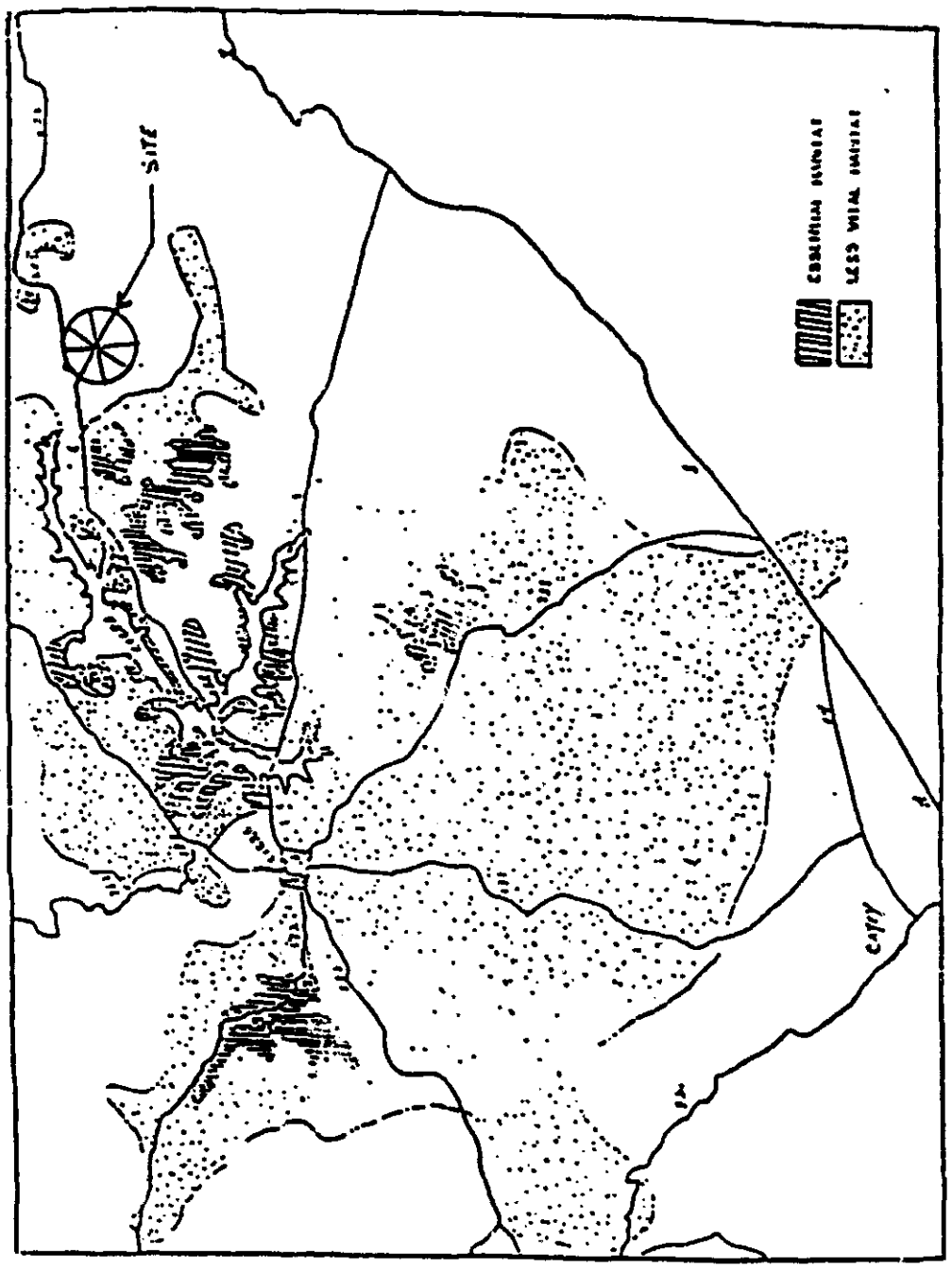
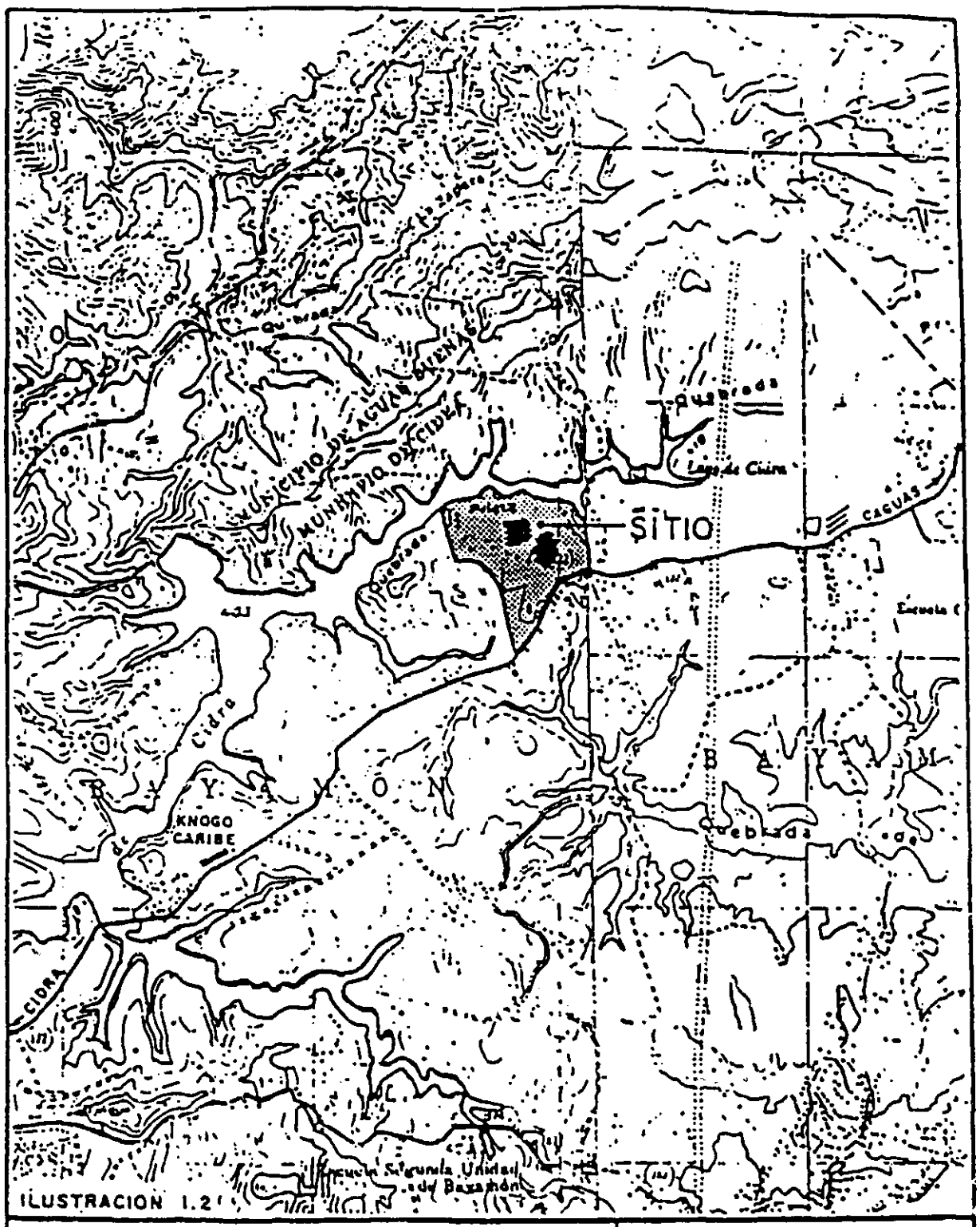


Fig. 1 Areas of Essential Habitat for the Specie Columba leucocata vatsmrai,

REDACTIONS MADE BY APPLICANT



ILUSTRACION 1.2

SB Pharmaceuticals
Cidra, Puerto Rico
Plant Locacion

SmithKline Beecham
Pharmaceuticals

REDACTIONS MADE BY APPLICANT

GENERAL COMPLIANCE STATEMENT

SmithKline Beecham Pharmaceuticals Co. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of 'Paroxetine' at its facilities in Cidra, Puerto Rico.

10/23/91
NAME: Ismael Guzmán DATE:
TITLE: Director of Engineering Services

10/23/91
NAME: Betsy Rodriguez DATE:
TITLE: Production Director

SmithKline Beecham Pharmaceuticals Co.
PO Box 11975, Road 172, KM 9.1
BO Certenejas, Cidra, Puerto Rico 00639-1975
Telephone (809) 766 4000

New NPDES Permit
English Translation from Spanish Original

Parameter	Limit	Frequency	Type of Sample
1. Flow	130,000 gal/day	Continuous	Continuous
2. BOD_5	10.0 mg/L average 15.0 mg/l daily max.	Monthly	Composite
3. Suspended Solids	None		
4. Dissolved Oxygen	> 5.0	Daily	Grab
5. Total coliform	10,000 col/100 mL	Monthly	Grab
6. Fecal coliform	2000 col/100 mL	Monthly	Grab
7. Residual chlorine	That will not affect receiving water	Daily	Grab
8. pH	>6.0 to <9.0	Daily	Grab
9. Color	10.0 Pt/Co SU	Dec & June	Grab
10. Turbidity	50.0 NTU	Mar & Sept	Grab
11. Cadmium	1.03 µg/L	Weekly/Monthly	Grab
12. Oil & grease	10.0 average	Monthly	Grab
13. Temperature	<32.2 °C	Daily	Grab
14. Phenol	Limit of detection (10.0 µg/L)	Mar & Sept	Grab
15. Lead	2.7 µg/L	Weekly/Monthly	Grab
16. Silver	1.0 µg/L	Dec & June	Grab
17. Zinc	50 µg/L	Monthly	Grab
18. Fluoride	700 µg/L	Monthly	Grab
19. Chloride	250 mg/L	2/Month	Grab
20. Copper	10.6 µg/L	Weekly/Monthly	Grab
21. Boron	1.0 mg/L	Monthly	Grab
22. Total Chromium	50 µg/L	Monthly	Grab
23. Cyanide	20 µg/L	Monthly	Grab
24. Mercury	1.0 µg/L	Monthly	Grab
25. Selenium	10 µg/L	Monthly	Grab
26. Surfactants	0.100 mg/L	Monthly	Grab
27. Sulfide	Limit of Detection (2.0 µg/L)	Monthly	Grab
28. TDS	500.0 mg/L	Monthly	Grab
29. Phosphorus	1.0 mg/L	Weekly/Monthly	Grab
30. NO3 + NO2	10.0 mg/L	Monthly	Grab
31. TSS	60.0 mg/L	Monthly	Composite
32. COD	126.0 mg/L	Monthly	Composite
33. Color & Taste	None	-	-
34. Floating solids	None	-	-

NOVEMBER 1993
CIDRA, PUERTO RICO

REDACTIONS MADE BY APPLICANT

SMITHKLINE BEECHAM PHARMACEUTICAL CO.
GDG-94-505-032

Permit N° GDG-94-505-032

In accordance with the regulations governing the provision of water and sewer services, as well as with any stipulations under Federal or Commonwealth laws, the Water and Sewer Authority (hereinafter the Authority), hereby authorizes Smithkline Beecham Pharmaceuticals Co., located in Cidra, to make bulk discharges in the Puerto Nuevo Regional Wastewater Treatment Plant, subject to all terms and conditions specified in the permit.

Issued on this day, July 1, 1994

Effective July 15, 1994

Expires July 16, 1996

(signature)
Lizette Lugo Santiago, MEH
Interim Director
Pretreatment Area

SMITHKLINE BEECHAM PHARMACEUTICAL CO.
GDG-94-505-032

REDACTIONS MADE BY APPLICANT

General information re the permit user

Permit N°:	**GDG-94-505-032**
Company name:	**Smithkline Beecham Pharmaceuticals Co.**
Address:	**Carretera 172, Km. 9.1** **Cidra, Puerto Rico**
Mailing address:	**P. O. Box 11975** **Cidra, Puerto Rico 00739-1975**
Telephone:	**(809) 766-4000**
Emergency number:	**(809) 250-3866**
Industrial classification (SIC):	**2834 Pharmaceutical compounds**
Industrial category:	40 CFR 439 Subpart D: **Manufacture of pharmaceutical products, Mixtures/compounds and formulation subcategory.**

SMITHKLINE BEECHAM PHARMACEUTICAL CO.
GDG-94-505-032

REDACTIONS MADE BY APPLICANT

I. GENERAL CONDITIONS (attached)

II. SPECIAL CONDITIONS

A. DESCRIPTION OF DISCHARGES TO BE TRANSPORTED TO THE AAA [Water and Sewer Authority] FACILITIES

Retro-osmosis (RO) system wastewater. These wastewaters have been treated by a tertiary system. The retro-osmosis system forms a part of the tertiary treatment plant which is located to the East of the facilities. See Diagram N° 1.

B. GENERAL REQUIREMENTS APPLICABLE TO ALL DISCHARGES

The permit user shall comply with all the general prohibitions and stipulations set forth in Section I of this permit.

Interconnections, relocation or mixing of flows between discharges shall not be permitted without the prior written consent of the Authority. Any bypass of pretreatment facilities shall likewise not be permitted.

Any projected facility expansions or process modifications which may give rise to new, different or larger discharges shall be notified to the Authority.

C. SPECIFIC EFFLUENT LIMITATIONS AND SAMPLING REQUIREMENTS FOR DISCHARGES TO BE TRANSPORTED

During the period covered under this permit, the permit user is authorized to make bulk discharges in the Puerto Nuevo Regional Treatment Plant facilities provided such permit user comply with the following sampling limits and requirements:

REDACTIONS MADE BY APPLICANT

SMITHKLINE BEECHAM PHARMACEUTICAL CO.
GDG-94-505-032

FINAL LIMITS AND SAMPLING REQUIREMENTS FOR BULK DISCHARGES

Parameter	Discharge limit		Type of sample	Frequency*
1. Temperature (°C)	40		Immediate laboratory measurement	Per tanker truck
2. pH (S.U.)	6.5-9.0		Immediate laboratory measurement	1/month
3. Total copper (mg/l)	1.00	1000 ppb	Random	1/month
4. Mercury (mg/l)	0.05	50 ppb	"	1/month
5. Nickel, (mg/l)	0.50	500 ppb	"	1/month
6. Total chromium (mg/l)	1.00	1.00 ppb	"	1/month
7. Silver (mg/l)	0.05	50 ppb	"	1/month
8. Cadmium (mg/l)	0.10	100 ppb	"	1/month
9. Zinc (mg/l)	0.50	500 ppb	"	1/month
10. Lead (mg/l)	0.20	200 ppb	"	1/month
11. Aluminum (mg/l)	SO to be reported		"	1/month
12. Selenium (mg/l)	0.20	200 ppb	"	1/month
13. Iron (mg/l)	SO to be reported		"	1/month
14. Manganese (mg/l)	2.0	2000 ppb	"	1/month
15. Tin (mg/l)	5.0	5000 ppb	"	1/month
16. Total cyanides (mg/l)	0.10	100 ppb	"	1/month
17. Oils and greases (mg/l)	50.0	50000 ppb	"	1/month
18. BOD5 (mg/l)	175.0	175.0	"	1/month
19. Volume (gallons)	1-7,000 gallon tanker truck/day [49,000/week] maximum			N/A

SMITHKLINE BEECHAM PHARMACEUTICAL CO.
GDG-94-505-032

FINAL LIMITS AND SAMPLING REQUIREMENTS FOR BULK DISCHARGES

Parameter	Discharge limit	Type of sample	Frequency*
20. COD (mg/l)	300.0	Random	1/month
21. TTO (mg/l)	2.13	"	2/year
22. SS (mg/l)	125.0	"	1/month
23. Flash point (°F)	>140	"	1/month
24. Phenols (mg/l)	0.50	"	1/month

MS = Sampling only

*** See Section E-3

D. TRANSPORTATION CONDITIONS

1. The permit user shall submit to the AAA a Transportation plan no later than 45 days following the permit effective date.

   This plan shall include:
   a. The name and address of the transporter.
   b. The number and expiration date of the transporter's discharge permit.
   c. Copy of the transportation agreement.

2. A bulk discharge manifest (parts I and II) shall be completed for each tanker truck load transported to the Authority's facilities. Exhibit A includes a copy of the manifest. This document shall include the most recent characterization of the wastewaters to be transported and shall be signed by the permit user, by the transporter and by the Authority official receiving the wastewaters.

3. This permit authorizes only bulk discharges of wastewaters originating from the retro-osmosis (RO) system, into the Puerto Nuevo Regional Wastewater Treatment Plant. Discharge of incinerator water is not authorized.

4. The permit user shall not discharge more than seven (7) tanker-trucks per week with a maximum of 7,000 gallons [49,000/week] each.

5. The permit user shall only discharge via tanker-truck between 8:00 a.m. and 4:00 p.m. each day.

6. The generator shall be responsible for ensuring that the transporter dispose of the wastes transported at the treatment plant designated in this permit and that the manifest be duly completed.

E. THE PERMIT USER SHALL COMPLY WITH THE FOLLOWING CONDITIONS:

1. Analysis procedures:

   a. Analyses of discharges shall be performed by a qualified laboratory and in accordance with methods approved by the Environmental Protection Agency (EPA), 40 CFR, Part 136.

b. Samples shall be analyzed by a certified laboratory or by a laboratory the quality assurance procedures of which are in accordance with those approved by the EPA.

c. In the event the analyses are to be performed by the in-house laboratory, such laboratory shall pass an audit carried out by the Authority Quality Assurance Department, Laboratory Area and shall satisfy the conditions set forth in preceding subparagraphs. Until such time as this requirement is satisfied, the user shall engage the services of an outside laboratory approved by the authority.

2. Sampling

a. Sampling of the wastewaters to be transported to the Authority facilities shall be taken directly from the truck by means of a "coliwaza" [sic].

b. All samples shall be preserved as indicated in the sample preservation procedures set forth by the EPA. The permit user shall maintain a appropriate record of the chain of custody forms.

c. The analysis of wastewater shall commence with the first tanker truck transported to the Authority facilities following the permit effective date.

d. The permit user is responsible for carrying out appropriate sampling, even when such sampling is performed by a third party. The Authority shall not accept the fact that inappropriate sampling was performed as a reason for the violation of any limitation herein set forth.

3. Total toxic organics (TTO)

With respect to Total Toxic Organics, the permit user shall be required to perform analyses only for TTO detected at concentrations equal to or in excess of 0.01 mg/l in the first analysis which includes all organics. TTO samples shall be taken in July and January of each year.

In the event no organics in concentrations equal to or in excess of 0.01 mg/l are detected in the first analysis, the permit user shall not be required to perform TTO analyses during the effective permit period.

Nevertheless, the permit user shall submit a letter prior to the next deadline for the filing of TTO analysis, indicating that this is the reason for not submitting the TTO analyses on the required deadline date.

4. Pretreatment compliance requirements

The permit user shall be responsible for complying with any revisions to 40 CFR 439, Subpart D and for submitting to the Authority the Industrial Users Preliminary Report (IUPR) or any other report required, in accordance with the General Pretreatment regulation 40 CFR 403.12. The limits set forth in this permit shall be considered pretreatment standards and any analyses giving results in excess of such limits shall be considered a violation of the conditions set forth in this permit. Any wastewaters which exceed the permit limits shall not be discharged in the Authority faciilities.

5. Emergencies

The permit user shall not discharge into the Authority system any bulk discharges which exceed the permit limits, even in the event the presence of a substance in excess of the permit limits is the result of an emergency.

6. Permit renewal

The permit user shall apply for a renewal of the permit no less than 120 days prior to its expiration [July 16, 1996], together with any new information or projected modification. This permit shall remain in force, including the analyses and reporting requirements with respect to discharge volume and quality, until such time as the new permit becomes effective, except when the AAA revoke this permit.

7. Sampling by the Water and Sewer Authority.

The Authority shall sample the wastewaters from the retro-osmosis (RO) system regulated hereunder and located within the complex, as well as the individual tanker trucks each time it consider necessary in order to verify compliance with the terms of the permit, determine the pretreatment plant efficiency or determine the source of any specific pollutant.

F. FINES

1. The permit user shall pay fines of up to $5,000 per day for violations due to noncompliance or violation of the conditions herein set forth and/or in the AAA rules and regulations.

2. The permit user shall likewise pay surcharges to the AAA when applicable, even if the permit user has paid fines for permit violations. The applicable surcharge factor (SF) shall be calculated in accordance with Section 5.02, Subpart F of the Water and Sewer Authority Regulation and the surcharge shall be calculated in accordance with the following formula:

$$\text{Surcharge} = \frac{\text{Volume discharged}}{2{,}000}\ (10)\ (SF)$$

G. PREPARATION OF REPORTS AND FILE MAINTENANCE

1. Auto-sampling and Analysis Reports (AAR) shall be received by the Authority prior to the 28th day of the month following the sampling. Each report shall contain the following information:

   a. Copy of the original laboratory report certified by a licensed chemist. The tanker truck shall be clearly identified. The concentration units shall be expressed in the same units set forth in the discharge limits in this permit (mg/l, S.U., Pt.-Co or GPD, in accordance with the parameter), as well as with the type of sample taken (random or immediate reading).

   b. Copy of the sample chain of custody form.

c. Copy of all Transportation Manifests generated during the period covered under the pertinent AAR.

d. Copy of all analyses performed during the sampling period, in addition to those required by this permit.

e. Certification required under Section T - General Conditions.

2. The permit user shall deliver to the Authority no later than December 31 and June 30 of each year a biannual report indicating the compliance status during the preceding six month period.

The biannual report to be submitted on December 31 shall include the compliance status for the months from June 1 through November 30, and the report to be submitted on June 30 shall include the compliance status for the months from December 1 through May 31.

This report shall include:

a. A summary of all analyses reported during the preceding six months, with maximum, minimum and average values for each parameter. With respect to volume discharged, weekly maximum, minimum and average are reported.

b. Those parameters that were the most difficult to control, and the steps taken to improve control thereof.

c. Operational abnormalities, whether or not planned, and accidental discharges shall be notified and documented, including dates, causes, measures taken to correct the situation and prevent future occurrences.

3. The permit user shall comply with all the reporting and file maintenance requirements set forth in Section I of this permit.

4. The permit user shall submit to the Authority the Industrial User Preliminary Report no later than 45 days following the permit effective date.

This report shall include all the information specified in Appendix B hereto.

5. The permit user shall submit to the Authority the Spill Prevention and Control Plan no later than 45 days following the permit effective date.

6. All reports shall be sent to:

Mr. Nelson Hernández (D-33)
Head, Division of Data Processing
Pretreatment Area - Edificio Barreras
Water and Sewer Authority
P. O.Box 7066, Estación Barrio Obrero
Santurce, Puerto Rico 00916

7. Division in charge

All reports forwarded to the AAA shall clearly indicate the permit number, the industrial facility and the division in charge. Division III of the Permits and Compliance Department has been designated to handle this permit.

SMITHKLINE BEECHAM PHARMACEUTICAL CO.
GDG-94-505-032

I. DEFINITIONS AND ABBREVIATIONS

1. Definitions

a. "Discharge" signifies any plant connection to the AAA sanitary sewer system.

b. "Stream" signifies any flow or discharge passing through the plant internal sewer.

c. "Compound sample" signifies a series of random samples taken at equal time intervals, either in a quantity proportional to the flow or of equal volume.

d. "Random (grab) sample" signifies an individual sample taken during a period of no more than 15 minutes.

e. "Immediate measurement" signifies any individual measurement taken at a single time.

2. Abbreviations

a. "AAA" refers to the Water and Sewer Authority.

b. "O & G" signifies Oils and Greases.

c. "BOD" signifies Biochemical Oxygen Demand.

d. "COD" signifies Chemical Oxygen Demand.

e. "EPA" signifies the Federal Environmental Protection Agency.

f. "GPD" signifies Gallons per Day.

g. "ASR" signifies Auto-sampling Report.

h. "IUPR" signifies Industrial User Preliminary Report.

i. "mg/l" signifies milligrams per liter.

j. "NSR" signifies No Sampling Required.

k. "TTO" signifies Total Toxic Organics.

l. "SPCP" signifies Spill Prevention and Control Plan.

m. "RWWTP" signifies Regional Wastewater Treatment Plant.

n. "WWTP" signifies Wastewater Treatment Plant.

o. "SS" signifies sedimentable solids.

p. "TSS" signifies total suspended solids.

q. "S.U." signifies standard units.

r. Pt-Co signifies color units in platinum/cobalt.

s. "TDS" signifies total dissolved solids.

SMITHKLINE BEECHAM PHARMACEUTICAL CO.
GDG-94-505-032

APPENDIX A

AAA BULK DISCHARGE MANIFEST - PART I

I hereby certify that:

1. These wastes are not hazardous, in accordance with the definition established by the Federal Resources Conservation and Recovery Act, CFR Part 261, and in accordance with the Commonwealth of Puerto Rico Control of Hazardous and Non-Hazardous Solid Wastes regulations, as amended.

2. These wastes do not contain isotopes or radioactive substances.

3. These wastes do not contain harmful or antibiotic elements which, in themselves or together with the discharges from other sources, are capable of reducing the efficiency of the treatment plant biological processes or of creating a hazard to AAA employees.

4. These wastes do not contain gasoline, benzene, naphtha, fuel oil or other volatile or flammable substances in sufficient quantities such that their presence in the treatment facilities constitute a health hazard, cause unpleasant odors or represent a fire or explosion hazard.

5. The analytical data attached hereto are representative of the quality of the wastes discharged in AAA facilities under this manifest.

Name of the Waste Generator's Authorized Representative	Authorized representative signature

Date

SMITHKLINE BEECHAM PHARMACEUTICAL CO.
GDG-94-505-032

APPENDIX B

CONTENTS OF IUPR

The IUPR (Industrial User Preliminary Report) shall contain the following information:

1. Name and address of the facility, including the names of operators and owners.

2. List of names and numbers of all environmental control permits issued for the facility.

3. Brief description of the nature, average production and SIC Code for each of the operations carried out, including a schematic process diagram indicating the process discharge points to the holding tank(s) for these wastewaters which will subsequently be transported to the RWWTP.

4. Flow measurement data or estimates for the regulated process wastes to be discharged in the AAA system via transportation. Flow data for other streams must be submitted in the event the Combined Wastestream Formula is to be applied. Include values (in gallons) for daily maximums and monthly averages.

5. Identification of the applicable pretreatment standards for each regulated process and the results of pollutant concentration and/or mass measurements. All samples shall be representative of daily operations and the results to be notified shall include values for daily maximum and average concentrations (or mass, when required).

6. Description of the holding facilities, including a schematic diagram indicating the location of the vessels within the plant. Specify, for each holding vessel: type (tank, pool, etc.), size, volume capacity, whether surface or underground and collection frequency.

7. Certification with regard to compliance or noncompliance with Pretreatment Standards.

SMITHKLINE BEECHAM PHARMACEUTICAL CO.
GDG-94-505-032

REDACTIONS MADE BY APPLICANT

8. In the event of noncompliance, a compliance schedule shall be submitted together with an IUPR describing the actions to be taken by the user and a schedule for their completion in order to achieve compliance with the standard. This compliance schedule shall contain the specific progress phases with respective commencement and completion dates for milestone events. No schedule phase shall exceed 9 months. No later than 14 days following each scheduled completion date, the industrial user shall submit a progress report to the Water and Sewer Authority indicating whether the specific phase was completed by the date in question and, in the event the deadline was not met, the date on which this phase is expected to be completed and the steps being taking to resume the schedule.

PART II

BULK DISCHARGE MANIFEST - AAA

Smithkline Beecham Pharmaceuticals Co.
NAME OF GENERATOR

Carr. 172, Km. 9.1, Cidra
ADDRESS AT WHICH WASTEWATER IS COLLECTED.

(809) 766-4000
TELEPHONE

UNITS IN mg/l (EXCEPT pH and temperatures)

DATE OF THIS ANALYSIS _____

pH (SU)		Lead		Greases	
Copper		Aluminum		BOD	
Mercury		Selenium		SS	
Nickel		Iron		COD	
Chromium		Manganese		(°F) Flash point	
Silver		Tin		(°C) Temp.	
Cadmium		Cyanides			
Zinc		Phenols			

GDG-94-505-032
AAA PERMIT NUMBER

July 16, 1996
PERMIT EXPIRY DATE*

Puerto Nuevo RWWTP
PLANT AT WHICH DISCHARGE IS AUTHORIZED

BRIEF DESCRIPTION OF WASTEWATERS

PLANT AT WHICH THEY ARE RECEIVED

DATE AND TIME RECEIVED IN PLANT

NAME (BLOCK LETTERS) OF THE AAA OFFICIAL RECEIVING THE WASTEWATERS

AAA OFFICIAL SIGNATURE

pH (SU) - Temperature (°C)

DISCREPANCIES/REMARKS

NAME OF TRANSPORTER

TRANSPORTER PERMIT NUMBER

EXPIRATION DATE

NAME OF DRIVER RECEIVING WASTEWATERS (PRINT)

DRIVER SIGNATURE

VOLUME (GALLONS) COLLECTED BY THE TRANSPORTER

DATE AND TIME OF COLLECTION

WERE SAMPLES TAKEN WHEN THE TANKER TRUCK ARRIVED?

SIGNATURE OF GENERATOR'S AUTHORIZED REPRESENTATIVE

NAME OF AUTHORIZED REPRESENTATIVE

- The permit shall continue in force except when expressly revoked. Requirements and limitations to continue in force, the plant shall be notified of any change.

000120

REDACTIONS MADE BY APPLICANT

REDACTIONS MADE BY APPLICANT

DMR JANUARY 1995

	AVE LOADING	MAX LOADING	MIN CONC	AVE CONC	MAX CONC
TEMPERATURE	**********	**********	24.80	27.00	30.00
FLOW IN	**********	**********	********	********	********
FLOW EFF	25,169.00	63,400.00	********	********	********
CHLORIDE FLOW	**********	**********	********	********	********
TURBIDITY	**********	**********	********	********	********
COLOR	**********	**********	********	********	********
DISSOLVED OXYGEN	**********	**********	5.90	[illegible]6	6.50
BOD IN	62.60	125.20	251.5	25[illegible].5	251.5
BOD EFF	0.03	0.06	0.48	0.48	0.48
COD IN	193.74	387.47	778.4	778.4	778.4
COD EFF	2.46	4.91	46.4	46.4	46.4
pH	**********	**********	6.20	7.23	7.90
TSS IN	419.71	839.42	1,686.3	1,686.3	1,686.3
TSS EFF	0.00	0.00	0.0	0.0	0.0
SETTLED SOLIDS	**********	**********	0.00	0.00	0.00
OIL AND GREASE	0.04	0.08	<5.0	<5.0	<5.0
NITRATE AND NITRITE	0.26	0.26	<5.0	<5.0	<5.0
PHOSPHOROUS	0.00	0.00	<1.0	<1.0	<1.0
CYANIDE	0.000000	0.000000	<0.02	<0.02	<0.02
CHLORIDE	0.0	0.00	25.2	28.2	31.2
FLUORIDE	0.00	0.00	<0.20	<0.20	<0.20
SULPHUR	0.000000	0.000000	<1.0	<1.0	<1.0
BORON	0.000025	0.000025	0.2367	0.2367	0.2367
CADMIUM	0.000000	0.000000	<0.001	<0.001	<0.001
TOTAL CHROMIUM	0.000000	0.000000	<0.05	<0.05	<0.05
COPPER	0.000467	0.000467	<0.0106	<0.0106	<0.0106
LEAD	0.000000	0.000000	<0.0027	<0.0027	<0.0027
SILVER	0.000000	0.000000	********	********	********
ZINC	0.000998	0.000998	<0.05	<0.05	<0.05
SELENIUM	0.000000	0.000000	<0.005	<0.005	<0.005
PHENOL	0.000000	0.000000	********	********	********
SURFACTANT	0.000133	0.000133	<0.10	<0.10	<0.10
RESIDUAL CHLORIDE	**********	**********	0.20	0.35	0.50
DISSOLVED SOLIDS	**********	**********	210.0	210.0	210.0
MERCURY	0.000000	0.000000	<0.0005	<0.0005	<0.0005
FECAL COLI	**********	**********	6.0	6.0	6.0

REDACTIONS MADE BY APPLICANT

DMR - DECEMBER 1994

	AVE LOADING	MAX LOADING	MIN CONC	AVE CONC	MAX CONC
TEMPERATURE	**********	**********	24.20	27.20	29.90
FLOW IN	**********	**********	********	********	********
FLOW EFF	46,288.87	163,900.00	********	********	********
CHLORIDE FLOW	**********	**********	********	********	********
TURBIDITY	**********	**********	N/A	N/A	N/A
COLOR	**********	**********	<5.0	<5.0	<5.0
DISSOLVED OXYGEN	**********	**********	6.00	6.16	6.30
BOD IN	42.63	85.07	249.0	249.0	249.0
BOD EFF	0.00	0.00	0.00	0.00	0.00
COD IN	88.51	178.02	524.0	524.0	524.0
COD EFF	0.00	0.00	0.0	0.0	0.0
pH	**********	**********	6.20	7.11	8.10
TSS IN	24.09	48.17	141.0	141.0	141.0
TSS EFF	0.00	0.00	0.0	0.0	0.0
SETTLED SOLIDS	**********	**********	0.00	0.00	0.00
OIL AND GREASE	0.18	0.36	<5.0	<5.0	<5.0
NITRATE AND NITRITE	0.01	0.01	<1.0	<1.0	<1.0
PHOSPHOROUS	0.00	0.00	<1.0	<1.0	<1.0
CYANIDE	0.000000	0.000000	<0.02	<0.02	<0.02
CHLORIDE	1.2	3.80	19.8	22.0	24.1
FLUORIDE	0.00	0.00	<0.20	<0.20	<0.20
SULPHUR	0.000000	0.000000	<1.0	<1.0	<1.0
BORON	0.000041	0.000041	0.2080	0.2080	0.2080
CADMIUM	0.000005	0.000005	<0.001	<0.001	<0.001
TOTAL CHROMIUM	0.000000	0.000000	<0.05	<0.05	<0.05
COPPER	0.001368	0.001368	<.001	<0.001	<0.001
LEAD	0.000037	0.000037	<0.0027	<0.0027	<0.0027
SILVER	0.000000	0.000000	<0.001	<0.001	<0.001
ZINC	0.002863	0.002863	<0.05	<0.05	<0.05
SELENIUM	0.000000	0.000000	<0.005	<0.005	<0.005
PHENOL	0.000000	0.000000	N/A	N/A	N/A
SURFACTANT	0.000000	0.000000	<0.10	<0.10	<0.10
RESIDUAL CHLORIDE	**********	**********	0.20	0.33	0.50
DISSOLVED SOLIDS	**********	**********	187.0	187.0	187.0
MERCURY	0.000017	0.000017	<0.001	<0.001	<0.001
FECAL COLI	**********	**********	45.0	45.0	45.0
TOTAL COLI	**********	**********	660.0	660.0	660.0

EFFICIENCIES	MEAN	MAXIMUM
BOD	100.00	100.00
COD	100.00	100.00
TSS	100.00	100.00

1/21/95

[signature] 1/2/95

REDACTIONS MADE BY APPLICANT

DMR NOVEMBER 1994

	AVE LOADING	MAX LOADING	MIN CONC	AVE CONC	MAX CONC
TEMPERATURE	**********	**********	26.40	28.10	30.40
FLOW IN	**********	**********	********	********	********
FLOW EFF	39,236.80	106,330.00	********	********	********
CHLORIDE FLOW	**********	**********	********	********	********
TURBIDITY	**********	**********	N/A	N/A	N/A
COLOR	**********	**********	N/A	N/A	N/A
DISSOLVED OXYGEN	**********	**********	5.90	6.17	6.50
BOD IN	66.50	131.00	226.50	226.50	226.50
BOD EFF	0.15	0.30	2.69	2.69	2.69
COD IN	126.84	253.67	437.00	437.00	437.00
COD EFF	0.00	0.00	0.00	0.00	0.00
pH	**********	**********	8.91	7.84	8.70
TSS IN	18.30	36.60	63.00	63.00	63.00
TSS EFF	0.00	0.00	0.00	0.00	0.00
SETTLED SOLIDS	**********	**********	0.00	0.00	0.00
OIL AND GREASE	0.09	0.18	<5.0	<5.0	<5.0
NITRATE AND NITRITE	0.03	0.03	<1.0	<1.0	<1.0
PHOSPHOROUS	0.02	0.02	<1.0	<1.0	<1.0
CYANIDE	0.00	0.00	<0.005	<0.005	<0.005
CHLORIDE	1.29	4.27	18.94	25.19	30.43
FLUORIDE	0.00	0.00	<0.10	<0.10	<0.10
SULPHUR	0.00	0.00	<1.0	<1.0	<1.0
BORON	0.00	0.00	0.0889	0.0889	0.0889
CADMIUM	0.00	0.00	<0.001	<0.001	<0.001
TOTAL CHROMIUM	0.00	0.00	<0.05	<0.05	<0.05
COPPER	0.00	0.00	0.0041	0.0041	0.0041
LEAD	0.00	0.00	<0.002	<0.002	<0.002
SILVER	0.00	0.00	N/A	N/A	N/A
ZINC	0.00	0.00	0.0226	0.0226	0.0226
SELENIUM	0.00	0.00	<0.001	<0.001	<0.001
PHENOL	0.00	0.00	N/A	N/A	N/A
SURFACTANT	0.00	0.00	0.00	0.00	0.00
RESIDUAL CHLORIDE	**********	**********	0.20	0.33	0.60
DISSOLVED SOLIDS	**********	**********	280.50	280.50	280.50
MERCURY	0.00	0.00	<0.001	<0.001	<0.001
FECAL COLI	**********	**********	46.60	46.60	46.60
TOTAL COLI	**********	**********	1.00	1.00	1.00

EFFICIENCIES	MEAN	MAXIMUM
BOD	99.77	99.77
COD	100.00	100.00
TSS	100.00	100.00

[official seal] SEAL COMMONWEALTH OF PUERTO RICO
Francisco Pérez
Santiago
Lic. 1575

000123

REDACTIONS MADE BY APPLICANT

DMR OCTOBER 1994

	AVE LOADING	MAX LOADING	MIN CONC	AVE CONC	MAX CONC
TEMPERATURE	[redacted]	[redacted]	23.70	27.00	29.20
FLOW IN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FLOW EFF	37,534.19	112,590.00	[redacted]	[redacted]	[redacted]
CHLORIDE FLOW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TURBIDITY	[redacted]	[redacted]	N/A	N/A	N/A
COLOR	[redacted]	[redacted]	N/A	N/A	N/A
DISSOLVED OXYGEN	[redacted]	[redacted]	6.00	6.15	6.50
BOD IN	59.64	119.28	234.9	234.9	234.9
BOD EFF	0.02	0.05	0.36	0.36	0.56
COD IN	142.61	285.22	561.8	561.8	561.8
COD EFF	1.49	2.97	21.5	21.5	21.5
pH	[redacted]	[redacted]	6.70	7.60	8.40
TSS IN	14.09	28.18	55.6	55.6	55.6
TSS EFF	0.02	0.07	0.5	0.5	0.5
SETTLED SOLIDS	[redacted]	[redacted]	0.00	0.00	0.00
OIL AND GREASE	0.33	0.66	<5.0	<5.0	<5.0
NITRATE AND NITRITE	0.21	0.21	1.495	1.495	1.495
PHOSPHOROUS	0.02	0.02	0.143	0.143	0.143
CYANIDE	0.000000	0.000000	<0.005	<0.005	<0.005
CHLORIDE	2.2	6.82	21.0	35.7	49.3
FLUORIDE	0.00	0.00	<0.10	<0.10	<0.10
SULPHUR	0.000000	0.000000	<0.002	<0.002	<0.002
BORON	0.019281	0.019281	0.139	0.139	0.139
CADMIUM	0.000104	0.000104	<0.001	<0.001	<0.001
TOTAL CHROMIUM	0.000000	0.000000	<0.05	<0.05	<0.05
COPPER	0.001083	0.001083	<0.01	<0.01	<0.01
LEAD	0.000000	0.000000	<0.0027	<0.0027	<0.0027
SILVER	0.000000	0.000000	N/A	N/A	N/A
ZINC	0.001624	0.001624	<.05	<.05	<.05
SELENIUM	0.000000	0.000000	<0.01	<0.01	<0.01
PHENOL	0.000000	0.000000	N/A	N/A	N/A
SURFACTANT	0.000000	0.000000	<0.10	<0.10	<0.10
RESIDUAL CHLORIDE	[redacted]	[redacted]	0.20	0.34	0.50
DISSOLVED SOLIDS	[redacted]	[redacted]	278.5	278.6	278.6
MERCURY	0.000004	0.000004	<.001	<.001	<.001
FECAL COLI	[redacted]	[redacted]	0.0	0.0	0.0
TOTAL COLI	[redacted]	[redacted]	1.0	1.0	1.0

EFFICIENCIES	MEAN	MAXIMUM
BOD	99.96	99.96
COD	98.96	98.96
TSS	99.76	99.76

ESTADO LIBRE ASOCIADO DE PUERTO RICO
Francisco Pérez Santiago
Lic. 1575
QUIMICO LICENCIADO

[official seal] SEAL COMMONWEALTH OF PUERTO RICO
[signature]
Francisco Pérez
Santiago
Lic. 1575

MSDS NUMBER: 10000071 PAGE: 1

MATERIAL SAFETY DATA SHEET

1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND OF THE COMPANY/UNDERTAKING

SUBSTANCE/PREPARATION:
PAROXETINE HYDROCHLORIDE HEMIHYDRATE
TRADENAMES/SYNONYMS:
(-)-TRANS-4-(4'-FLUOROPHENYL)-3-(3',4'-METHYLENEDIOXY-PHENOXYMETHYL)PI PERIDINE HYDROCHLORIDE HEMIHYDRATE * BRL-29060A * SEROXAT * AROPAX * PAXIL * 29060A (BRL)
CHEMICAL FAMILY:
Substituted phenylpiperidine.
MOLECULAR FORMULA:
C19-H20-F-N-O3 . H-Cl . 1/2(H2-O)
MOLECULAR WEIGHT:
375.0
EINECS NUMBER:
Not Assigned
ELINCS NUMBER:
Not Assigned
COMPANY:
SMITHKLINE BEECHAM, CORPORATE ENVIRONMENT & SAFETY

U.S. OFFICE:	U.K. OFFICE:
709 SWEDELAND ROAD	NORFOLK HOUSE, DOWNSBROOK TRADING ESTATE
KING OF PRUSSIA, PA, 19406	SOUTHDOWNVIEW WAY, WORTHING
U.S.A.	WEST SUSSEX, BN14 8NQ, ENGLAND
PHONE NUMBERS:	
++1-610-270-7807	++44-(0)903-822650

EMERGENCY AND AFTER HOURS CONTACT:
++1-800-228-5635 (EXTENSION 157)

2.COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENTS	CAS REGISTRY NO	PERCENT
PAROXETINE HYDROCHLORIDE HEMIHYDRATE	110429-35-1	99

CONTAMINANTS:
No significant hazardous contaminants present.

3. HAZARDS IDENTIFICATION

PRIMARY ROUTES OF EXPOSURE:
Avoid breathing dust, skin contact, eye contact, ingestion.
SKIN CONTACT:
Irritation after direct contact and allergic skin reaction are not expected, based on animal studies. However, skin contact should be avoided.
EYE CONTACT:
Irritation can occur following direct contact. Symptoms might include redness, swelling, blurred vision, pain, lachrymation or permanent eye damage.
INHALATION:
This material is a potent pharmaceutical agent, small amounts of dust can produce pharmacologic effects. Symptoms after breathing dust might include weakness, dizziness, insomnia, tremor, agitation, nervousness, nausea, dry mouth, diarrhea, constipation or loss of appetite.
INGESTION:
Symptoms after over exposure might include weakness, dizziness, insomnia, tremor, agitation, nervousness, nausea, dry mouth, diarrhea, constipation or loss of appetite.

MATERIAL SAFETY DATA SHEET

CONDITIONS AGGRAVATED BY EXPOSURE:
Individuals taking other medications, including monoamine oxidase inhibitors, might be sensitive to the effects of this material. In cases of over exposure, seek medical assistance concerning possible drug interactions.

4. FIRST-AID MEASURES

SKIN CONTACT:
Remove contaminated clothing and wash exposed area with soap and water. Obtain medical attention if unusual symptoms occur.

NOTE TO PHYSICIAN:
None.

EYE CONTACT:
Wash eyes with water for at least 15 minutes then obtain medical attention.

NOTE TO PHYSICIAN:
Because of the possibility for long lasting damage following eye contact, refer all such cases to an ophthalmologist.

INHALATION:
In case of over exposure, move exposed subject to fresh air. Refer to a physician if individual experiences chest pain, difficulty breathing or loss of consciousness. If breathing has stopped, institute basic life support seek immediate medical attention.

NOTE TO PHYSICIAN:
Effects on the nervous system are of prime concern in cases of over exposure. Treatment should be symptomatic and supportive. For additional information consult the most recent Physicians Desk Reference for treatment of overdosages by serotonin uptake inhibitors.

INGESTION:
In the event of swallowing this material, the decision to induce vomiting must be made by appropriately trained personnel. Seek medical attention in such cases. Gastric lavage can also be considered.

NOTE TO PHYSICIAN:
Effects on the nervous system are of prime concern in cases of over exposure. Treatment should be symptomatic and supportive. For additional information consult the most recent Physicians Desk Reference for treatment of overdosages by serotonin uptake inhibitors.

ANTIDOTES:
None.

5.FIRE-FIGHTING MEASURES

FIRE CONTROL:
Toxic or corrosive gases are expected from fires involving this material. Use water, carbon dioxide, foam or dry chemical extinguishers.

SPECIAL FIREFIGHTING PROCEDURES:
Toxic or corrosive gases including oxides of carbon and nitrogen together with chlorine, fluorine, hydrogen chloride and hydrogen fluoride are expected in fires involving this material. Self contained breathing apparatus and full protective equipment are recommended for firefighters. Move containers from fire area if possible without increased personal risk. Dike area if possible to contain water for later disposal.

6. ACCIDENTAL RELEASE MEASURES

SPILLS:
Instruct all personnel not involved in clean up operations to keep at a designated, safe distance. Do not allow this material to enter surface

drainage systems. Wear protective clothing and equipment consistent with the degree of hazard. Carefully scoop up the spillage, avoid dust generation and place in a suitable, properly labeled container for recovery or disposal. Take care to avoid excessive dust during cleanup. Wash down spillage area with copious amounts of water. This must only be undertaken if waste water can be directed to an on-site waste water treatment system.

7. HANDLING AND STORAGE

HANDLING:

All plant, equipment and operators must be earthed (grounded) to ensure that no isolated conductors are present. Minimise the use of plastics when handling this material. This material should be handled in conductive or anti-static liners (bags). This material is of low conductivity and coupled with its appreciable charge decay time might represent a source of electrostatic charge accumulation. Use only with adequate local exhaust ventilation to routinely control airborne dust levels below 0.2 mg/m3 (8hr TWA)

STORAGE:

Store in a cool, dry, secure area. Use conductive or anti static liners for storage. Avoid contact with direct sunlight.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

EXPOSURE CONTROLS:

PAROXETINE HYDROCHLORIDE HEMIHYDRATE:
SmithKline Beecham(PEL):
0.2 MG/M3 (8 HR TWA)
INDUSTRIAL HYGIENE METHOD:
SB/1102/2 analytical or SB/1001 gravimetric method.

PERSONAL PROTECTION:

RESPIRATORS:

If dust is greater then 0.2 mg/cubic meter a laboratory fume hood or approved respirator should be used. The type of respirator will depend on air levels present. Follow all regulations for respirator are use in the workplace.

GLOVES:

Wear impervious gloves.

EYE PROTECTION:

Wear chemical splash goggles when handling this material. In addition, a face shield is recommended.

HYGIENE PRACTICES:

Wash hands and arms thoroughly after handling this material. Clean up spills immediately.

OTHER PROTECTIVE EQUIPMENT:

An eye wash station should be available. Wear lab coat or other protective clothing with long sleeves.

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE:

White to off white powder. Will discolor on exposure to light.

FLASH POINT:

Greater than 55 degrees C.

AUTOIGNITION TEMP:

Not determined.

LOWER EXPLOSIVE LIMIT:

Not applicable.

UPPER EXPLOSIVE LIMIT:
Not applicable.
MELTING POINT:
120 to 129 degrees C.
BOILING POINT:
Not determined.
VAPOUR DENSITY:
Expected to be negligible.
VAPOUR PRESSURE:
Expected to be negligible.
EVAPORATION RATE:
Expected to be negligible.
VOLATILE COMPONENTS (%):
None expected.
VISCOSITY:
Not applicable for solids.
PH OF AQUEOUS SOLUTIONS:
Neutral.
RELATIVE DENSITY:
Not determined.
CONDUCTIVITY:
Not applicable for solids.
OCTANOL/WATER DISTRIBUTION COEFFICIENT:
Kow = 14.1 (176 mg/l) or 12.2 (1760 mg/l) at pH 5.
Kow = 20.0 (176 mg/l) or 22.2 (1760 mg/l) at pH 7.
Kow = 1930 (176 mg/l) or 1800 (1760 mg/l) at pH 9.
DISSOCIATION CONSTANT (pKA):
9.6
SOLUBILITY:
Soluble in water (8g/l), ethyl alcohol (200 g/l) and methyl alcohol (200 g/l).
OXYGEN BALANCE:
This material is considered to be of low energy hazard potential based on its oxygen balance. Oxygen balance is calculated as minus 207.
TRAIN FIRE TEST:
This material is classified as a non combustable solid. It is therefore considered not to support combustion in bulk quantities.
DUST EXPLOSIVITY:
Classification: A
Minimum explosive concentration (grams/cubic metre): Not determined.
Minimum ignition temperature - cloud (degrees C): Not determined.
Minimum ignition temperature - layer (degrees C): Not determined.
Minimum oxygen concentration (% v/v): Not determined.
Explosion characteristics:
Pmax (bar): 7.7
dP/dT (bar/second): 875
Kst (bar metre/second): 237
St class: 2
DUST ELECTRICAL PROPERTIES:
Minimum ignition energy (mjoules): 5-8
Resistivity at ambient humidity (ohm meter): 2 X 10e14
Charge decay time at ambient humidity (seconds): 7.4
Resistivity at low humidity (ohm metre): 1.2 x 10e15
Charge decay time at low humidity (seconds): 34.2

10. STABILITY AND REACTIVITY

CONDITIONS TO AVOID:

Avoid generating dust clouds. Avoid using plastic materials when handling or storing this material.

INCOMPATIBILITY:
None known.

STABILITY:
Stable but decomposes at elevated temperatures (greater than 180 degrees C). Will discolor if exposed to light.

THERMAL STABILITY:
Capillary tube test: Not determined.
Differential scanning calorimetry: Not determined.
Accelerating rate calorimeter: Not determined.

HAZARDOUS POLYMERIZATION:
Will not occur.

HAZARDOUS DECOMPOSITION PRODUCTS:
None known.

FIRE AND EXPLOSION HAZARDS:
Paroxetine is non combustible in the train fire test and is therefore considered to be non flammable in bulk quantities. However, it is combustible if dispersed as a dust cloud and care should be taken to avoid dust dispersion. It is moderately sensitive to electrostatic ignition and all plant equipment and operators should be earthed (grounded) to minimize this risk. Plastic materials should be avoided when handling this material and conductive or anti static liners should be used for storage or handling.

11. TOXICOLOGICAL INFORMATION

ORAL TOXICITY:
Moderate doses are required to produce lethality following a single ingestion. Oral LD50 values were 378 mg/kg in mice and 415 mg/kg in rats.

INHALATION TOXICITY:
Not determined

SKIN IRRITATION:
This material was classified as a non irritant to rabbit skin. No signs of irritation occurred up to 3 days after direct application for 4 hours in rabbits.

EYE IRRITATION:
This material was classified as a very severe to extremely severe irritant to rabbit eyes. Water irrigation reduced irritation after direct application of a reduced volume of this material.

SENSITIZATION:
This material was classified as a non sensitizer to guinea pig skin. No irritation or adverse skin reactions occurred in guinea pigs used to test for sensitization or allergic skin reaction (modified Maguire/Split Adjuvant Test).

MUTAGENICITY:
This material was not mutagenic in bacteria (Ames test) or other aboratory tests.

CARCINOGENICITY:
This material is not listed as a carcinogen by IARC, NTP, UK HSE or US OSHA. It was not carcinogenic in studies with rats or mice.

REPRODUCTIVE EFFECTS:
No teratogenic (birth defects) or embryotoxic effects resulted in rats or rabbits. Fertility in female rats was reduced at relatively low dose levels.

OTHER EFFECTS:
This material is an anti-depressant agent that selectively blocks

serotonin reuptake and can affect the nervous system.

12. ECOLOGICAL INFORMATION

ACUTE AQUATIC EFFECTS:
Not determined.
BIODEGRADATION:
Not determined.
ACTIVATED SLUDGE RESPIRATION INHIBITION (OECD 209 PROTOCOL):
Not determined.
SOIL ADSORPTION:
Not determined.
OTHER EFFECTS:
Not determined.

13. DISPOSAL CONSIDERATIONS

Dispose of waste on site in a chemical incinerator if allowed by the incinerator permit. If no on-site incinerator is available, dispose of waste in a licensed chemical incinerator.

14. TRANSPORT INFORMATION

FOR AIR TRANSPORT (IATA REQUIREMENTS):
Proper Shipping Name: OTHER REGULATED SUBSTANCES
Technical Name (for n.o.s.,not otherwise specified): Not applicable
UN/Identification Number: ID8027
Class/Division: 9
Sub Risk: Not applicable
Packing Group: Not applicable
RQ (Reportable Quantity): Not applicable
Emergency Response Guide Number: 11
FOR MARITIME TRANSPORT (IMDG REQUIREMENTS):
Proper Shipping Name: NOT RESTRICTED
Technical Name (for n.o.s., not otherwise specified): Not applicable
UN/Identification Number: Not applicable
Class: Not applicable
Sub Risk: Not applicable
Packing group: Not applicable
IMDG page number: Not applicable
MFAG number: Not applicable
EMS number: Not applicable
Marine Pollutant: Not applicable
Emergency Response Guide Number: Not applicable
FOR UNITED STATES GROUND TRANSPORT (DOT REQUIREMENTS):
Proper Shipping Name: NOT RESTRICTED
Technical Name (for n.o.s., not otherwise specified): Not applicable
UN/Identification Number: Not applicable
Class/Division: Not applicable
Sub Risk: Not applicable
Packing Group: Not applicable
RQ (Reportable Quantity): Not applicable
Emergency Response Guide Number: Not applicable
FOR EUROPEAN GROUND TRANSPORT (ADR/RID/ROAD/RAIL REQUIREMENTS):
Not determined. Hazards according to ADR/RID requirements not identified.
EMERGENCY INFORMATION:
HAZCHEM code: Not identified.

DATE APPROVED: 04 May 92 DATE REVISED: 29 November 94 PRINTED: 23 March 95

MATERIAL SAFETY DATA SHEET

TREMCARD Number: Not identified.

15. REGULATORY INFORMATION

EUROPEAN UNION CLASSIFICATION AND LABELLING REQUIREMENTS:

FIRE CLASSIFICATION
Not classified as a significant fire hazard
HEALTH CLASSIFICATION
Harmful Irritant

ENVIRONMENTAL CLASSIFICATION
Not classified as a significant environmental hazard
RISK PHRASES:
Harmful if swallowed. (R22)
Risk of serious damage to eyes.(R41)
SAFETY PHRASES:
Avoid contact with eyes. (S25)
In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. (S26)
Wear eye/face protection. (S39)
SYMBOL:
Saint Andrew's Cross.(Xn) & Saint Andrew's Cross.(Xi)

16. OTHER INFORMATION

HAZARD LABEL:
**** NOT CLASSIFIED AS A SIGNIFICANT FIRE HAZARD ****
**** HARMFUL & IRRITANT ****
**** NOT CLASSIFIED AS A SIGNIFICANT ENVIRONMENTAL HAZARD ****
** HARMFUL IF SWALLOWED.
** RISK OF SERIOUS DAMAGE TO EYES.
** AVOID CONTACT WITH EYES.
** IN CASE OF CONTACT WITH EYES, RINSE IMMEDIATELY WITH PLENTY OF WATER AND SEEK MEDICAL ADVICE.
** WEAR EYE/FACE PROTECTION.
** TARGET ORGAN- PHARMACEUTICAL AGENT- CAN HAVE AN AFFECT ON BEHAVIOR AND THE NERVOUS SYSTEM.
** SYMBOL: SAINT ANDREW'S CROSS.(XN) & SAINT ANDREW'S CROSS.(XI)

REFERENCES:
SB HAZARD DETERMINATION

DATE APPROVED: 04 May 92 DATE REVISED: 29 November 94 PRINTED: 23 March 95

SMITHKLINE BEECHAM ENVIRONMENTAL RESEARCH LABORATORY

SUMMARY OF ENVIRONMENTAL FATE AND EFFECT STUDIES

compound - BRL 29060A (PAROXETINE HCl)

concentrations given as free-base

summary prepared by - Scott Ziegenfuss revised as of 3/23/95

ENVIRONMENTAL FATE

Water Solubility

	mg/L
pH 5 -	5696 to 7881
pH 7 -	1132 to 1133
pH 9 -	318 to 341 (426 to 430 in repeat)
DI water -	5050 to 6804

Octanol/Water Distribution Coefficient (Kow)

	176 mg/L		1760 mg/L	
pH	Kow	log Kow	Kow	log Kow
5	14.1	1.15	12.2	1.09
7	20.0	1.30	22.2	1.35
9	1930	3.29	1800	3.26

Sludge Adsorption log K-biomass = 2.94 (y intercept of log x/m vs. log Ce plot)

Vapor Pressure < 8.25E-6 torr

UV/vis Spectrum

pH 5		pH 7		pH 9	
lambda	E	lambda	E	lambda	E
234	3732	234	3823	234	3806
292	3828	292	3817	292	3797

Dissociation Constant (pKa) 9.6

Aerobic Biodegradation none observed for BRL 29060A

metabolite (BRL 36610A)

* degraded at k=0.03/hr to < detection limit in 5 days (in-house), t1/2 = 23 hrs

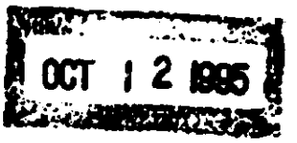
Photolysis k = 0.29/hr in DI H2O and 0.27/hr in pH 7 buffer

t1/2 = 2.4 hours in DI H2O and 2.6 hrs in pH 7 buffer

ENVIRONMENTAL EFFECTS

		BRL 29060A	BRL 36610A
D. magna 48-hr acute	EC50 =	2.5 mg/L	35 mg/L
	NOEC =	0.49 mg/L	14 mg/L
	slope =	4.4	15
Bluegil 96-hr acute	EC50 =	1.6 mg/L	-
	NOEC =	0.18 mg/L	-
	slope =	8.5	-
Microbics Microtox	EC50 =	8.2 mg/L	29 mg/L
photodegraded solution		non-toxic	-
biodegraded solution		-	non-toxic
Activated Sludge Respiration Inhibition (OECD 209)	EC50 =	25 to 26 mg/L	80 to 83 mg/L

NDA 20-031/S-007



SmithKline Beecham Pharmaceuticals
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Route 23 & Woodmont Avenue, P.O. Box 1510
King of Prussia, Pennsylvania 19406-0939

Dear Dr. Brennan:

Please refer to your supplemental New Drug Application dated December 6, 1994, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act providing for the use of Paxil® (paroxetine hydrochloride) 20 and 30 mg tablets in obsessive compulsive disorder (OCD).

We acknowledge receipt of your amendments dated February 17, April 4, May 3, May 15, June 9, July 6, and July 15, 1995 submitted to your NDA, a well as your amendment dated July 24, 1995, providing for a final study report of long term treatment with Paxil in patients with OCD submitted to your IND,

We have completed the review of this supplemental application and it is APPROVABLE. Before the application may be approved, however, it will be necessary for you to submit the following information and respond to the following issues:

CLINICAL

1. Labeling

Accompanying this letter (Attachment) is the Agency's proposal for the labeling of Paxil®. Our proposal is based on your labeling proposal submitted in your original supplement.

We have proposed a number of changes to your draft labeling, and explanations for these changes are provided in the bracketed comments embedded within the proposed text. In certain instances, we have asked you to further modify labeling. Division staff would be happy to meet with you to discuss any disagreements you might have with any part of the proposed labeling format or content.

We have additionally highlighted, in the attached labeling, revisions requested by the Division in previous correspondences. It is our intention that all of these pending revisions can be resolved as part of a final action on this supplement.

2. Safety Update

Our review of the safety of paroxetine in the treatment of OCD was based on data accumulated through 12-10-93 for the integrated database and through 5-31-94 for serious events. You will need to submit a final safety update including safety data accumulated since these cutoff dates.

The safety update should include an update on spontaneous reports for Paxil worldwide. We note that in your earlier safety submission, you did not segregate and report separately on reports in patients being treated for OCD. We ask that, as part of this safety update, you provide such a report, for the entire postmarketing experience for Paxil thus far.

In addition, we ask that you conduct analyses to explore for age and gender effects on adverse event incidence.

3. World Literature Update

Prior to the approval of paroxetine for OCD we require an updated report on the world's archival literature pertaining to the safety of paroxetine in this population. This report should cover all relevant published papers, including clinical or preclinical data, that were not submitted with the original NDA or in subsequent amendments.

We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of paroxetine in this population. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

4. Foreign Regulatory Update/Labeling

We require a review of the status of all actions with regard to paroxetine in the treatment of OCD, either taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. If paroxetine is approved for use in OCD in any countries, we ask that you provide us current labeling for paroxetine in those countries, along with English translations when needed.

5. Efficacy Data

We ask that you perform and provide to us the results of exploratory analyses of the efficacy data for interactions on the basis of age and gender.

6. Pediatric OCD Studies

Another deficiency in your development program for this indication was the absence of safety and efficacy data for children and adolescents. This is a potentially important problem for OCD because of the very early age of onset for this disorder (peak age of onset is 9 for males and 12 for females). In fact, it is likely that many children and adolescents are already being treated with paroxetine for OCD, and it would be expected that such treatment would increase with the approval of this new indication. Although it is true that you have not specifically sought approval for this indication in these age groups, ideally, data would be available to support (or refute) what is already occurring in clinical practice. We would like your commitment as well as a proposed completion date to conduct such studies following the approval of Paxil® for this indication.

PHARMACOLOGY

As with other serotonin reuptake inhibitors, we find it necessary to request that the decreased survival of rat pups in reproduction toxicology studies receive more emphasis in labeling. Because it is not clear whether this finding was related to effects of the drug on the developing fetus *in utero* or was secondary to postnatal drug effects on the dams and/or pups, we have labeled PAXIL® pregnancy category C. If you were to conduct a cross-fostering study that clearly established that the adverse effect on pup survival occurred as a result of a postnatal effect rather than an *in utero* effect of drug on the fetus, the labeling may be changed from pregnancy category C to pregnancy category B. We recommend that you submit the protocol for this study for our concurrence before initiating it.

Please submit fifteen copies of the printed labels and other labeling, ten of which are individually mounted on heavy weight paper or similar paper.

In addition, please submit three copies of the introductory promotional and/or advertising campaign that you propose to use for this new indication. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert, directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications
HFD-240, Room 17B-17
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action on your part, the FDA may proceed to withdraw the application.

In accordance with the policy described in 21 CFR 314.102(d) and in the Center for Drug Evaluation and Research Staff Manual Guide CDB 4820.6, you may request an informal conference with the Division to discuss what further steps you need to secure approval. The meeting is to be requested at least 15 days in advance. Alternatively, you may choose to receive such a report via a telephone call. Should you wish this conference or a telephone report, or should any questions arise concerning this NDA, please contact Mr. Paul David, Regulatory Management Officer, at (301) 594-2777.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of this invoice.

This drug may not be legally marketed for the indication provided by this application until you have been notified in writing that the application is approved.

Sincerely yours,

10/12/95

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ATTACHMENT

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA #:	20,031 (S-007)
Sponsor:	SmithKline Beecham Pharmaceuticals
Clock Date:	December 6, 1994

Drug Name

Generic Name:	Paroxetine HCl
Trade Name:	Paxil

Drug Categorization

Pharmacological Category:	Selective Serotonin Reuptake Inhibitor
Proposed Indication:	Obsessive Compulsive Disorder
NDA Classification:	6 S
Dosage Forms, Strengths, and Route of Administration:	20 mg and 30 mg film-coated tablets.

Reviewer Information

Clinical Reviewer:	Paul J. Andreason, M.D.
Review Completion Date:	September 5, 1995

Table of Contents

APPENDICES

1.0 Material Utilized in Review

1.1 Material from NDA Supplement

The following items were examined during the course of this clinical review:

NDA Volume(s)	Submission Date	Material Reviewed
49.019	December 6, 1994	Study Report: 116
49.025	December 6, 1994	Study Report: 118
49.031	December 6, 1994	Study Report: 136
49.043	December 6, 1994	Integrated Summary of Efficacy
49.044	December 6, 1994	Integrated Summary of Safety
49.103-237	December 6, 1994	Case Report Forms: Withdrawals due to Adverse Experiences
Addendum SE1-007	May 3, 1995	Efficacy Summary Tables
54.001-007	May 15, 1995	Response to agency request for further information.
Addendum SE1-007	June 9, 1995	Analysis of Emergent Suicidality
Addendum SE1-007	July 17, 1995	Additional Efficacy Summary Table
Memorandum from Rosemary Oakes and William Bushnell of SmithKline Beecham Biometrics	August 15, 1995	Additional Analyses of Studies 116 and 136

1.2 Related Reviews

NDA 20-031: Paxil in the treatment of depression, approved December 29, 1992.

2.0 Background

2.1 Indication

Paroxetine (Paxil), a selective serotonin reuptake inhibitor

(SSRI), is marketed by SmithKline Beecham as an antidepressant.

There are currently three FDA approved medications for the treatment of OCD, clomipramine (Anafranil), fluoxetine (Prozac), and fluvoxamine (Luvox). Clomipramine is from the tricyclic antidepresant drug family (TCA), fluoxetine and fluvoxamine are both selective serotonin re-uptake inhibitors (SSRI's). The efficacy of these three drugs in the treatment of OCD symptoms are putatively due to greater effect on blocking the reuptake of serotonin than other anti-depressants.

Clomipramine carries the common side-effects of the TCA family, namely, dry mouth, blurry vision, constipation, urinary retention, orthostatic hypotension, weight gain, sedation, and potential cardiac conduction problems. Fluoxetine carries the common side effects of anxiety, nervousness, sleeplessness, headache, asthenia, nausea, and abdominal pain. Fluvoxamine carries the common side effects of asthenia, nausea, somnulence or insomnia, and nervousness.

Paroxetine, compared to clomipramine, has a different side-effect profile that many patients find more tolerable to the side-effects of clomipramine.

Its side-effect profile is similar to that of the other SSRIs. However, there are pharmacokinetic differences between the SSRI's: norfluoxetine, the primary metabolite of fluoxetine with equipotent pharmacological activity, has a very long half-life and this drug appears to be associated with inhibition of multiple P450 enzyme systems; fluvoxamine has a half-life of about 16 hours and no known active metabolites, but also seems to inhibit multiple P450 systems. Paroxetine has a half-life of about 21 hours, no known significantly active metabolites, and, while it is a potent P450IID6 inhibitor, is not known to inhibit other P450 isozymes. Thus, paroxetine may offer some clinical advantages over fluoxetine and fluvoxamine.

2.2 Related INDs and NDAs

IND is the sponsor's IND for paroxetine HCl.

There are no other INDs for the use of paroxetine in the treatment of OCD.

2.3 Administrative History

In December, 1983, IND was submitted to study paroxetine for depression. In November, 1989 the submission of paroxetine NDA 20-031 for treatment of depression was made. In December, 1990 the first approval of paroxetine for the treatment of depression, in the United Kingdom, was granted. In January 1991, the first pivotal efficacy trial using paroxetine in Panic Disorder was started and, in July 1991, the initial pivotal trial for the use of paroxetine in the treatment in OCD was begun. In

December, 1992 the FDA approved paroxetine for the treatment of depression. In February 1994, the pre-sNDA meeting between SmithKline Beecham and the Division of Neuropharmacological Drug Products concerning the OCD and Panic Disorder development programs took place. The sNDA 20-031 "Paxil in the treatment of Obsessive Compulsive Disorder" was received December 19, 1994, reviewed for completeness, and found to be fileable on January 23, 1995.

2.4 Directions for Use
Paxil is indicated for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD) as defined in the DSM-IV. The efficacy of Paxil for OCD was established in two 12-week trials with obsessive compulsive outpatients whose diagnosis corresponded most closely to the DSM-III-R category of obsessive-compulsive disorder.

Obsessive-Compulsive Disorder

Usual Initial Dosage: Paxil (paroxetine hydrochloride) should be administered as a single daily dose, usually in the morning. Patients should be started at 20 mg/day and the dose can be increased in 10mg/day increments, with dose changes at intervals of at least one week. The recommended dose of Paxil in the treatment of OCD is 40mg daily. Some patients may benefit from having their dose increased up to a maximum of 60mg/day.

Patients were dosed in a range of 20 to 60mg/day in the clinical trials demonstrating the effectiveness of Paxil in the treatment of OCD.

It is useful to determine whether the adverse event profile for paroxetine in the treatment of patients with OCD varies from the adverse events commonly associated with the treatment of depression that is presented in NDA 20031.

The sponsor also wishes to increase the dosage range for paroxetine to 20-60mg/day in the treatment of OCD from 20-50mg/day, the current dosing range in the treatment of depression. It is therefore useful to know if there is an increase in the quality or quantity of adverse event reporting with this dose increase.

2.5 Foreign Marketing
Paxil (paroxetine hydrochloride) is not currently marketed for the treatment of obsessive compulsive disorder and to date has not been the subject of a marketing application for this indication in any country. However, as of September 1994, paroxetine has been approved for depression in 50 countries and is marketed for that indication in 28 countries. It has not been withdrawn from any market for any reason.

3.0 Chemistry
There are no outstanding chemistry, manufacturing, or control issues to be addressed.

4.0 Animal Pharmacology
In vitro studies using radioligands have demonstrated that paroxetine is a potent and highly selective inhibitor of serotonin reuptake by neurons; it has only very weak effects on norepinephrine and dopamine reuptake and little affinity for muscarinic, adrenergic (α-1, α-2, β), D2, 5-HT1, 5-HT2, and H1 receptors. The mechanism of action of paroxetine in OCD is not specifically known but is felt by many to involve the pre-synaptic inhibition of serotonin reuptake in CNS neurons.

The recommended maximum human dose for OCD is slightly higher than that recommended for depression (60 mg/day vs. 50 mg/day). Consultation with the pharmacology reviewer for this supplement indicates that the safety of this increased dose cannot practically be judged from animal data because of this small magnitude of change.

Although some segment II studies in the rat and rabbit did not indicate any teratogenic effect on the embryo, a different rat study showed an increase in pup deaths during the first 4 days of lactation. This effect occurred at a dose equal, on a mg/kg basis, to a maximum human daily dose of 50 mg/day. The "no effect dose" for rat pup mortality was not determined. It was not clear whether the observed deaths were related to an embryotoxic effect or due to exposure to paroxetine during lactation. There are no controlled studies in pregnant women. Given this data, it is now recommended that paroxetine be used in pregnancy only if clearly indicated until this finding can be clarified, that is, a change from Pregnancy Category B to Pregnancy Category C is now recommended.

In addition, the effects of paroxetine on fertility were assessed in the rat and there were no indications from the general toxicity studies that the female reproductive system has been adversely affected in these studies. However, irreversible lesions were observed in the reproductive tracts of male rats after 2-52 weeks of dosing at 25X a maximum human dose (50 mg/day) on a mg/kg basis, specifically vacuolation of epididymal tubular epithelium, atrophic changes in the semiferous tubules, and arrested spermatogenesis.

Mutagenicity tests carried out for examining the effects on the gene were the bacterial Ames and mouse lymphoma tests, both of which are in vitro tests. In neither system (with and without a metabolic activating system) were significant increases in mutation frequency observed. The potential to cause chromosomal aberrations was studied by examining the bone marrow cells for

micronuclei following the administration of paroxetine to mice at the very high doses of 75 and 150 mg/kg. There was no evidence for any chromosomal damage.

The only toxicity study submitted with this supplement was "BRL 29060: Mutation tests with E. coli, WP2 pKM101, and WP2 uvrA pKM101." There was no evidence of a mutagenic effect by paroxetine.

In a two year carcinogenicity study in rats, there was a significantly greater number of high-dose male rats with reticulum cell sarcomas (20X a maximum recommended human dose (50 mg/day) on a mg/kg basis) and a significant linear trend across dose groups for lymphoreticular tumors in male rats. Females were not affected. The relevance of these findings to humans is not known.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

5.1.1 Study Type and Design/Patient Enumeration

SmithKline Beecham's development program for Paxil in the treatment of OCD consisted of three studies performed under three different protocols. The study designs for these trials are summarized in the following table.

Table 5.1.1.1:
Table of Controlled Studies in OCD

Study	Design
116	Randomized, double-blind, placebo-controlled, parallel group, 15-center, US, 12-week fixed dose trial, paroxetine (20, 40, or 60 mg/day) vs placebo; outpatients with OCD (n=approx 87 per group).
118	Randomized, double-blind, placebo-controlled, parallel group, 13-center, US, 12-week flexible dose trial, paroxetine (20-60mg/day) vs clomipramine (25-250mg/day) vs placebo; outpatients with OCD (n=approx 80 per group).
136	Randomized, double-blind, placebo controlled, parallel group, 64-center, non-US, 12-week flexible dose trial, paroxetine (20-60mg/day) vs clomipramine (50-250mg/day) vs placebo; outpatients with OCD (n=99 in each of the placebo and clomipramine groups and 201 in the paroxetine group).

126	An extension of paroxetine treatment in patients with OCD from those treated in study 116. This was an open label study for 6 months duration after which patients were randomized to either continue paroxetine or to be withdrawn in a double-blind fashion. Only data on serious adverse events is given in the submission.
127	An extension of paroxetine treatment in patients with OCD from those treated in study 118. This was an open label study for 6 months duration after which patients were randomized to either continue paroxetine or to be withdrawn in a double-blind fashion. Only data on serious adverse events is given in the submission.
241	An extension of paroxetine treatment in patients with OCD from those treated in study 136. This was an open label study for 6 months duration after which patients were randomized to either continue paroxetine or to be withdrawn in a double-blind fashion. Only data on serious adverse events is given in the submission.

Patient samples are enumerated in Table 5.1.1.2 below.

Table 5.1.1.2:
Patient Enumeration in Controlled OCD Studies.

Protocol	Paroxetine	Clomipramine	Placebo
FIXED DOSE STUDY			
116	259 *	0	89
FLEXIBLE DOSE STUDIES			
118	82	82	77
136	201	99	99
Total	542	181	265

* Paroxetine 20 mg/day= 88.
" 40 mg/day= 86.
" 60 mg/day= 85.

Data from the three completed protocols and their extended treatment protocols constitute the integrated OCD clinical trials database for this supplement. As shown above, there were 542

patients exposed to paroxetine in the integrated data base, almost half of which were treated with fixed doses. Protocols 116, 118 and 136 each had a long-term extension protocol (126, 127 and 241, respectively) in which patients were treated for periods of up to one year to evaluate the long-term use and the effectiveness of paroxetine in relapse prevention of OCD. However data from the long-term studies are not included in this integrated summary of efficacy. Serious adverse event data only is presented from the extended treatment protocols. The patients in these protocols are patients originally enrolled in protocols 116, 118, and 136, and do not represent additional numbers of patients exposured to paroxetine. The data sets for studies 116, 118, and 136 were closed on December 10, 1993 and safety data from studies 126, 127, and 241 was included up through May 31, 1994.

5.1.2 Demographics

Table 5.1.2 presents the demographic profile for patients participating in the integrated database studies. About three-fourths of each group were in the age range 25-54 years old, with a mean age just under 40. Slightly more than half of each group were male. Caucasians comprised the vast majority of each treatment group.

TABLE 5.1.2
Demographic Profile for Paroxetine OCD Clinical Trial Integrated Database

Parameter	Paroxetine (n=542)	Placebo (n=265)	Clomipramine (n=181)
AGE (years)			
Mean	39.75	39.13	37.33
Range	16-78	16-74	16-70
Age Groups (%)			
16-24 Years	66 (12)	29 (11)	29 (16)
25-34 Years	147 (27)	75 (28)	53 (29)
35-44 Years	148 (27)	74 (28)	45 (25)
45-54 Years	108 (20)	60 (23)	35 (19)
55-64 Years	48 (9)	17 (6)	17 (10)
≥65 Years	25 (5)	10 (4)	2 (1)
SEX (%)			
Male	330 (61)	158 (60)	104 (57)
Female	212 (39)	107 (40)	77 (43)
Race (%)			
White	524 (97)	251 (95)	171 (94)
Non-white	18 (3)	14 (5)	10 (6)
Mean Weight (kg)	74.77	74.90	70.05

5.1.3 Extent of exposure (dose/duration)

Table 5.1.3 depicts the mean daily dose and duration of paroxetine treatment for the 542 patients in the OCD clinical trial database. A total of about 78% (424/542) of the paroxetine patients received a mean daily dose of at least 20 mg/day for a duration of at least nine weeks; 18% (99/542) of all paroxetine patients were exposed to a mean dose of at least 50 mg/day for nine weeks or longer.

Table 5.1.3:
Enumeration of all Paroxetine Patients According to Mean Daily Dose and Duration of Therapy in OCD Studies (n=542)

Duration (Weeks) ↓	<10 mg	≥10-<20 mg	≥20-<30 mg	≥30-<40 mg	≥40-<50 mg	≥50mg	Unk	Tot.	(%)
<3	2	11	32	6	0	1	2	54	10
3-4	0	0	11	9	5	0	0	25	5
5-8	0	0	6	13	4	3	0	26	5
9-12	0	10	66	87	81	73	0	317	58
>12	0	3	23	26	42	26	0	120	22
Total	2	24	138	141	132	103	2	542	100
(%)	<1	4	25	26	24	19	<1	100	

Exposure may also be expressed in terms of patient-years, a duration of exposure equivalent to one patient being exposed for one year (or two patients receiving the drug for six months, etc.):

Drug	N	Patient-years
Paroxetine	542	109
Clomipramine	181	33
Placebo	265	53

5.1.4 Random audit of safety an efficacy data.

Twelve cases were audited for safety and efficacy from the paroxetine clinical studies with positive clinical outcomes. Six cases were chosen at random from the list of patients who withdrew from studies 116 and 136 for lack of efficacy, and six cases for withdrawal due to adverse events. The case report forms were compared to the case report tabulations (see Section 11 of sNDA index to case report tabulations) in order to verify that investigator and line listing reason for withdrawal matched.

The following table is a report of this audit.

Protocol	Patient	Rx	Reason for Withdrawal in LL	Comments
116	004.0001			
116	013.0335			
136	001.0052			
136	009.0304			
136	014.0392	P60		
136	022.0135	PL		at
118	006.0038	P30		
116	010.0133	P20		
136	032.0163	P20		
136	074.0429	P20		
118	002.0028	C25		
116	005.0021	PL		

Key to Abbreviations:
AE =Adverse event
C... =Clomipramine and end-study daily dose
CRF =Case report form
LL =Line listing
P... =Paroxetine and end-study daily dose
SAE =Significant adverse event

The six cases chosen at random from the list of patients who withdrew from studies 116 and 136 for lack of efficacy were also audited for consistency in efficacy results. The line listings for YBOCS and NIMHOCS scores (Appendices 9 & 10 of Integrated Summary of Efficacy) were compared with the case report forms. In all cases the line listing reports of theses scores were completely consistent with the case report forms.

5.2 Secondary Sources of Clinical Information
5.2.1 Non-IND Studies
No non-IND studies are reported. Seven patients have been treated under compassionate use protocols in the U.S.: no serious adverse experiences were reported in these patients. These protocols are no longer active.

5.2.2 Post-marketing Experience
The sponsor states that the post-marketing experience reported in this submission, that is, tables of worldwide spontaneous adverse drug event reports, reflects reports in depressed patients only. Therefore, no ADR spontaneous reports involving patients with OCD were available for review.

5.2.3 Literature
The sponsor's process for selection, storage and retrieval of published adverse events is as follows:

Profiles listing all SmithKline Beecham (SB) compounds from Phase II in development up to, and including, all marketed products have been established and are run against external databases which index biomedical literature. All references retrieved which mention any side effect or toxicity (preclinical as well as clinical) linked to an SB product are included in references input to the central product literature database, SBLine. The main source of references for SBLine is the Excerpta Medica database produced by Elsevier. This database covers about 3,500 biomedical journals. This source is supplemented by profiles run against the Medline and Biosis databases, plus manual scanning of major journals. Updates from the profiles are received weekly. Additional in-house indexing is added by trained SB information staff working from the full text of the articles. Weekly alerts are issued throughout the company listing papers added within the last week which mention specific SB compounds or adverse events associated with any SB product. All adverse event papers are notified to the Central Safety group through these weekly alerts. The database is also available for retrospective searching.

As a result of the above search, 400 references were provided as part of the CANDA submission of this supplement. Publications reported within the original submission of this NDA (for depression) or within the publications update of November 12, 1992, were not included in this submission. The criteria for reviewing these references started with an examination of the

title of each reference for topical content, and proceeded as follows:

Titles relating to efficacy data for indications other than OCD were screened out from further review. Abstracts for all articles dealing with efficacy in OCD, based on the title, were reviewed.

If the title indicated presentation of safety data, the abstract was reviewed, regardless of diagnostic indication.

If the topic of an article was not clear from the title, the abstract was reviewed.

Any articles for which abstracts were felt to be incomplete were reviewed in entirety.

Important findings resulting from this search process are presented in Section 7 (efficacy) or Section 8 (safety) of this review.

6.0 Human Pharmakokinetics

Food intake does not significantly affect absorption of orally administered paroxetine, and peak plasma levels are reached 5-6 hours during steady state oral dosing. Paroxetine exhibits dose-dependent pharmacokinetics, probably due to inhibition of its own metabolism as described below.

Paroxetine is 93-95% bound to plasma protein but does not alter the in vitro protein binding of warfarin or phenytoin.

Paroxetine is extensively metabolized after oral administration. Metabolism of paroxetine is accomplished in part by the cytochrome $P_{450}IID_6$ enzyme system. Saturation of this enzyme system occurs early during paroxetine dosing and is thought to be the reason for the non-linearity of paroxetine's kinetics. The principal metabolites are polar and represent products of conjugation and methylation. Data indicate that the metabolites of paroxetine are not more than 1/50 as potent as the parent compound and are easily cleared.

Paroxetine steady state elimination half-life is 21 hours at a dose of 30mg/day for 30 days. After a 10-day post-dosing period, 64% of paroxetine and its metabolites were excreted in the urine with only 2% as the parent compound. 36% of paroxetine and its metabolites are excreted in the feces (presumably via biliary excretion) with 1% as the unchanged parent compound.

Doses in the elderly produced plasma levels that were 70-80% greater than in younger cohorts. Also, patients with renal or hepatic impairment exhibited a two-fold increase in Cmax and AUC compared to normals. The mean plasma concentration in patients

with a creatinine clearance <30 ml/min was four-fold higher than that observed in normal volunteers. For these reasons, initial doses of paroxetine should be decreased in the elderly or in patients with hepatic or renal insufficiency.

7.0 Efficacy Findings
7.1 Overview of Studies Pertinent to Efficacy
SmithKline Beecham conducted three efficacy studies under three protocols numbered 116, 118, and 136. Study 116 was a fixed dose study comparing placebo with paroxetine 20, 40, and 60mg/day. Studies 118 and 136 compared placebo to flexible doses of paroxetine and clomipramine. All three studies will be reviewed here in detail.

7.2 Summary of Studies Pertinant to Efficacy
7.2.1 Fixed Dose Study 116
Investigators and Location
There were a total 15 sites in study 116; investigators and site locations may be found in Appendix 7.2.1.

Objectives and Rationale
The objective of study 116 was to determine the safety and efficacy of three fixed doses of paroxetine versus placebo in the treatment of OCD.

Population
About 350 outpatients with OCD participated in this study. Eligibility was determined by the inclusion and exclusion criteria listed in Appendix 7.2.1.

Design
Study 116 was a randomized, double-blind, placebo-controlled, fixed dose comparison of placebo, 20, 40, and 60mg/day of paroxetine. All medications were in the form of pink tablets identical in size, shape, and color. All patients who completed the 2-week placebo washout and qualified for this study were randomized to one of four treatment groups: placebo, 20 mg paroxetine, 40 mg paroxetine, and 60 mg paroxetine. Patients assigned to the 40 mg and 60 mg groups were titrated to these levels at a rate of 20mg/week. Dosing was once daily. After 2 weeks of treatment, if the patient had adverse experiences that he/she or the investigator considered sufficiently severe to cause premature termination, the investigator had the option of lowering the patient's daily dose. However, only a single level reduction in the dosage was permitted during the course of the study. The study drug (or placebo) was given for 12 weeks. Compliance was monitored via pill count. Except for disallowing use of other investigational drugs within 30 days of baseline (Day 0) or psychotropic drugs within 14 days of baseline, there were no restrictions on use of medications prior to the study. The concomitant use of any other psychotropic drug was contraindicated during the study except for chloral hydrate (up

to 1000mg) for sleep disturbance; the concomitant use of non-psychotropic medications was allowed.

Assessments
The screening visit, to determine eligibility for the study, was conducted 14 days prior to the baseline visit. The following observations were performed at screen:

- General patient information.
- A detailed psychiatric and medication history, listing drug dosage, length of administration and therapeutic response.
- DSM-IIIR multiaxial evaluation.
- (21-item) HAMD
- Y-BOCS.
- NIMHOCS.
- SCL-90.
- Physical examination.
- A 12-lead ECG.
- Vital signs: systolic and diastolic blood pressure and heart rate to be measured after 3 minutes sitting and 1 minute standing.
- Laboratory evaluations, to consist of hematology, clinical chemistry, and urinalysis.
- Pregnancy test.
- Body weight determination.

If subjects met screening criteria, they entered the baseline, two-week single-blind placebo washout phase. The following observations were performed at baseline (Day 0):

- (21-item) HAMD
- Y-BOCS.
- NIMHOCS.
- SCL-90.
- Severity of Illness item of the CGI.
- GAF.
- Vital signs.
- Laboratory evaluation.
- Plasma sample for paroxetine pharmacokinetic analysis.
- Body weight determination.
- Adverse event monitoring.
- Concomitant medication and study medication records.

The treatment phase followed the baseline phase: patients were randomized to one of the three active medication groups or the placebo group. Assesment visits were scheduled at weekly intervals during the first month of the study and at biweekly intervals during the remaining two months, for a total of 8 visits during the double-blind medication phase. The following observations were performed during treatment:

- Y-BOCS at each visit.
- NIMHOCS at each visit.
- Severity of Illness, Global Improvement, and Efficacy Index items of the CGI at each visit except Weeks 6 and 10.
- Hamilton Scale for Depression (21-item HAMD) at Week 12.

- SCL-90 at Weeks 4, 8 and 12.
- GAF at Weeks 4, 8 and 12.
- Vital signs at each visit except Weeks 6 and 10.
- Laboratory evaluations at Weeks 4, 8, and 12.
- Plasma samples for pharmacokinetic analysis at weeks 4,8 and 12 or at the time of withdrawal from the study.
- Body weight determination at each visit except Weeks 6 and 10 (or at termination if the patient withdrew from the study).
- Physical examination at Week 12 (or at termination if the patient withdrew from the study).
- Adverse event monitoring at each visit.
- Concomitant medication and study medication records at each visit.

Study design included two major modifications. On July 30, 1991, the protocol was modified to exclude women of childbearing potential at the request of the Neuropharmacologic Drug Products Division of the FDA. On February 10, 1992, the protocol was modified to allow for two interim analyses of efficacy. As a result, the overall alpha level for tests of hypothesis was reduced from 0.05 to 0.04588.

Analysis Plan

The primary efficacy criteria were predetermined to be the proportion of patients with a reduction in the Y-BOCS OCD rating scale score ≥ 25% and statistically significant reduction in these rating scales when compared to placebo. Though other scales were administered, they are considered secondary variables. The sample to be analyzed was the intent-to-treat (ITT) group (subjects who passed screening and had at least one post-baseline evaluation). Two datasets were relevant:

1. The visit-wise data set-consisting of each patient's observations at each week of the study.

2. The extender data set (or last observation carried forward data set) is based on the visit-wise data set with the modification that missing data for a given week are estimated by bringing forward (extending) the data from the previous week.

Change from baseline scores (change = score - baseline score) of efficacy scales were analyzed using parametric analysis of variance methodology. Some efficacy scales were not evaluated at baseline, the raw scores of these scales were used. The GLM procedure of the SAS system was used to perform the analyses. The analysis in the original submission was weighted for treatment-by-site interactions; by request of the Division of Biometrics, the efficacy data was re-analyzed by the sponsor. The requested model included effects for treatment, investigational site, treatment-by-site ineraction.

Demographics
The demography of the four treatment groups is presented in Appendix 7.2.1. The treatment groups were roughly comparable with respect to mean age, age range, and gender and racial distribution. The majority from each group were male (67% to 82%) and caucasian (94%-97%).

Baseline Illness Severity
Treatment groups were comparable at baseline with respect to mean Y-BOCS, NIMHOCS, and CGI-severity scores.

Patient Disposition
The ITT population was comprised 348 patients who had previously been randomized to treatment as follows: 89 patients to placebo, 88 patients to 20 mg paroxetine, 86 patients to 40 mg paroxetine and 85 patients to 60 mg paroxetine. Two-hundred and eighty patients (80%) of the 348 patients randomized to treatment completed the study. In no group did fewer than 70% of patients complete the study. The number of patients remaining in the study at weekly intervals is presented in Appendix 7.2.1. Some patients could not tolerate the dose level to which they were assigned and had their dose reduced and remained in the study. These data from these patients was considered, for purposes of these statistics and efficacy analyses discussed in this review, as if they had remained in their originally assigned dose group.

Concomitant Medications
Concomitant medications taken during the study were numerous and varied. The most frequently used concomitant medications (> 10% in any treatment group) included: analgesics, antacids, antibiotics, antiinflammatories, cough and cold preparations, nasal preparations, chloral hydrate, and systemic antihistamines.

The concomitant use of any other psychotropic drug was contraindicated during the study except for chloral hydrate for sleep disturbance. The distribution of chloral hydrate (i.e. psycholeptic) use among the 3 paroxetine dose groups was comparable (8%-12%) with higher use in the placebo group (19%). Two patients admitted to using other psychotropic agents during the course of the study. I.V. cocaine use was reported by one patient and alprazolam use by the other.

Efficacy Results
Though the sponsor's primary efficacy variable was the YBOCS, this review also examines the NIMHOCS and the CGI severity and improvement scales. Comparisons include the mean changes in Y-BOCS, NIMHOCS, CGI severity and CGI improvement scales and a table showing relative clinical progress in patients at week 12 as measured by the NIMHOCS. These results are found in tabular form in Appendix 7.2.1.

All of the rating scales showed statistically significant

improvement over placebo at the endpoint of the study (week-12) at the 40 and 60 mg/day dose levels. This efficacy result was present in both the observed case data set and the extender data set. The 20 mg/day dose level was not significantly different from placebo at endpoint by any rating scale on either the observed case or extender data sets. The 60 mg/day dose group showed significant improvement on all scales in both data sets by week 4 of the study. The 40 mg/day dose group did not show significant improvement on all subscales until week 6.

Conclusion
Paroxetine was effective in reducing symptoms associated with OCD as measured by multiple rating scales. The 60 mg/day dose displayed significant improvement by week 4. The 40 mg/day dose displayed significant improvement by the week 6. This study supports the sponsor's efficacy claims for paroxetine in the treatment of OCD.

7.2.2 Study 118
Investigators/Sites
A table of the 13 sites and investigators can be found in Appendix 7.2.2.

Objectives
Study 118 was designed to demonstrate the effectiveness and safety of paroxetine in the treatment of OCD in a 12-week, randomized, double-blind, placebo- and clomipramine-controlled study.

Population
A total of 241 patients were enrolled in this trial: 82, 77 and 82 patients were randomized to the paroxetine, placebo, and clomipramine groups, respectively. A comprehensive list of inclusion and exclusion criteria are listed in Appendix 7.2.2.

Design/Assessments
This was a 12-week, multicenter, randomized, double-blind, parallel group study of paroxetine, clomipramine and placebo in the treatment of outpatients with DSM-III-R OCD.

A single-blind placebo pretreatment period was used to screen potential candidates for inclusion in the study. Patients were given placebo capsules and instructed to take one capsule each morning during this 2 week period. Psychotropic medications were not allowed during this time.

All patients who qualified for the double-blind treatment phase of the study were randomly assigned to one of three treatment groups: paroxetine in daily doses starting at 20 mg, clomipramine in daily doses starting at 25 mg, and placebo. Depending on the therapeutic response and tolerance to side effects, the

paroxetine daily dose could be increased in increments of 10 mg every four days to a maximum of 60 mg, and the clomipramine daily dose was increased in increments of 25 mg every four days to a maximum of 250 mg. The initial doses were taken in the morning. Because of inter-individual variation of response, the investigator could instruct the patient to vary the number of capsules taken during specific time periods (AM or PM) depending upon the degree of sedation or activation experienced by the patient. In this study division of daily doses and time were left to the discretion of the patient and investigator. Also, if gastrointestinal distress occurred, doses could be administered following meals.

The length of double-blind phase under this protocol was 12 weeks. Post-baseline visits were scheduled weekly for the first month and biweekly for the remaining two months, for a total of 8 visits during the double-blind treatment phase of the study. After receiving 12 weeks of blinded treatment, patients could enter a long term extension study. Those who did not were taken off medication. A schedule of the assessments performed can be found in Appendix 7.2.2.

Analysis Plan
No interim efficacy analyses were performed. The sponsor's primary efficacy variable was the mean change from baseline in the YBOCS total score. The secondary efficacy variables were the YBOCS Obsessive and Compulsive subtotal scores, NIMHOCS scores, items of CGI, and SCL-90, HAMD, and GAF scales.

The efficacy ITT population consisted of all patients randomized to study medication and having at least one on-therapy efficacy evaluation. For inclusion in the analysis, there was no time limit between the day of a patient's last dose and the day of a subsequent efficacy evaluation.

Two datasets were used to analyze the efficacy data, observed cases and extender (last observation carried forward). Change from baseline scores (change = score - baseline score) of efficacy scales were analyzed using parametric ANOVA methodology. Some efficacy scales were not evaluated at baseline, so the raw scores of these scales were used. The GLM procedure of the SAS system was used to perform the analyses.

Patient Disposition
A total of 232 patients comprised the efficacy ITT (79 paroxetine, 75 placebo, and 78 clomipramine patients). For the study as a whole, 70% (162/232) of all patients completed the study. The completion rate across treatment groups is as follows: 67% (53/79) for paroxetine, 75% (56/75) for placebo and 68% (53/78) for clomipramine. The number of patients remaining in the study across time is presented in Appendix 7.2.2.

Baseline Demographics
All three treatment groups were comparable with respect to race distribution (Caucasian: 92 to 94%). The placebo and clomipramine groups were comparable with respect to mean age (mean = 36.3 and 36.0 years, respectively), but the paroxetine group was, on average, 5 years older than the placebo and clomipramine groups (mean = 41.3 years). Males were more than twice as prevalent as females in the placebo group (70.1 vs. 29.9%), whereas males were only slightly more prevalent in the paroxetine and clomipramine groups (53.7 and 58.5%, respectively). Based on a covariate analyses of demographic variables done by the sponsor, these differences in age and gender distribution did not affect the efficacy results.

Baseline Illness Severity
Baseline mean Y-BOCS scores were within a range of 1.4 points and not felt to be substantially different. Mean NIMHOCS and CGI severity scores were comparable at baseline.

Dosing Information
The mean doses of paroxetine and clomipramine among completers by visit is listed in Appendix 7.2.2. The mean daily dose of paroxetine increased up through week 6 and ranged from 56-57 mg from week-8 through week-12. The mean daily dose of clomipramine increased through week-8 ranged from 163-171 from week-8 to week-12. The mean daily clomipramine dose was well under the maximum recommended dose for OCD recommended in labeling.

Concomitant Medications
Concomitant medications taken during the study were numerous and varied and no discernable pattern of use was apparent by visual inspection across treatment groups. The most frequently used concomitant medications (> 10% in any treatment group) included: analgesics (35-44%), antiinflammatory/antirheumatic products (10-35%), and systemic antihistamines (15-21%).

The concomitant use of any other psychotropic drug was prohibited during the study, except for chloral hydrate for sleep disturbance. The use of chloral hydrate among the three treatment groups was low (2%-8%). No analysis is reported in this study of the potential interaction of concomitant medications.

Efficacy Results
Efficacy results for study 118 are found in Appendix 7.2.2. Comparisons include the mean changes in Y-BOCS, NIMHOCS, CGI severity and CGI improvement scales and a table showing relative clinical progress of patients at week 12 as measured by the NIMHOCS. In the LOCF dataset, decreases in YBOCS total score in the paroxetine group at week 8 were in the trend range (p=0.08). Decreases relative to placebo in the clomipramine group at weeks 6, 8, 10, and 12 were statistically significant (p<0.009). At

weeks 8 and 10, the mean change in YBOCS total score in the paroxetine group was significantly less than the change in the clomipramine group ($p<0.03$). In the observed cases data set, the change in YBOCS total score in the paroxetine group at week 8 was statistically significant relative to placebo ($p= 0.02$); however, this superiority did not persist.

The NIMHOCS LOCF dataset changes in the paroxetine group were not statistically significant relative to placebo at any visit except for borderline significance at week 8 ($p=0.051$). The changes in the clomipramine group at weeks 2, 3, 6, 8, 10, and 12 were statistically significant relative to placebo ($p<0.02$). In the OC dataset, paroxetine was superior to placebo at Week 8 ($p= 0.026$) with a trend at Week 10 ($p= 0.075$). At Week 12, the difference was not statistically significant.

Changes in CGI Severity of Illness scores (extender data set) in the paroxetine group were not statistically significant relative to placebo at any visit. The change in the clomipramine group at weeks 8 and 12 were statistically significant relative to placebo ($p= 0.031$ and 0.014). In the observed cases data set, the change in CGI Severity of Illness score in the paroxetine group showed a trend relative to placebo at week 8 ($p=0.093$) and, by week 12, the change was significant ($p=0.041$). In the clomipramine group, changes at weeks 8 and 12 were statistically significant relative to placebo ($p<0.01$).

In the extender data set, the CGI Global Improvement score in the paroxetine group was significantly less relative to placebo at weeks 8 and 12 ($p<0.05$). In the clomipramine group, scores at weeks 3, 8 and 12 were statistically significant relative to placebo ($p<0.01$). Similar results were obtained in the observed cases data set.

Conclusions
Study 118 did not offer convincing evidence that paroxetine was better than placebo in the treatment of OCD. Three of the four measuring scales using either extender or observed case data sets failed to show significant differences from the placebo group. Clomipramine, the active control, was significantly better than placebo on all measures.

The sponsor examined various baseline characteristics to see if there were treatment interactions between age, sex, duration of disease, and baseline severity of OCD which might explain the inadequate response in the paroxetine group. Since the paroxetine group mean age was 5 years older than the placebo or clomipramine, and it contained more patients with a longer duration of illness, it might seem that the improvement in in this group might be lower due to these patients having a more resistant form of the disease. This was not, however, borne out by the sponsor's analysis. The mean effect size in the

paroxetine patients with longer durations of OCD (>5 years) was numerically higher than the effect size for similar patients in the clomipramine group. Also, the fact that the placebo response in this study was greater than in studies 116 and 136 may have contributed to the lack of statistically significant comparisons in this study; nonetheless, clomipramine's effect size was large enough to outstep this greater placebo response.

This, therefore, represents a negative outcome in a trial paroxetine's efficacy in the treatment of OCD.

7.2.
Inv / Sites
Thi .4 center, multi-national, non-US study. The prin investigators and sites are listed in Appendix 7.2.3.

Objectives
Study 136 was designed to demonstrate the effectiveness and safety of paroxetine in the treatment of OCD over a 12-week period.

Population
A total of 406 patients were enrolled in this study. Patients were generally healthy, had no history of psychotic disorders or bipolar disorder, and took no psychotropic agents except the study medications, chloral hydrate, or a few selected benzodiazepines. For a complete list of the inclusion/exclusion criteria see Appendix 7.2.3.

Design/Assessments
This was a 12-week, multicenter, randomized, double-blind, parallel group study of paroxetine, clomipramine and placebo (2:1:1 randomization ratio) for the treatment of outpatients with DSM-III-R OCD. Patients returned to the clinic at the end of two weeks of the placebo run-in period and their compliance in taking study medication was assessed. If patients still met the inclusion and exclusion criteria, they were randomized to one of the three treatment groups and a supply of double-blind medication was dispensed.

Patients took two capsules in the morning and two in the evening, on both occasions with food. Capsules were taken orally. During the placebo run-in phase, all capsules were of placebo. During the double-blind phase of the study, active paroxetine capsule(s) were taken only in the morning and active clomipramine capsules were taken both morning and evening (except for week 1 when they were taken only in the evening).
Patients started treatment with either paroxetine (10mg daily, increasing to 20mg daily after three days), clomipramine (25mg daily, increasing to 50mg daily after three days) or placebo. They returned to the clinic at the end of the first week (day 7) when the dose of study medication remained at 20mg daily in the paroxetine group and 50mg daily in the clomipramine group. At the end of the second week they returned again to the clinic (day 14) when the dose of study medication could be increased (in the paroxetine group to 30 mg daily and in the clomipramine group to 100mg daily). At the visits at the end of 3, 4, 6, 8 and 10 weeks of treatment, the dose of study medication could be increased or decreased. The maximum possible dose of clomipramine was 250 mg/day and the maximum dose of paroxetine was 60 mg/day. The investigator made a decision on whether or not to increase or decrease the dose of study medication on the basis of the efficacy index of the CGI or by the patient's

individual tolerence.

Appendix 7.2.3 outlines the schedule of assessments and medication dosing. Assessments of efficacy included the Y-BOCS, NIMHOCS, CGI-Severity and CGI-Improvement scales.

Analysis Plan
The efficacy ITT consisted of patients who had been randomized to treatment, received their randomized treatment, and for whom at least one assessment (either efficacy or safety) was available during the double-blind treatment period. The treatment groups were to be compared for the following primary efficacy variables:
-change from baseline in Y-BOCS total score.
-proportion of patients with a ≥25% reduction in total Y-BOCS from baseline.
-change from baseline in NIMHOCS score.

The following statistical tests were used:
-continuous efficacy variables were analysed using ANOVA with factors treatment, country and treatment-country interaction. Least squares means for each pair of treatments were compared.
-Categorical variables were analysed using Cochran-Mantel-Haenszel chi-square tests adjusting for country, and pairwise comparisons made. Breslow-Day tests for homogeneity of the odds ratio were used to test for homogeneity over countries for binary data.

The significance of the treatment by country interaction was reported for the primary variables. Due to the large number of reporting centers, centers were grouped by country for the analysis, as follows: Belgium, France, Germany/Holland, Italy/Spain, Israel, Sweden, UK/Canada. The analysis in the original submission was weighted for treatment-by-country interactions; by request of the Division of Biometrics, the efficacy data was re-analyzed by the sponsor.
The requested model included effects for treatment, country, treatment-by-country interaction in a manner such that the result of the analysis was unweighted. based on cell size.

Baseline Demographics
Group demographic characteristics age, sex and race are outlined in Appendix 7.2.3. There were no significant differences in sex and race by Fisher's Exact Test (α=0.05). Inter-group mean age comparisons showed no differences.

Patient Disposition
Of a total of 406 enrolled patients, 205 were randomized to the paroxetine group, 101 to the clomipramine group, and 100 to the placebo group. The efficacy ITT population comprised 201 in the paroxetine group, 99 in the placebo group, and 99 in the clomipramine group. In the paroxetine group, 152 patients (76%) completed the study, compared with 60 patients (61%) in the

placebo group and 64 patients (65%) in the clomipramine group. The number (percent) of the ITT, by treatment group, in-study over time is depicted in Appendix 7.3.2.

Baseline Illness Severity
Visual inspection revealed no notable differences between groups with respect to mean scores on the Y-BOCS, NIMHOCS, or CGI-severity at baseline.

Dosing Information
Mean dose by visit data for completers over time is presented in Appendix 7.2.3. During the final four weeks of the trial, paroxetine completers were receiving, on average, a dose of about 50 mg/day and clomipramine patients about 170 mg/day.

Concomitant Medication
Chloral hydrate (or triazolam or temazepam if chloral hydrate was ineffective) for sleep was the only concomitant psychotropic medication allowed during the study. No other psychotropic medication was permitted. There were 16 patients who took prohibited concomitant medication and were considered protocol violators: 7 paroxetine patients (3%), 5 placebo patients (5%), and 4 clomipramine patients (4%). Concomitant medications for the 7 paroxetine violators[1] were reviewed: these were generally sedative-hypnotic agents other than those allowed, with the exception of one patient who took amitriptyline on Day 74 only.

Efficacy Results
Efficacy analysis by visit for Y-BOCS, NIMHOCS, CGI-Severity and CGI-Improvement scales are listed in Appendix 7.2.3. Comparisons also include a table showing relative clinical progress in patients at week 12 as measured by the NIMHOCS. Both paroxetine and clomipramine show statistically significant improvement over placebo from the 6-week evaluation through the end of the 12-week study using the Y-BOCS, NIMHOCS, CGI-Severity and CGI-Improvement scales in the LOCF dataset. The observed cases dataset shows that neither paroxetine nor clomipramine were significantly effective using the Y-BOCS or NIMHOCS. The CGI-severity and improvement scales showed significant improvement for clomipramine but not for paroxetine at weeks 10 and 12. The sponsor analyzed for treatment by country effect and found no effect.

Conclusions
This 64 center, non-US study of efficacy of paroxetine compared to placebo and clomipramine found paroxetine to be significantly effective compared to placebo and equivalent to chlomipramine in the treatment of OCD.

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[1]Patients (by site#.patient#): 6.0317, 22.0352, 23.0122, 30.0519, 43.0191, 54.0082, 78.0447.

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

The sponsor's subgroup analyses of efficacy based on severity of OCD and demographic subgroups of patients with OCD indicated no significant effect of these covariates on therapeutic response in the LOCF dataset, with respect to the Y-BOCS.

7.3.2 Size of Treatment Effect

This evaluation of treatment effect size will focus on the 40mg and 60mg dose groups of Study 116 and on Study 136, in particular, on the change from baseline in the Y-BOCS, NIMHOCS, and CGI-severity scores among completers at the final (Week 12) visit. The unadjusted changes* and placebo-adjusted changes** are summarized in **Table 7.3.2** below, which includes corresponding efficacy data clomipramine in Study 136, as well as for the last approved drug for OCD, fluvoxamine.

Table 7.3.2:
Summary of Treatment Effect Sizes

TX Group	Y-BOCS		NIMHOCS		CGI-Severity	
	Unadj.	Adj.	Unadj.	Adj.	Unadj.	Adj.
116-par40mg	-6.8	-3.3	-2.3	-1.5	-.9	-.6
116-par60mg	-8.0	-4.5	-2.4	-1.6	-.9	-.6
136-parox	-8.6	-2.7	-2.8	-1.1	-1.4	-.5
136-clomip	-9.1	-3.2	-3.0	-1.3	-1.4	-.5
5529-fluvox	-5.8	-4.0	-2.0	-1.2	N/A	N/A
5534-fluvox	-5.2	-3.5	-1.7	-1.2	N/A	N/A

* Calculated as: (Mean score at final visit) minus (Mean baseline score).
** Calculated as: (Mean active drug change from baseline) minus (Mean placebo change from baseline).

Paroxetine performed about the same as the clomipramine control in 136

and slightly better than fluvoxamine; however, with respect to the change in the Y-BOCS and NIMHOCS in the pivotal trials which supported the approval of clomipramine, paroxetine did worse than clomipramine (10 point drop in the Y-BOCS and 3.5 point drop in the NIMHOCS versus minimal placebo change, according to Anafranil labeling).

Overall, although the treatment effect sizes are not striking, they can be considered to represent notable clinical improvement.

7.3.3 Choice of Dose

Based on the one fixed dose study (116), the minimum effective dose of paroxetine in the treatment of Obsessive-Compulsive Disorder is 40mg, and the effective dose range for paroxetine is 40mg to 60mg. The 20mg group did not show consistent improvement over placebo in this study. However, both the 40 mg/day and 60 mg/day paroxetine treatment groups were significantly better than placebo at numerous timepoints for all variables examined in both the LOCF and OC datasets.

There were no significant differences between the 40 and 60 mg/day dose groups via pairwise comparisons. Nonetheless, when mean change from baseline in the Y-BOCS was tested for linearity over all dose groups, there were highly significant linear relationships ($p < 0.001$) in both the LOCF and OC datasets at Weeks 8, 10, and 12. Thus, it is felt that some patients who demonstrate an inadequate response at 40 mg/day may benefit from an increase in dose up to a maximum of 60 mg/day.

7.3.4 Duration of Treatment

There are no well-controlled trials of paroxetine in the treatment of OCD longer than 12 weeks in duration. Thus, no definitive statement can be made regarding the efficacy of paroxetine in the long-term treatment of OCD.

7.4 Conclusions Regarding Efficacy Data

Table 7.4. summarizes the efficacy results for the three pivotal OCD studies at week 12 in these three 12 week studies.

Clearly, the 40mg and 60mg dose groups in the fixed dose trial (116) showed highly significant improvement over placebo for all variables; the 20mg group was not significantly better than placebo in this trial.

Table 7.4 Summary of efficacy results for pivotal OCD trials program (significance of drug/placebo comparisons for mean change from baseline at week 12)[1].

Study	Active Drug Group	Y-BOCS		NIMHOCS		CGI-Severity		CGI-Improvement	
		LOCF[2]	OC[2]	LOCF	OC	LOCF	OC	LOCF	OC
116	PAROXETINE 20 mg	NS	NS	TR	NS	NS	NS	NS	NS
	PAROXETINE 40 mg	**	**	**	**	**	**	**	**
	PAROXETINE 60 mg	**	**	**	**	**	**	**	**
118	PAROXETINE	NS	NS	NS	NS	NS	*	*	*
	CLOMIPRAMINE	**	*	**	**	*	*	**	**
136	PAROXETINE	**	*	**	**	**	*	**	*
	CLOMIPRAMINE	**	*	**	**	*	TR	**	**

1. Significance codes: **=very significant ($p<0.01$)
* =significant ($0.01 \leq p<0.05$)
TR=trend toward significance ($0.05 \leq p<0.10$)
NS=not significant ($p \geq 0.10$)

2. LOCF=Last observation carried forward. OC=Observed cases.

In 118, although paroxetine was superior to placebo on the global measures, it failed to demonstrate superiority on the symptom-specific measures (Y-BOCS and NIMHOCS). Clomipramine showed superiority over placebo on all measures. Thus, this must be considered a negative study. This finding cannot be attributed to an excessive number of dropouts, inadequate dosing, or duration of illness. It is possible that there was a problem in randomization, as signaled by the mean age in the paroxetine group being substantially higher than that in the placebo and clomipramine groups (41.3 vs. 36.3 vs. 36.0, respectively). However, age itself does not appear to be the critical factor and it is unlikely that the responsible covariate could be identified, from a practical point of view.

Study 136 provided strong evidence supporting the efficacy of paroxetine in the treatment of OCD, with efficacy paralleling that of clomipramine, on average.

In summary, of the three pivotal studies, two support and one refutes the efficacy of paroxetine in the treatment of OCD. This pattern of study outcomes is unexpected, that is, a positive trial (136) with an unusually large number of centers which was conducted in numerous countries and a negative finding in a domestic study (118) with a much smaller number of centers. Nonetheless, the preponderance of evidence is that paroxetine is effective in the treatment of OCD at a minimum dose of 40 mg/day.

8.0 Safety Findings

8.1 Methods

The basic approach to examining the safety of paroxetine in the treatment of OCD in the pivotal OCD studies included 1) an exploration of the pivotal OCD database for adverse events at the more serious end of the nonserious/serious continuum in order to identify the more important adverse experiences associated with paroxetine use and 2) an evaluation of the routinely collected safety data in order to describe the common adverse event profile for paroxetine in an OCD population. The search for the more serious events included an evaluation of dropouts due to adverse events (**Section 8.3**), and an evaluation of any other events identified by the sponsor as "serious" (**Section 8.4**). The evaluation of routinely collected safety data (**Sections 8.5.1-8.5.4**), in addition to providing a basis for describing the common adverse event profile, was also utilized to identify serious adverse events. Data regarding withdrawal phenomena and abuse potential are presented in **Section 8.5.6**. Human reproduction experience is summarized in **Section 8.5.7**. Data pertinent to paroxetine overdoses is discussed in **Section 8.5.8**. A summary of those adverse experiences considered to be both important and possibly/probably related to paroxetine use is provided in **Section 8.6**; serious events considered unlikely to be drug-related are displayed in **Section 8.7**. Drug-demographic, drug-disease, and drug-drug interactions are described in **Section 8.8**.

These safety findings are based on the pivotal trials population sample, with a treatment group distribution, in terms of both number of patients (N) and exposure in patient-years, as follows:

Drug	N	Patient-years
Paroxetine	542	109
Clomipramine	181	33
Placebo	265	53

8.2 Deaths

There were no deaths reported from any of the three studies in the OCD clinical trial program either during treatment or during the period 30 days post study up to the clinical cut-off of December 10, 1993.

In addition, no deaths in the extended treatment protocols for OCD (protocols 126, 127, and 241) were reported up through May 31, 1994.

8.3 Assessment of Dropouts

8.3.1 Overall Pattern of Dropouts

The table below provides an enumeration of subjects who prematurely discontinued treatment in the OCD integrated clinical trial data base, categorized on the basis of the investigator's judgement regarding the single most important reason for withdrawal.

Table 8.3.1:
Rates of Dropout by Treatment Group and Reason: Integrated OCD Database, Studies 116, 118, and 136.

	Patients Dropping Out n(%)		
Reason for Dropout	Paroxetine n=542	Placebo n=265	Clomipramine n=181
Lack of Efficacy/Relapse	23 (4.2)	29 (10.9)	5 (2.8)
Adverse Events[1]	64 (11.8)	21 (7.9)	34 (18.7)
Lack of Compliance	15 (2.8)	7 (2.6)	5 (2.8)
Patient Lost to Follow-up	18 (3.3)	8 (3.0)	10 (5.5)
Patient Improvement	2 (0.4)	2 (1.1)	3 (1.7)
Other Reasons	9 (1.7)	7 (3.9)	9 (5.0)
Total Dropouts	131 (24.2)	74 (27.9)	66 (36.5)

8.3.2 Adverse Events Associated with Dropout

Almost 12% (64/542) of the paroxetine treated patients in the pool of these studies dropped out, at least in part, due to an adverse event. Table 8.3.2 lists adverse events that led to premature discontinuation of treatment at an incidence of at least 1% in the paroxetine group. These were defined as all adverse events that were treatment emergent and followed by the action "drug withdrawn" in the CRF.

[1]This row combines patients who were designated by the investigators as dropped out due to an "adverse event" and those who dropped out due to "lack of efficacy and adverse events".

Table 8.3.2

Summary of Treatment Emergent Adverse Experiences Leading to Dropout-all studies.

Body System Preferred Term	Paroxetine N=542 n %	Clomipramine N=181 n %	Placebo N=265 n %
Body as a Whole			
Asthenia	10 (1.9)	2 (1.1)	1 (0.4)
Digestive System			
Nausea	10 (1.9)	8 (4.4)	0 (0.0)
Constipation	6 (1.1)	4 (2.2)	0 (0.0)
Nervous System			
Insomnia	9 (1.7)	5 (2.8)	0 (0.0)
Dizziness	8 (1.5)	5 (2.8)	0 (0.0)
Urogenital System*			
Abnormal ejaculation	7 (2.1)	1 (1.0)	0 (0.0)
Impotence	5 (1.5)	3 (2.9)	0 (0.0)

* Percentages corrected for gender

All of the above events occurred at a rate of at least 1% in the paroxetine group and at least twice the placebo rate. For all but two of these adverse experiences (asthenia and abnormal ejaculation) the incidence was greater for clomipramine than either paroxetine or placebo.

For comparison, in a larger pool of subjects exposed to paroxetine in the safety data base for the depression NDA 21% (881/4,126) of subjects taking paroxetine discontinued treatment due to adverse events. The most common adverse events leading to withdrawal were nausea, somnolence, insomnia, asthenia, and abnormal ejaculation. In the OCD database, dropouts due to adverse events represented 11.8% of the subject group, a much lower incidence than the depression group.

8.4 Safety Findings Discovered with Other Specific Search Strategies

8.4.1 Serious Adverse Events

The FDA defines serious adverse events as fatal, life threatening, permanently disabling, congenital anomalies, overdoses, cancers, or requiring hospitalization. Of the 542 patients randomized to the paroxetine group in the three studies there were 10 adverse events reported as serious by the FDA definition during the study; one of these patients never received paroxetine. There were another 13 serious adverse events reported in the post-trial treatment extensions. Serious adverse events that are judged by the reviewer as being possibly or probably related to paroxetine will be discussed in the following

subsections of this safety review. Events that were not related to paroxetine are listed in tabular form in the appendix to section 8.7.

8.4.2 Search for Emergence of Suicidality

The paroxetine OCD clinical trials database was analyzed for the emergence of suicidal ideation during treatment. This analysis was similar to the analysis performed on the paroxetine depression clinical trials database in 1991. The following variables were examined:

1) Frequency of completed suicides.
2) Frequency of suicidal ideation reported as an adverse event.
3) The paroxetine mean changes from baseline on the suicide items of the Hamilton Depression Rating Scale (HAMD) and the Montgomery Asberg Depression Rating Scale (MADRS) compared with placebo and clomipramine during treatment.
4) The emergence of suicidal ideation in the paroxetine group as measured by the HAMD and MADRS during therapy compared with placebo and clomipramine groups
5) The differential effect of paroxetine and clomipramine on the suicide item and the retardation item of the HAMD compared with placebo.

All patients in the safety ITT population were considered. The MADRS was only available on patients in study 136. The HAMD was only available on patients in studies 116 and 118. Analysis was performed on observed cases only.

Results from the above comparisons are as follows:

1) There were no completed suicides in any group in the combined database.

2) The saftey database was searched by the sponsor for any term with a character string "SUIC". The verbatim terms: passive suicidal thoughts; suicidal ideation; suicidality; suicidal gesture; suicidal; suicidal risk; suicide attempt; suicide attempt by drugs; suicidal ideas. Only 8 reported patients reported adverse events which were suicide related. The incidence of suicidality reported as an adverse event was 0.74%(n=4) in the paroxetine group compared to 1.66%(n=3) in the placebo group and 0.38%(n=1) in the clomipramine group. There was not a statistically significant difference between these reporting rates.

3) In studies 116 and 118 the mean change from baseline in item 3 of the HAMD showed small but statistically significant increase in the item 3 score change in the placebo versus the paroxetine group (see Table 8.4.2.1).

Table 8.4.2.1 HAMD Suicide Item (Item 3): Baseline and mean change from baseline at week twelve in studies 116 and 118, pooled: observed cases.						
	Parox	Placebo	Clomip	Pairwise Comparisons (p)		
	N=289	N=146	N=64	Par v Pla	Par v Clo	Clo v Pla
Baseline	0.22	0.14	0.19	-	-	-
Change at Week-12	-0.04	0.05	-0.06	0.038	0.663	0.063

Comparison of baseline versus visit-wise MADRS suicide item scores in study 136 always showed mean numerical improvement in the paroxetine group over the placebo group. Some visits were statistically significantly better than placebo; however, the improvements were small and the clinical significance is unclear.

Table 8.4.2.2 MADRS Suicide Item: Baseline and change from baseline at week twelve in study 136, observed cases.						
	Parox	Placebo	Clomipramine	Pairwise Comparisons (p)		
	score (N)	score (N)	score (N)	Par v Pla	Par v Clo	Clo v Pla
Baseline	0.66 (198)	0.67 (99)	0.50 (94)			
Change at Week-12	-0.39 (147)	-0.29 (62)	-0.20 (64)	0.62	0.20	0.45

4) The effect of paroxetine on the emergence of suicidal ideation was measured by the HAMD and MADRS during therapy compared with placebo and clomipramine in the following ways. "Emergence of suicidal thoughts" was defined as those patients who had a baseline score of 0-1 on the HAMD or MADRS suicide item and who went on to have $\geq$3 on the HAMD or $\geq$4 on the MADRS at any time during treatment. Three (1.1%) paroxetine patients (N=276) experienced emergent suicidal ideation by this criteria while no placebo (N=142) or clomipramine patients (N=63) met this criteria in studies 116 and 118, pooled, using the HAMD (p=0.55 Wilcoxon rank-sum test). In study 136, one paroxetine patient (0.6%, N=169), four placebo patients (4.8%, N=83) and 1 clomipramine patient (1.1%, N=83) experienced emergent suicidal ideation as defined above using the MADRS. In study 136, the paroxetine group had significantly lower incidence of emergent suicidality than placebo (p=0.04).

5) Improvement in psychomotor retardation prior to improvement to suicidal ideation can lead to an increase in suicidal behavior. To measure this potential effect the HAMD suicide item

(item 3) was compared to the psychomotor retardation item (item 8). If the suicide item score was at least two points greater than the retardation item at any time during therapy the patient was considered "at risk". If patients had a difference >1 at baseline, subsequent differences had to exceed the baseline difference for that patient to be considered at risk. Nine paroxetine patients (3.1%), 2 placebo patients (1.4%), and 1 clomipramine patient (1.6%) met the at risk criteria (comparison of paroxetine vs placebo via Wilcoxon rank-sum test p=0.35). This analysis revealed no significant increased risk of emergent suicidal ideation or risk of attempt due to paroxetine treatment over placebo treated patients with OCD.

8.4.3 Search for Emergence of Hostility and Aggression
The effect of study treatment on the mean change from baseline in the Hostility Factor of the Hopkins Symptom Checklist (SCL) was examined.

In study 116, there was neither a significant improvement nor exacerbation of hostility as measured by the SCL Hostility Factor for paroxetine versus placebo during the trial.

In study 118, in the extender case dataset, improvement was greater in the paroxetine group compared to placebo at weeks 4, 8 and 12 for the SCL Hostility Factor. The observed cases dataset showed improvement at weeks 4 and 8 but there was no difference from the placebo group at week 12.

In study 136 there were no significant differences between baseline and visitwise SCL Hostility Factor scores.

In conclusion, there is no evidence that paroxetine induced treatment emergent hostility and aggression.

8.5 Other Safety Findings

8.5.1 Adverse Event Incidence Tables

Appendix 8.5.1.1 displays the adverse events which occurred at an incidence of at least 1% in patients receiving paroxetine during clinical trials 116, 118, and 136.

Common and Drug-Related Events

As an indication of which events were common and likely to be paroxetine related, those adverse events with an incidence among paroxetine patients of ≥5%, and an incidence at least twice that among placebo patients, were selected from the pooled OCD clinical trials database shown above: these are displayed in Table 8.5.1.1 below.

Table 8.5.1.1:
Common and paroxetine related adverse events in the OCD Database

	Paroxetine	Clomipramine	Placebo
Body System Preferred Term	n=542 %	n=181 %	n=265 %
Digestive System			
Nausea	23	25	10
Dry Mouth	18	51	9
Constipation	16	27	6
Decreased Appetite	9	7	3
Nervous System			
Somnolence	24	24	7
Dizziness	12	29	6
Tremor	11	32	1
Skin/Appendages			
Sweating	9	25	3
Urogenital System			
*Abnormal Ejaculation	23	19	1
*Impotence	8	9	1

*Corrected for sex.

It is possible to compare the common drug related adverse events to similarly derived lists of adverse events from other patient diagnostic groups. The table below shows the common paroxetine related adverse events (as defined above) for the depression and

OCD patient groups.

Table 8.5.1.2:
Comparison of common and paroxetine related symptoms in depression and OCD patient groups.

Adverse Event	OCD %	Depression %
Asthenia	22	15
Insomnia	24	13
Nervousness	8	5
Somnolence	24	23
Abnormal Ejaculation	23	13
Nausea	23	26
Dry Mouth	18	18
Constipation	16	14
Dizziness	12	13
Tremor	11	8
Decreased Appetite	9	6
Sweating	9	11

Other Observed Events
Other events that occurred infrequently (from .1 to 1% regardless of the occurrence rate in the placebo group) are listed below:

Body as a whole: allergic reaction, Cellulitis, facial edema, flu syndrome, malaise, neoplasm.

Cardiovascular: bradycardia,hypertension, hypotension, peripheral vascular disorder, phlebitis, pulmonary embolus, syncope, tachycardia.

Digestive: bruxism, colitis, duodenitis, dysphagia, eructation, gastritis, gastroenteritis, gingivitis, hepatitis, oropharynx disorder, rectal disorder, stomatitis.

Endocrine: testicular disorder

Hemic/Lymphatic: anemia, leukocytosis, leukopenia, lymphadenopathy, monocytosis, purpura.

Metabolic/Nutritional: CPK increased, hypercholesterolemia,

hyperglycemia, hypoglycemia, peripheral edema, SGOT increased, thirst.

Musculoskeletal: arthritis, arthrosis, myasthenia,tendinous disorder, tetany.

Nervous System: alcohol abuse, aphasia, ataxia, confusion, diplopia, dystonia, euphoria, hallucinations, hostility, incoordination, lack of emotion, libido increased, manic reaction, neurosis, nystagmus, paralysis, paranoid reaction, personality disorder, psychosis, reflexes increased, stupor, vertigo.

Respiratory system: bronchitis, dyspnea, epistaxis, hemoptysis, larynx disorder, pleura disorder, pneumonia, sputum increased.

Skin/Appendages: acne, contact dermatitis, eczema, fungal dermatitis, furunculosis, herpes simplex, herpes zoster, seborrhea, skin hypertrophy, sweat gland disorder, urticaria, vesiculobullous rash.

Special Senses: abnormality of accommodation, anisocoria, blephatitis, conjunctivitis, deafness, ear disorder, ear pain, eye disorder, eye pain, glaucoma, keratoconjunctivitis, mydriasis, otitis media, photophobia.

Urogenital System: breast pain, cystitis, dysuria, kidney calculus, leukorrhea, menorrhagia, menstrual disorder, nocturia, penis disorder, prostate disorder, unintended pregnancy, urinary incontinence, urine abnormality, uterine spasm.[2]

Evidence of Dose-relatedness for Certain Adverse Events
Appendix 8.5.1.2 summarizes the adverse experiences by dose level in study 116 (the fixed dose study).

There were no clear dose-response relationships across all dose levels for these adverse events. However, considering the possibility that event incidence may plateau beyond 40 mg/day, one could envision a dose-relationship up to that dose for dry mouth, decreased appetite, nausea, tremor, sweating, and abnormal ejaculation.

The titration regimen used in study 116 to achieve the 60mg dose did not lead to an increase in the frequency of adverse experiences over that seen at 40 mg/day. Thus, the analysis of adverse experiences by dose at onset provides assurance for the tolerability and safety of the 60mg dose.

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[2]All gender related specific terms were statistically corrected for sex.

8.5.2 Laboratory Findings

Protocols for the three 12-week clinical OCD studies required that laboratory parameters be measured at baseline, week 4, 8, and 12. Specific measures include the following:

Hematology	Blood Chemistry
Hemoglobin	Blood Urea
Hematocrit	Blood Urea Nitrogen
White Blood Cells (WBC)	Serum Creatinine
Neutrophils	Total Bilirubin
Lymphocytes	SGOT (AST)
Monocytes	SGPT (ALT)
Basophils	Alkaline Phosphate
Eosinophils	Total Protein
Bands	Albumin
Platelets	Globulin
Segmented Neutrophils	

The assessment below focuses on the pool of patients in these three clinical studies. Laboratory data was examined with repsect to:

1) mean change from baseline.
2) proportion of patients with markedly abnormal values.
3) dropouts due to laboratory abnormalities.

Table 8.5.3.1 lists the critera used to flag patients with potentially clinically significant laboratory values.

Table 8.5.3.1

Criteria used to flag abnormal laboratory values in the OCD clinical database.

Blood Chemistry		
Blood Urea		>10.71 mmol/L
Blood Urea Nitrogen		> 30 mg/dL
Serum Creatinine		> 2 mg/dL
Total Bilirubin		> 2 mg/dL
SGOT (AST)		> 150 U/L
SGPT (ALT)		> 165 U/L
Alkaline Phosphate		> 390 U/L
Total Protein		> 10 g/dl
		< 4.5 g/dl
Albumin		< 2.5 g/dl
Globulin		< 1 g/dl
Hematology		
Hemoglobin	Males	<11.5 g/dl
	Females	< 9.5 g/dl
Hematocrit	Males	< 37%
	Females	< 32%
White Blood Cells (WBC)		< 2.8 or > 16 x 10^3/L

Neutrophils	< 15%
Lymphocytes	> 75%
Monocytes	> 15%
Basophils	> 10%
Eosinophils	> 10%
Bands	> 10%
Platelets	> 700 x 10^9/L
Segmented Neutrophils	< 15%

8.5.2.1 Serum Chemistry

Mean changes from baseline to final visit for chemistry variables are demonstrated in appendix 8.5.2.1. There were no clinically significant changes observed in serum chemistry values.

A display of the number of patients in each group with abnormal lab values is listed in appendix 8.5.2.1. With respect to clinical (blood) chemistry, generally very few patients (0-2%) had values of potential clinical concern in any of the three treatment groups. The greatest percentage of patients flagged in the paroxetine group was for urea where 3 (2%) of patients were flagged.

Comparable mean changes and comparable proportions of patients with laboratory values of potential clinical concern were seen across all treatment groups.

Three patients withdrew due to an abnormal laboratory finding, of whom two were on paroxetine. All patients were withdrawn due to abnormal liver function tests, one patient was diagnosed as having hepatitis A. The two paroxetine patients are described below.

Patient number 116.005.0018 was a 24 year old male who was assigned to receive 40mg paroxetine. After 2 months of this treatment, the patient developed elevated ALT (baseline= 15; day-57= 107) and AST (baseline= 31; day-57= 228) and was withdrawn from the study. Two months after withdrawal from the study, liver function test values had returned to normal. The investigator reported these findings as probably related to study medication.

Patient number 136.035.0262 (paroxetine) was withdrawn due to abnormal liver function test values. This adverse experience was regarded as serious. The patient was a 54 year old female who had been receiving paroxetine 40mg for 5 days when she developed jaundice and elevated transaminases. Viral screening revealed hepatitis A infection. The investigator considered all of the events to be unrelated to study medication (although hepatitis was elsewhere initially reported as probably related). This adverse experience was continuing at the end of the study.

8.5.2.2 Hematology
With respect to hematological parameters, the greatest number of paroxetine patients with flagged values for any single parameter was 9 (2%) for eosinophils, and 2 of these patients were flagged at baseline. Generally, the numbers of patients flagged for any hematological parameter for any treatment group was extremely small, ranging from 0 - 2%.

Comparable mean changes and comparable proportions of patients with laboratory values of potential clinical concern were seen across all treatment groups.

There were no dropouts due to hematology abnormalities.

All-in-all, there were no hematologic data that indicated safety concerns in the OCD database.

8.5.2.3 Urinalysis
Urinalysis data was not addressed in the Integrated Summary of Safety. Urinalysis data is not available for study 136. Studies 116 and 118 present partial urinalysis data. There are no reported dropouts or serious adverse events due to urinalysis values in any study.

8.5.3 Vital Signs

The following vital signs were measured in each of the twelve-week studies in OCD:

- systolic blood pressure
  - -lying or sitting (after 3 minutes)
  - -standing (after 1 minute)
- diastolic blood pressure
  - -lying or sitting (after 3 minutes)
  - -standing (after 1 minute)
- pulse rate-lying or sitting
  - -standing
- weight

Pulse rate and blood pressure data was evaluated in three ways:

Firstly, patients were flagged if their vital signs were outside a prespecified range and changes from baseline exceeded pre-determined changes indicating levels of potential clinical concern. Table 8.5.3 shows these pre-determined criteria for potential clinical concern.

Table 8.5.3
Vital Signs and Weight Ranges for the Flagging of Values of Potential Clinical Concern

Variable	Normal Range	Threshold
Diastolic Blood Pressure (mmHg)	50 - 105	- 20, + 30

Systolic Blood Pressure (mmHg)	90 - 180	- 30, + 40
Pulse Rate (beats per minute)	50 - 120	- 30, + 30
Weight (change from baseline)		± 7%

Secondly, mean changes from baseline for all parameters were calculated for each treatment group, i.e., paroxetine, clomipramine and placebo.

Third the data were examined for dropouts due to abnormal vital signs.

In the analyses of both mean vital sign parameters and changes of potential clinical concern, a single baseline value was identified for each vital sign parameter for each patient. If a patient had more than one pre-treatment observation then the pre-treatment observation closest to the day of the first dose of randomized medication was considered the baseline value.

Appendix 8.5.3 displays the numbers of patients who were flagged for vital signs in the range of potentially clinically significant. Also displayed is a tabulation of mean change from baseline to last visit for vital sign variables. The proportions of patients with potentially clinically significant vital signs were comparable among the treatment groups. Mean changes in vital signs of paroxetine patients were not clinically significant.

No paroxetine patients were withdrawn due to abnormal vital signs.

8.5.4 ECGs
There was no analysis of the effects of paroxetine on ECG findings in the pooled OCD data. No clinically significant changes were seen in the ECGs of paroxetine and placebo treated patients in the premarketing studies of paroxetine for depression.

8.5.5 Special Studies
A pharmacodynamic study was designed to examine the effect of paroxetine on bleeding time, 29060/110[3]. This study was designed to investigate whether the 5-HT depleting effect of paroxetine in human platelets has any effect on the bleeding time in healthy volunteers. 20 volunteers (16 male and 4 female) were equally divided into 2 groups, one of which received placebo for 28 days and the other paroxetine 40 mg od for 21 days, after an initial 7 day titration period from 10 to 40 mg. Bleeding times, using a validated Simplate device, were determined on Days 1, 28,

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[3]29060/110, Link MH, A double-blind placebo controlled study to assess the effects of paroxetine on the bleeding time of volunteers. (Individual study report).

(predose and 4 hr postdose) and 42, where Day 1 was the first day of dosing. In addition, prothrombin time, activated partial thromboplastin time and ADP/collagen induced platelet aggregation were measured. No statistically significant effects were seen on any of the measured parameters with the exception of a small decrease in bleeding time with paroxetine (p=0.028) on day 28, although the change was too small to be of potential clinical concern.

8.5.6 Abuse Potential/Withdrawal Phenomenon
Paroxetine is not a controlled substance. Paroxetine has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. The sponsor reports that while the pre-marketing clinical experience and post-marketing experience in over 2.5 million patients treated with paroxetine did not reveal any tendency for any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted and/or abused.

There have been spontaneous reports that abrupt discontinuation may lead to symptoms such as dizziness, sensory disturbance, agitation or anxiety, nausea or sweating; these events are generally self-limiting.

8.5.7 Human Reproduction Studies
There are no adequate and well-controlled studies in pregnant women. Pregnancy category C is currently recommended for labeling based on animal data (see section 4.0 Animal Pharmacology) .

The effect of Paxil on labor and delivery in humans is unknown. Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when Paxil (paroxetine hydrochloride) is administered to a nursing woman.

8.5.8 Overdose Experience
Human Experience - No deaths were reported following acute overdose with paroxetine alone or in combination with other drugs and/or alcohol (20 cases with doses up to 850 mg) during pre-marketing clinical trials for depression and OCD. Since first marketing, there have been 50 validated spontaneous reports of overdose. There have been no validated spontaneous reports of death due to overdose where paroxetine was used alone (up to 2000 mg) .

Symptoms of overdose with paroxetine include nausea, vomiting, drowsiness, sinus tachycardia and dilated pupils. There are no reports of ECG abnormalities, coma, or convulsions following overdosage with paroxetine alone.

Management of Overdose - Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. There are no specific antidotes for paroxetine. Establish and maintain an airway; insure adequate oxygenation and ventilation. Gastric evacuation either by the induction of emesis, lavage, or both, should be performed. In most cases following evacuation, 20 to 30 grams of activated charcoal may be administered every 4 to 6 hours during the first 24 to 48 hours after ingestion. An ECG should be taken and monitoring of cardiac function instituted if there is any evidence of abnormality. Supportive care with frequent monitoring of vital signs and careful observation is indicated. Due to the large volume of distribution of paroxetine, forced diuresis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

8.6 Summary of Potentially Important Adverse Events Considered Drug Related.

8.6.1 Mania/Hypomania

During premarketing testing in the depression NDA, hypomania or mania occurred in approximately 1.0% (39/3992) of Paxil-treated unipolar patients compared to 1.1% (21/1868)of active-control and 0.3% (2/625) of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% (3/134)for Paxil and 11.6% (10/86) for the combined active-control groups. In the 542 patients in the ITT paroxetine treatment group there were no patients with reported mania/hypomania. There was one patient who is in a blinded extended treatment group who was reported to have a hypomanic reaction that lasted 5 days. Treatment was not discontinued nor reduced in dose. The reported hypomania was considered unrelated to the medication by the investigator and was of no consequence. A past manic episode was a criteria for exclusion in the OCD pooled clinical studies. As with all antidepressants, paroxetine should be used cautiously in patients with a history of mania; there appears to be little or no increased risk of mania/hypomania in the OCD patients without a history of mania over placebo treated patients.

8.6.2 Seizure

During premarketing testing, seizures occurred in 0.1% of Paxil treated patients, a rate similar to that associated with other anti-depressants. There were no reported seizures in the combined OCD data base.

8.6.3 Bleeding/Purpura

Preliminary data suggested that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the

face of unaltered prothrombin time) between paroxetine and warfarin. In the spontaneous post-marketing reporting there have been 6 episodes of purpura with thrombocytopenia, 32 cases of bleeding without thrombocytopenia, 7 episodes of gynocologically related abnormal bleeding, and 12 other episodes of miscellaneous bleeding. The relationship of these events to paroxetine is not clear. On the other hand, Study 110 (see Section 8.5.5) suggests no clinically significant effect of paroxetine on bleeding. Nonetheless, on the basis of the spontaneous reports and a report of impaired platelet aggregation in the literature,[4] the sponsor has been asked to change its special precaution section in labeling because of these events:

"Abnormal Bleeding- There have been several reports of abnormal bleeding (mostly ecchymosis and purpura) associated with paroxetine treatment, inclucing a report of impaired platelet aggregation. While a causal relationship to paroxetine is unclear, impaired platelet aggregation may result from platelet serotonin depletion and contribute to such occurences."

There is no information that the risk of purpura/bleeding is increased in the OCD group.

8.6.4 Sexual Dysfunction

Abnormal ejaculation was identified as the most reported sexual dysfunction in the current paroxetine labeling (13% in males). 23% of males in the pooled OCD database reported abnormal ejaculation (compared to 18% with clomipramine and 1% with placebo). Abnormal ejaculation caused the greatest percentage of withdrawals in the paroxetine group at 2.1% (corrected for gender), n=7 patients. In no case of withdrawal due to this adverse experience was the experience classified as serious. Analysis of the occurence of this adverse event by dose revealed no significant relationship between dose and abnormal ejaculation.

Also, Appendix 8.5.1 identifies impotence, other females disorders, and vaginitis as adverse events occurring more often in the paroxetine treated group than in placebo.

There was one dropout due to groin and testicular pain that began 4 days after the start of paroxetine treatment. This adverse event led to discontinuation of treatment with subsequent abatement of groin and testicular pain. Priapism is a rare but serious adverse event associated with antidepressants that influence the serotonin system. Whether or not this adverse event represents a variant of priapism is not evaluatable.

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[4]Ottervanger JP, et al. Bleeding Attributed to the Intake of Paroxetine [letter]. Am J Psychiatry 1994; 151(5): 781-782.

8.6.5 Weight Change

The majority of vital signs flagged as potentially clinically significant in the pooled OCD database were changes in weight (±7%). Of the 542 paroxetine treated parients, 11 reported weight gain and 13 reported weight loss. In no case did a change in weight lead to premature withdrawal from the study.

8.6.6 Hepatoxicity

Rare cases of severe hepatic dysfunction have been spontaneously reported in association with paroxetine use, to include one case of liver necrosis; a causal relationship to paroxetine is unproven. Section 8.5.2.1 discusses one patient (116.005.0018) from the OCD database with possibly paroxetine-related transaminase elevation, which abated on drug discontinuation. Otherwise, this database suggested no further evidence of hepatoxicity in this population.

8.7 Significant Adverse Events Considered Unrelated to Paroxetine

The search strategy described in section 8.4 identified 24 patients in the OCD pooled database with serious adverse events (paroxetine 10/542; clomipramine 3/181; placebo 11/265). (Patients who clearly experienced a worsening of psychiatric symptoms for which they were treated are not included.) Those events considered unlikely to be related to paroxetine treatment are listed in Appendix 8.7, and includes patients treated in the extended treatment protocols.

8.8 Drug Interactions

8.8.1 Drug-Demographic Interactions

The following demographic subgroups were compared in the combined OCD studies database:
-elderly (>65 years old) vs. nonelderly.
-white vs. non-white.
-less than vs. greater than 72.1 kg in body weight.
-male vs. female groups.

Statistical comparisons revealed no significant drug demographic interactions in the incidence of common and drug related adverse events.

8.8.2 Drug-Disease Interactions

There has been limited clinical trials experience in the use of paroxetine in patients with sytemic illness. Past studies and current labeling indicate that paroxetine clearance is reduced in patients with hepatic or renal impairment. Therefore, caution in the dosing and administration of paroxetine to this population is advised.

8.8.3 Drug-Drug Interactions

Chloral hydrate-Only one study of drug-drug interactions was performed on this database, an investigation of potential drug-drug interactions of paroxetine with chloral hydrate was undertaken in 36 patients who received this combination during treatment for OCD. Overall, no unexpected adverse experiences resulted from the co-administration of paroxetine and chloral hydrate compared with paroxetine without concomitant chloral hydrate. Generally no new adverse experiences, i.e. from the known pharmacology of the drug and from experience with paroxetine in depressed patients, resulted from the co-administration of paroxetine and chloral hydrate compared with paroxetine without concomitant chloral hydrate.

Anticonvulsants-The consequences of co-administration of paroxetine with anticonvulsants was evaluated in a recent study by Andersen[5]. In patients with well-controlled epilepsy, paroxetine was introduced at a dose of 30 mg daily while existing therapy (either phenytoin, sodium valproate or carbamazepine) was continued. At paroxetine steady state, there were no changes either in total plasma drug concentrations or in plasma free fraction of any of the anticonvulsants, no significant adverse events were reported, and no seizures occurred. It was therefore concluded that the combination of paroxetine with these anticonvulsants is safe. There were no emergent seizures in this sample.

When a single oral dose of paroxetine 30 mg was administered at phenytoin steady state (300 mg po qd for 14 days), paroxetine AUC and t1/2 were reduced (by an average of 50% and 35% respectively) compared to paroxetine administered alone. In another study when a single oral dose of phenytoin 300 mg was administered at paroxetine steady state (paroxetine 30 mg po qd for 14 days) phenytoin AUC was reduced (mean 12%)compared to phenytoin administered alone.

Based on previous studies submitted in support of NDA 20-031 the following conclusions were made:

1) The steady-state pharmacokinetics of paroxetine were not altered when administered with digoxin at steady state. Mean digoxin AUC decreased by 15% in the presence of paroxetine.
2) A multiple-dose study has shown that there is no pharmacokinetic interaction between paroxetine and lithium carbonate.
3) Co-administration of MAOI antidepressants and paroxetine should not be undertaken. One case of serotonin syndrome has been reported in a patient who began taking an MAOI three days

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[5]Andersen BB et al., No influence of the antidepressant paroxetine on carbamazepine, valproate and phenytoin. Epilepsy Res 1991; 10: 201-204.

after discontinuing paroxetine. There were also two spontaneous reports of symptoms consistant with neuroleptic malignant syndrome after overdose with paroxetine and MAOI. At least 14 days should elapse between discontinuation of paroxetine and initiation of therapy with an MAOI.
4) Adverse experiences consisting of nausea, headache, sweating, and dizziness have been reported by patients administered tryptophan while taking paroxetine.
5) Co-administration of alcohol and paroxetine is not advised.
6) Paroxetine is metabolized by the $P_{450}IID_6$ enzyme system. Due to the fact that paroxetine inhibits $P_{450}IID_6$ activity, the concomitant use of drugs that are metabolized by this system should be used with caution. Similarly, drugs that inhibit or are metabolized by the cytochrome P_{450} system (such as tricyclic antidepressants, phenothiazines, and type 1C anti-arrhythmics should be used cautiously with paroxetine. Procyclidine usage leads to increases in AUC, Cmax, and Cmin of paroxetine.
7) Phenobarbital induces the metabolism of paroxetine.

9.0 Labeling Review

There are some modifications that may be necessary in the section reviewing adverse events. The sponsor presents a table of adverse events that occurred ≥2% of the time; a table that presents adverse events that occurred ≥1% of the time may be more consistent with current labeling practices. Within the framework of a ≥2% table of reported adverse events it appears that the following adverse events were omitted from that table: **Gastrointestinal:** Dypepsia 4%, Flatulence 3%; **Nervous System:** Anxiety 4%; **Musculoskeletal System:** Myalgia 3%; **Respiratory System:** "Respiratory Disorder" 8%, Pharyngitis 4%. It is unclear what the term "respiratory disorder" means or why the term was deleted from the proposed labeling; the term is of little clinical value in its current form, but a revised table of adverse events that redefines terms like this has not been submitted.

The proposed labeling does not list the following symptoms under adverse events in the infrequent or rare sections that occurred at least one time in the pool of 542 patients with OCD treated with paroxetine: leukocytosis, monocytosis, CPK increased, myasthenia, tendinous disorder, aphasia, confusion, hallucinations, incoordination, neurosis, personality disorder, vertigo, hemoptysis, larynx disorder, pleura disorder, seborrhea, vesiculobullous rash, blepharitis, ear disorder, eye disorder, mydriasis, leukorhea, menstrual disorder, urine abnormality, unintended pregnancy, and uterine spasm. Terms such as "menstrual disorder" are too vague to be clinically useful in labeling. The sponsor was asked to redefine/reassign these terms to clinically useful terms but stated that they were not able to do so.

The warning section of the proposed labeling states that patients should not use MAOI antidepressants and paroxetine concomitantly. In addition to this, MAOIs and paroxetine should not be used within 14 days of each other due to the fact that "In patients receiving another serotonin reuptake inhibitor drug in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on a MAOI." This warning does not include reference to the serotonin syndrome. Serotonin syndrome has been reported in a patient who was taking paroxetine three days prior to starting an MAOI in an IND study.

This proposed labeling suggests pregnancy category B. Recent reviews by DNDP pharmacologists have suggested changing

paroxetine's pregnancy category to C.[1]

10. Conclusions
Two of the three studies that are presented support the sponsor's claim that paroxetine is safe and efficacious in the treatment of OCD. The single negative study presented was well designed as were the positive studies. This reviewer could not detect any significant bias or systematic error in the safety or efficacy analyses.

11. Recommendations
I recommend that paroxetine be approved for the treatment of OCD. Available data does not, however, address two important issues regarding the use of paroxetine in treating OCD:

1) safety and efficacy in a pediatric population.
2) long-term safety and efficacy.

Accordingly, it is recommended that the sponsor commit to taking appropriate action post-approval to adequately address these issues in labeling.

9/5/95
Paul J. Andreason, M.D.
Medical Reviewer
Psychiatric Drug Products Group

cc: NDA 20, 031
HFD-120
HFD-120/GDubitsky
/TLaughren

9-5-95
I agree that this supplement is approvable. See memo to file for more detailed comments.
Thomas P. Laughren, MD
GC, PDP

[1]Memo to Division File for NDA 20-031, January 18, 1995 from Steven Sparenborg, Ph.D.

APPENDICES

STUDY 116

Table 7.2.1.1.1 Investigators and study sites in study 116

Investigator	Center Address
Baxter, Lewis R., Jr., M.D.	NPI/UCLA - Rm. 27-360 760 Westwood Plaza Los Angeles, CA 90024
Black, Donald W., M.D.	Psychiatric Hospital 500 Newton Road Iowa City, IA 52242
Clary, Cathryn, M.D.	Clary Research Associates 1601 Concord Pike, Suite 92-100 Wilmington, DE 19803
Davidson, Jonathan R.T., M.D.	Duke University Medical Center P.O. Box 3812 Dept. of Psychiatry Durham, NC 27710
DuBoff, Eugene A., M.D. Cohn, Richard A., M.D.	Rocky Mountain Psychiatric Center 4704 Harlan Street Suite #430 Denver, CO 80212
Goodman, Wayne, M.D.	Yale University School of Medicine Department of Psychiatry 34 Park Street New Haven, CT 06519
Hollander, Eric, M.D.	New York Psychiatric Institute 722 West 168th Street New York, NY 10032
Jenike, Michael A., M.D.	Mass. General Hospital East Dept. of Psychiatry OCD Clinic Building 149 - 13th Street - 9th Floor Charlestown, MA 02129
Kim, Suckwon, M.D.	Dept. of Psychiatry Hennepin County Medical Center 701 Park Avenue, S. Minneapolis, MN 55415
Kozak, Michael J., M.D., Bianchi, Michael D., M.D., Kavoussi, Richard J., M.D., Kessel, Julie B., M.D.	Medical College of Pennsylvania Department of Psychiatry 3200 Henry Avenue Philadelphia, PA 19129
Mallya, Gopinath, M.D.	McLean Hospital - Harvard Medical School Wyman Bldg. - Room 211 115 Mill Street Belmont, MA 02178
Rasmussen, Steven, M.D.	Butler Hospital 345 Blackstone Boulevard Providence, RI 02906
Schwab, John, M.D. Kennedy, Barbara L., M.D.	University of Louisville Department of Psychiatry & Behavioral Sciences Louisville, KY 40292

Westermeyer, Joseph, M.D., Ph.D., and Tucker, Phebe, M.D.	University of Oklahoma Health Sciences Center Department of Psychiatry & Behavioral Sciences 920 Stanton Young Boulevard Room 5SP463 Oklahoma City, OK 73190
Winter, Gregory, M.D.	Sinai Samaritan Medical Center Good Samaritan Campus - UW Psychiatry 2000 West Kilbourn Avenue Milwaukee, WI 53233

STUDY 116

Inclusion Criteria

- Patient must have met the DSM-IIIR diagnostic criteria for OCD.
- The patient must have had a documented history of OCD for a minimum duration of 6 months.
- The patient must have been at least 16 years old. (All patients less than 18 years old were required to have an additional written informed consent signed by a parent or legal guardian.)
- Patients must have had a baseline score of 7 or above on the NIMHOCS and a baseline score of 16 or above on the Y-BOCS.
- The patient must have had a HAMD score at both the screen and baseline visits of less than or equal to 16 on the first 17 items of the 21-item scale. Furthermore, the response on item 1 of the HAMD Scale must not have exceeded the score of 2.

Exclusion Criteria

- Patients with any Axis I disorders other than OCD.
- Patients with a history of major depressive disorder within the last 3 months.
- Patients with personality disorders of sufficient severity to compromise their participation in and completion of the study.
- Patients with any serious concomitant medical condition.
- Patients with a history of seizure disorders (except for febrile seizures in childhood).
- Patients requiring concomitant therapy with other psychotropic drugs except chloral hydrate (up to 1000 mg) for sleep disturbance.
- Patients who met DSM-IIIR criteria for substance abuse (alcohol or drugs) within the past 6 months.
- Patients having clinically significant abnormal laboratory or ECG findings at the screen (Day -14) or baseline (Day 0) examinations.
- Patients who, in the investigator's judgment, posed a serious suicidal or homicidal risk.
- Patients who had received other investigational drugs within 30 days of baseline (Day 0).
- Patients who had received other psychotropic drugs (including MAO inhibitors) within 14 days of baseline (Day 0).
- Patients who had previously received paroxetine.
- A postive pregnancy test was required.
- Participation in ongoing behavioral therapy (i.e., exposure and response prevention) during the conduct of this study was specifically prohibited by this protocol.

Study: 116

Demographic Characteristics

Treatment Groups	n	Age (years)		Sex [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-White
Parox 20mg	88	40.2	17-78	64 (73)	24 (27)	86 (97)	2(3)
Parox 40 mg	86	42.1	19-73	62 (72)	24 (28)	82 (95)	4 (5)
Parox 60 mg	85	40.0	16-73	70 (82)	15 (18)	80 (94)	5(6)
PLAC	89	43.1	20-73	60 (67)	29 (33)	85 (94)	4(5)

Study: 116

Patient Completion Rates

Treatment Groups	Number Randomized	Intent-to-Treat Sample	Completers [n(%)]					
			Wk3	Wk4	Wk6	Wk8	Wk10	Wk12
Parox 20mg	88	88	81 (99%)	79 (90%)	76 (86%)	75 (85%)	75 (85%)	75 (85%)
Parox 40 mg	86	86	77 (90%)	76 (88%)	75 (87%)	71 (83%)	69 (80%)	66 (77%)
Parox 60 mg	86	85	73 (86%)	71 (84%)	70 (82%)	70 82%)	69 (81%)	66 (78%)
PLAC	89	89	84 (94%)	81 (91%)	79 (89%)	76 (85%)	75 (84%)	74 (83%)

Study: 116
Mean Change from Baseline in Y-BOCS Total Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week													
	BL Mean		Wk3		Wk4		Wk 6		Wk 8		Wk10		12Wk	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Parox 20mg	84	25.9	84	-2.1	84	-2.5	84	-3.4	84	-3.8	84	-4.6	84	-4.0
Parox 40 mg	83	25.4	83	-2.5	83	-4.0	83	-4.7	83	-5.8	83	-6.2	83	-6.3
Parox 60 mg	83	25.3	82	-3.7	83	-4.4	83	-5.6	83	-6.5	83	-7.2	83	-7.2
PLAC	88	25.6	88	-2.4	88	-2.6	88	-2.8	88	-3.1	88	-2.7	88	-3.4
2-sided p-values for pairwise comparisons														
20mg vs PLAC	0.83		0.74 0.77#		0.89 0.88#		0.45 0.46#		0.47 0.56#		0.05 0.02#		0.51 0.46#	
40mg vs PLAC	0.48		0.84 0.88#		0.08 0.18#		0.03 0.10#		0.007 0.02#		<0.001 0.001#		0.004 0.012#	
60mg vs PLAC	0.36		0.09 0.39#		0.03 0.14#		0.002 0.02#		0.001 0.006#		<0.001 <0.001#		<0.001 0.002#	

-OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week													
	Baseline		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Parox 20mg	84	25.6	77	-1.9	81	-2.3	72	-3.6	74	-4.1	69	-4.9	73	-4.1
Parox 40 mg	83	25.4	75	-2.6	76	-4.4	70	-5.3	71	-6.3	65	-6.7	62	-6.8
Parox 60 mg	83	25.3	74	-3.9	72	-4.6	71	-6.1	67	-7.0	68	-7.6	65	-8.0
PLAC	88	25.6	79	-1.9	82	-2.6	76	-2.6	75	-2.9	72	-2.5	73	-3.5
2-sided p-values for pairwise comparisons														
20mg vs PLAC	0.83		0.97 0.82#		0.73 0.82#		0.30 0.52#		0.23 0.47#		0.02 0.02#		0.54 0.78#	
40mg vs PLAC	0.48		0.36 0.46#		0.36 0.46#		0.005 0.04#		0.001 0.003#		<0.001 <0.001#		0.003 0.004#	
60mg vs PLAC	0.36		0.02 0.20#		0.02 0.20#		<0.001 0.01#		<0.001 0.002#		<0.001 <0.001#		<0.001 0.002#	

unweighted analysis

Study: 116
Mean Change from Baseline in NIMHOCS Total Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week													
	BL Mean		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Parox 20 mg	84	9.6	84	-0.7	84	-0.8	84	-1.0	84	-1.1	84	-1.4	84	-1.2
Parox 40 mg	83	9.5	83	-0.6	83	-1.1	83	-1.4	83	-1.6	83	-1.9	83	-2.1
Parox 60 mg	83	9.1	83	-0.8	83	-1.1	83	-1 4	83	-1.6	83	-1.8	83	-2.0
PLAC	88	9.2	88	-0.2	88	-0.4	88	-0.4	88	-0.3	88	-0.5	88	-0.6
2-sided p-values for pairwise comparisons														
20mg vs PLAC	0.410		0.009	0.05#	0.04	0.10#	0.02	0.05#	0.006	0.006#	0.005	0.002#	0.09	0.12#
40mg vs PLAC	0.461		0.03	0.12#	0.001	0.005#	<0.001	<0.001#	<0.001	<0.001#	<0.001	<0.001#	<0.001	<0.001#
60mg vs PLAC	0.254		0.003	0.07#	0.001	0.002#	<0.001	0.002#	<0.001	<0.001#	<0.001	<0.001#	<0.001	<0.001#

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week													
	Baseline		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Parox 20 mg	84	9.6	77	-0.8	81	-0.9	72	-1.1	74	-1.3	70	-1.6	74	-1.4
Parox 40 mg	83	9.5	75	-0.7	76	-1.2	70	-1.6	72	-1.8	65	-1.9	66	-2.3
Parox 60 mg	83	9.1	73	-0.8	72	-1.2	71	-1.6	68	-1.8	68	-2.0	65	-2.4
PLAC	88	9.2	80	-0.2	82	-0.4	76	-0.5	75	-0.4	72	-0.6	73	-0.8
2-sided p-values for pairwise comparisons														
20mg vs PLAC	0.410		0.005	0.05#	0.06	0.10#	0.02	0.05#	0.002	0.006#	0.003	0.002#	0.11	0.12#
40mg vs PLAC	0.461		0.02	0.12#	0.002	0.005#	<0.001	<0.001#	<0.001	<0.001#	<0.001	<0.001#	<0.001	<0.001
60mg vs PLAC	0.254		0.003	0.07#	0.001	0.04#	<0.001	0.002#	<0.001	<0.001#	<0.001	<0.001#	<0.001	<0.001#

Unweighted analysis

Study: 116

Mean Change from Baseline in CGI-Severity of Illness Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week									
	BL Mean		Wk 3		Wk 4		Wk 8		Wk 12	
	n	X	n	X	n	X	n	X	n	X
Parox 20mg	84	4.8	84	-0.3	84	-0.3	84	-0.4	84	-0.5
Parox 40 mg	83	4.8	83	-0.3	83	-0.5	83	-0.6	83	-0.8
Parox 60 mg	83	4.7	82	-0.3	83	-0.4	83	-0.6	83	-0.7
PLAC	88	4.7	88	-0.1	88	-0.2	88	-0.2	88	-0.3
2-sided p-values for pairwise comparisons										
20mg vs PLAC	0.76		0.06 0.34[a]		0.34 0.44[a]		0.17 0.30[a]		0.19 0.28[a]	
40mg vs PLAC	0.86		0.05 0.13[a]		0.009 0.03[a]		0.002 0.01[a]		<0.001 0.001[a]	
60mg vs PLAC	0.52		0.03 0.14[a]		0.04 0.10[a]		0.003 0.009[a]		0.001 0.005[a]	

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week									
	Baseline		Wk 3		Wk 4		Wk 8		Wk 12	
	n	X	n	X	n	X	n	X	n	X
Parox 20 mg	84	4.8	77	-0.3	81	-0.3	67	-0.4	73	-0.5
Parox 40 mg	83	4.8	74	-0.3	76	-0.5	66	-0.6	65	-0.9
Parox 60 mg	83	4.7	73	-0.3	72	-0.5	64	-0.7	64	-0.9
PLAC	88	4.7	79	-0.1	82	-0.2	71	-0.1	73	-0.3
2-sided p-values for pairwise comparisons										
20mg vs PLAC	0.76		0.08 0.52[a]		0.46 0.52[a]		0.09 0.12[a]		0.16 0.22[a]	
40mg vs PLAC	0.86		0.08 0.20[a]		0.008 0.02[a]		0.003 0.007[a]		0.001 <0.001[a]	
60mg vs PLAC	0.52		0.06 0.14[a]		0.02 0.03[a]		0.001 0.004[a]		<0.001 0.001[a]	

[a] Unweighted analysis

Study: 116
Mean CGI-Improvement Subscale Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week									
	2 Wk		Wk 3		Wk 4		Wk 8		Wk 12	
	n	X	n	X	n	X	n	X	n	X
Parox 20mg	78	3.8	85	3.6	85	3.5	85	3.4	85	3.3
Parox 40 mg	82	3.9	83	3.6	83	3.3	83	3.1	83	2.9
Parox 60 mg	78	3.8	82	3.5	83	3.3	83	3.0	83	2.8
PLAC	84	3.9	88	3.7	88	3.6	88	3.7	88	3.6
2-sided p-values for pairwise comparisons										
20mg vs PLAC			0.30	0.42[a]	0.23	0.30[a]	0.02	0.02[a]	0.11	0.12[a]
40mg vs PLAC			0.32	0.29[a]	0.005	0.01[a]	<0.001	<0.001[a]	<0.001	0.001[a]
60mg vs PLAC			0.06	0.13[a]	0.01	0.07[a]	<0.001	<0.001[a]	<0.001	<0.001[a]

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week									
	2 Wk		Wk 3		Wk 4		Wk 8		Wk 12	
	n	X	n	X	n	X	n	X	n	X
Parox 20 mg	78	3.8	78	3.5	82	3.5	68	3.2	75	3.2
Parox 40 mg	82	3.9	74	3.5	76	3.2	66	3.0	65	2.8
Parox 60 mg	78	3.8	73	3.4	72	3.2	64	2.9	64	2.6
PLAC	84	3.9	79	3.7	82	3.6	71	3.7	73	3.5
2-sided p-values for pairwise comparisons										
20mg vs PLAC			0.32	0.62[a]	0.26	0.43[a]	0.003	0.004[a]	0.14	0.22[a]
40mg vs PLAC			0.22	0.25[a]	0.004	0.01[a]	<0.001	<0.001[a]	<0.001	0.001[a]
60mg vs PLAC			0.04	0.09[a]	0.009	0.08[a]	<0.001	<0.001[a]	<0.001	<0.001[a]

[a] Unweighted analysis

Enumeration of NIMHOC Score by Level of Severity at Baseline versus Week 12 Study 116

	Baseline # of Patients	Normal n	Subclinical n	Clinical n	Severe n	Very Severe n
		Number of patients at week 12				
Paroxetine 20 mg completers						
Normal	0	0	0	0	0	0
Subclinical	0	0	0	0	0	0
Clinical	37	2	17	15	3	0
Severe	34	1	1	11	21	0
Very Severe	2	0	0	0	0	2
Paroxetine 40 mg completers						
Normal	0	0	0	0	0	0
Subclinical	0	0	0	0	0	0
Clinical	37	7	13	14	3	0
Severe	26	3	3	10	12	0
Very Severe	1	0	0	0	1	0
Paroxetine 60 mg completers						
Normal	0	0	0	0	0	0
Subclinical	0	0	0	0	0	0
Clinical	39	4	17	17	1	0
Severe	27	2	5	7	13	0
Very Severe	0	0	0	0	0	0
Placebo completers						
Normal	0	0	0	0	0	0
Subclinical	0	0	0	0	0	0
Clinical	48	5	5	31	7	0
Severe	26	0	1	6	19	0
Very Severe	0	0	0	0	0	0

Appendix 7.2.2

Table 7.2.1.2.1 Investigators and study sites in study 118

Investigator	Center Address
Apter, Jeffrey T., M.D.	Princeton Biomedical Research, P.A., 330 N. Harrison Street, Suite #6, Princeton, NJ 08540
Ballenger, James C., M.D.	Medical University of South Carolina Department of Psychiatry - Room 407 USB, 171 Ashley Avenue, Charleston, SC 29415
Bastani, Bijan, M.D.	Case Western Reserve University, 2040 Abington Road, Cleveland, OH 44106
Borison, Richard L., M.D., Ph.D.	Behavioral Medicine Associates, 520 Shartom Drive, Augusta, GA 30907
Cain, John, M.D.	St. Paul Professional Building I, Fifth Floor, 5959 Harry Hines Blvd., Dallas, TX 75235-9101
Claghorn, James L., M.D.	Clinical Research Associates, 3120 Southwest Freeway, Suite 555 Houston, TX 77098
de la Gandara, Jose E., M.D.	Dominion Tower, Room 307-A, 1400 N.W. 10th Avenue Miami, FL 33136
Diamond, Bruce I., Prof.	Behavioral Medicine Associates, 520 Shartom Drive, Augusta, GA 30907
Dominguez, Roberto A., M.D.	Dominion Tower, Room 307-A, 1400 N.W. 10th Avenue, Miami, FL 33136
Ferguson, James M., M.D.	Pharmacology Research Corporation, 448 East 6400 South, Suite 350, Murray, UT 84107
Lydiard, Robert B., M.D.	Medical University of South Carolina, Department of Psychiatry - Room 407 USB, 171 Ashley Avenue, Charleston, SC 29415
Meltzer, Herbert Y., M.D.	Case Western Reserve University, 2040 Abington Road, Cleveland, OH 44106
Ninan, Philip T., M.D.	The Emory Clinic Department of Psychiatry, 1365 Clifton Road, NE - Room 5301, Atlanta, GA 30322
Pigott, Teresa, M.D.	Georgetown University Medical Center, Department of Psychiatry, Kober-Cogan Building - Rm. 316, 3800 Reservoir Road, N.W., Washington, DC 20009
Sheehan, David V., M.D.	U.S.F. Psychiatry Center University Professional Center, 3515 East Fletcher Avenue, Suite 321, Tampa, FL 33613
Zajecka, John, M.D.	Rush-Presbyterian - St. Luke's Medical Center, Rush Institute for Mental Well-Being, 1725 W. Harrison Street, Suite 955 Chicago, IL 60612

Appendix 7.2.2

Inclusion and Exclusion Criteria for Study 118

Inclusion Criteria

•The patient must have been at least 16 years old. (All patients less than 18 years old were required to have an additional written informed consent signed by a parent or legal guardian.)
•Patient must have met the DSM-IIIR diagnostic criteria for OCD.
•The patient must have had a documented history of OCD for a minimum duration of 6 months.
•Patients must have had a baseline score of 7 or above on the NIMHOCS and a baseline score of 16 or above on the YBOCS.
•The patient must have had a HAMD score at both the screen and baseline visits of less than or equal to 16 on the first 17 items of the 21-item scale. Furthermore, the response on item 1 of the HAMD Scale must not have exceeded the score of 2.
•Written informed consent was obtained for all eligible patients.

Exclusion Criteria

•Patients with a history of major depressive disorder within the last 3 months.
•Patients with personality disorders of sufficient severity to compromise their participation in and completion of the study.
•Patients with body dysmorphic disorder as a primary diagnosis (DSM-IIIR 300.70).
•Patients with a history of bipolar affective disorders.
•Patients with any serious concomitant medical condition.
•Patients with a history of seizure disorders (except for febrile seizures in childhood).
•Patients requiring concomitant therapy with other psychotropic drugs except chloral hydrate (up to 1000 mg) for sleep disturbance.
•Patients who met DSM-IIIR criteria for substance abuse (alcohol or drugs) within the past 6 months.
•Patients having clinically significant abnormal laboratory or ECG findings at the screen (Day -14) or baseline (Day 0) examinations.
•Patients who, in the investigator's judgment, posed a serious suicidal or homicidal risk.
•Patients who had received other investigational drugs within 30 days of the baseline visit (Day 0).
•Patients who had received other psychotropic drugs (including MAO inhibitors) within 14 days of the baseline visit (Day 0).
•Patients who had previously received paroxetine.
•Patients currently receiving any of the following drugs or drug classes: guanethidine, clonidine, methylphenidate, cimetidine, warfarin, digoxin or sulfonylureas.
•Women of childbearing potential who were lactating or had a positive pregnancy test at screening.
•Women of childbearing potential who did not employ adequate means of contraception, i.e., oral contraception, systemic contraception (i.e., Norplant), surgical sterilization, I.U.D., and diaphragms in conjunction with spermicidal foam and condom. Women who were 6 months postmenopausal were not considered to be of childbearing potential.
•Participation in ongoing behavioral therapy (i.e., exposure and response prevention) during the conduct of this study was specifically prohibited by this protocol.

Appendix 7.2.2

Schedule of Assessments in Study 118											
Visit	Screening	Baseline	1	2	3	4	6	8	10	12	Post Study
Evaluation											
Med & psych history	x										
Pregnancy test	x										
ECG	x										
HAMD	x	x									
Inclusion/Exclusion	x	x									
Randomization		x									
Efficacy Evaluations											
Y-BOCS	x	x	x	x	x	x	x	x	x	x	
NOMHOCS	x	x	x	x	x	x	x	x	x	x	
SCL-90	x	x	x	x	x	x	x	x	x	x	
CGI		x	x	x	x	x		x		x	
GAF		x				x		x		x	
Safety Evaluations											
Physical exam	x									x	x
Vital signs	x	x	x	x	x	x		x		x	x
Laboratory exams	x	x				x		x		x	x
Body weight	x	x	x	x	x	x		x		x	
Adverse events		x	x	x	x	x	x	x	x	x	x

Appendix 7.2.2

Study 118: Demographic Characteristics							
Treatment Groups	n	Age (years)		Sex [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-White
Paroxetine	82	41.3	19-77	44 (54)	38 (46)	77 (94)	5 (6)
Clomipramine	82	36.0	17-66	48 (59)	34 (42)	75 (92)	7 (9)
PLACEBO	77	36.3	16-67	54 (70)	23 (30)	71 (92)	5* (6)

Study 118: Patient Completion Rates							
Treatment Groups	Number Randomized	Intent-to-Treat Sample	Completers [n(%)]				
			Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
Parox	82	79	59 (75)	55 (70)	55 (70)	53 (67)	53 (67)
CMI	82	78	61 (78)	58 (74)	58 (74)	55 (71)	53 (68)
PLACEBO	77	75	68 (91)	60 (80)	60 (80)	57 (76)	56 (75)

Study 118: Dosing Information						
Treatment Groups	Mean Daily Dose (mg/day) for Completers in Active Drug Groups					
	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
Paroxetine	44.3	53.8	54.7	56.9	56.3	56.8
Clomipramine	89.3	142.4	155.5	164.2	170.3	163.3

Appendix 7.2.2

Study 118: Mean Change from Baseline in YBOCS Total Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week											
	BL Mean		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X
Paroxetine	79	23.3	79	-3.7	79	-4.4	79	-5.4	79	-5.2	79	-5.6
Clomipramine	78	23.9	78	-4.9	78	-6.1	78	-7.7	78	-7.7	78	-7.7
PLACEBO	75	24.7	75	-3.5	75	-3.4	75	-3.5	75	-4.2	75	-4.6
2-sided p-values for pairwise comparisons												
Par vs PBO			0.797		0.318		0.085		0.364		0.398	
CMI vs PBO			0.111		0.006		<0.001		0.002		0.009	
Par vs CMI			0.175		0.076		0.027		0.023		0.070	

OBSERVED CASES ANALYSIS

	Baseline		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X
Paroxetine	79	23.3	66	-4.5	60	-5.1	57	-6.9	54	-6.7	53	-7.4
Clomipramine	78	23.9	66	-5.4	58	-7.1	57	-9.2	55	-9.0	54	-9.1
PLACEBO	75	24.7	69	-3.7	67	-3.7	63	-4.0	60	-4.6	56	-5.6
2-sided p-values for pairwise comparisons												
Par vs PBO			0.430		0.206		0.015		0.112		0.193	
CMI vs PBO			0.073		0.002		<0.001		0.001		0.015	
Par vs CMI			0.320		0.070		0.068		0.098		0.268	

Appendix 7.2.2

Study 118: Mean Change from Baseline in NIMHOCS Total Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week											
	BL Mean		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X
Paroxetine	79	8.8	79	-0.8	79	-1.0	79	-1.3	79	-1.3	79	-1.4
Clomipramine	78	8.9	78	-1.0	78	-1.4	78	-1.7	78	-2.0	78	-2.1
PLACEBO	75	8.9	75	-0.8	75	-0.8	75	-0.8	75	-0.9	75	-1.0
2-sided p-values for pairwise comparisons												
Par vs PBO			0.763		0.304		0.051		0.188		0.239	
CMI vs PBO			0.218		0.007		0.001		<0.001		0.002	
Par vs CMI			0.345		0.092		0.113		0.020		0.046	

OBSERVED CASES ANALYSIS

	Baseline		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X
Paroxetine	79	8.8	65	-1.0	59	-1.2	57	-1.6	54	-1.7	53	-1.9
Clomipramine	78	8.9	66	-1.1	58	-1.7	56	-2.1	56	-2.5	54	-2.6
PLACEBO	75	8.9	70	-0.8	68	-0.8	63	-0.9	60	-1.1	56	-1.4
2-sided p-values for pairwise comparisons												
Par vs PBO			0.377		0.215		0.026		0.075		0.164	
CMI vs PBO			0.164		0.002		<0.001		<0.001		0.001	
Par vs CMI			0.626		0.074		0.145		0.037		0.075	

Appendix 7.2.2

Study 118: Mean Change from Baseline in CGI Severity of Illness Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week							
	BL Mean		Wk 4		Wk 8		Wk 12	
	n	X	n	X	n	X	n	X
Paroxetine	79	4.5	79	-0.4	79	-0.5	79	-0.6
Clomipramine	78	4.5	78	-0.5	78	-0.7	78	-0.8
PLACEBO	75	4.6	75	-0.4	75	-0.4	75	-0.4
2-sided p-values for pairwise comparisons								
Paroxetine vs PBO			0.556		0.362		0.239	
CMI vs PBO			0.638		0.031		0.014	
Paroxetine vs CMI			0.284		0.203		0.193	

OBSERVED CASES ANALYSIS

	Baseline		Wk 4		Wk 8		Wk 12	
	n	X	n	X	n	X	n	X
Paroxetine	79	4.5	65	-0.4	55	-0.7	53	-0.9
Clomipramine	78	4.5	66	-0.5	58	-0.9	53	-1.0
PLACEBO	75	4.6	69	-0.4	63	-0.4	56	-0.5
2-sided p-values for pairwise comparisons								
Paroxetine vs PBO			0.975		0.093		0.041	
CMI vs PBO			0.450		0.007		0.010	
Paroxetine vs CMI			0.442		0.319		0.604	

Appendix 7.2.2

Study 118: Mean CGI Improvement Subscale Score						
LAST OBSERVATION CARRIED FORWARD ANALYSIS						
Treatment Group	Wk 4		Wk 8		Wk 12	
	n	X	n	X	n	X
Paroxetine	79	3.3	79	3.0	79	2.9
Clomipramine	78	3.2	78	2.8	78	2.7
PLACEBO	75	3.4	75	3.4	75	3.3
2-sided p-values for pairwise comparisons						
Paroxetine vs PBO	0.448		0.022		0.046	
CMI vs PBO	0.123		<0.001		0.002	
Paroxetine vs CMI	0.425		0.184		0.265	
OBSERVED CASES ANALYSIS						
Treatment Group	Wk 4		Wk 8		Wk 12	
	n	X	n	X	n	X
Paroxetine	65	3.1	55	2.8	53	2.6
Clomipramine	66	3.1	55	2.5	53	2.4
PLACEBO	69	3.3	63	3.3	56	3.1
2-sided p-values for pairwise comparisons						
Paroxetine vs PBO	0.103		0.006		0.017	
CMI vs PBO	0.079		<0.001		0.002	
Paroxetine vs CMI	0.917		0.194		0.466	

Appendix 7.2.2

Enumeration of NIMHOC Score by Level of Severity at Baseline versus Week 12 Study 118

	Baseline # of Patients	Normal n	Subclinical n	Clinical n	Severe n	Very Severe n
		Number of patients at week 12				
Paroxetine completers						
Normal	0	0	0	0	0	0
Subclinical	0	0	0	0	0	0
Clinical	47	5	18	22	2	0
Severe	6	0	1	3	2	0
Very Severe	1	0	0	0	1	0
Clomipramine completers						
Normal	0	0	0	0	0	0
Subclinical	0	0	0	0	0	0
Clinical	34	5	14	15	0	0
Severe	20	2	6	6	6	0
Very Severe	0	0	0	0	0	0
Placebo completers						
Normal	0	0	0	0	0	0
Subclinical	0	0	0	0	0	0
Clinical	46	4	7	35	0	0
Severe	11	1	1	5	4	0
Very Severe	0	0	0	0	0	0

Appendix 7.2.3

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Appendix 7.2.3

Study 136: Inclusion/Exclusion Criteria

Inclusion Criteria
-Male and female patients aged 16 to 70.
-Patient must have met the DSM-III-R diagnostic criteria for OCD.
-The patient must have had a documented history of OCD for a minimum duration of 6 months.
-Patients must have had a baseline score of 7 or above on the NIMHOCS and a baseline score of 16 or above on the YBOCS.

Exclusion Criteria
-Patients with a history of major depressive disorder within the last 3 months.
-OCD must be the primary diagnosis; other psychiatric diagnoses not otherwise excluded may be present as long as they are considered secondary to OCD.
-Patients with a history of bipolar affective disorders.
-Patients with any serious concomitant medical condition.
-Patients with a history of seizure disorders (except for febrile seizures in childhood).
-Patients requiring concomitant therapy with other psychotropic drugs except chloral hydrate, temazepam, or triazolam for sleep disturbance.
-Patients with a history of substance abuse (alcohol or drugs) within the past 6 months.
-Patients having clinically significant abnormal laboratory or ECG findings at the screening or baseline examinations.
-Patients who, in the investigator's judgment, posed a serious suicidal or homicidal risk.
-Patients who had received other investigational drugs within 90 days of the baseline visit.
-Patients who had received other psychotropic drugs within 14 days (or 28 days if depot neuroleptic)of the baseline visit.
-Patients who had previously received paroxetine.
-Patients currently receiving any of the following drugs or drug classes: class 1c anti-arrhythmics and oral anticoagulants.
-Pregnant or lactating women.
-Patients with urinary retention or closed angle glaucoma.

Appendix 7.2.3

Table of Assessments in Study 136										
Procedure	Screen	Basel	Active Phase							
Week	-2	0	1	2	3	4	6	8	10	12
Med/Psych History	x									
History of	x									
Physical Exam	x									x
Inclusion/exclusio	x	x								
DSM-IIIR axis I&II	x									
Y-BOCS	x	x	x	x	x	x	x	x	x	x
NIMHOCS	x	x	x	x	x	x	x	x	x	x
MADRS	x	x	x	x	x	x	x	x	x	x
SCL-90	x	x				x		x		x
CGI		x	x	x	x	x	x	x	x	x
Patient's Global		x	x	x	x	x	x	x	x	x
Dose Change				x	x	x	x	x	x	
Vital signs	x	x	x	x	x	x	x	x	x	x
Labs	x	x*				x		x		x
ECG	x									
Limited symptom		x	x	x	x	x	x	x	x	x
Concomitant	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x

*-If abnormal at assessment

Appendix 7.2.3

Study 136: Demographic Characteristics							
Treatment Groups	n	Age (years)		Sex [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-White
Paroxetine	201	37.8	17-72	90 (45)	111 (55)	199 (99)	2 (1)
Clomipramine	99	38.4	16-70	56 (57)	43 (43)	96 (97)	3 (3)
PLACEBO	99	37.8	19-74	44 (44)	55 (56)	95 (96)	4 (4)

Study 136: Patient Completion Rates							
Treatment Groups	Number Randomized	Intent-to-Treat Sample	Completers [n(%)]				
			Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
Parox	205	201	182 (91)	175 (87)	167 (83)	156 (78)	152 (76)
CMI	101	99	80 (81)	76 (77)	72 (73)	65 (66)	64 (65)
PLACEBO	100	99	85 (86)	78 (79)	69 (70)	62 (63)	60 (61)

Study 136: Mean daily dose by visit						
Treatment Groups	Mean Daily Dose (mg/day) for Completers in Active Drug Groups					
	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
Paroxetine	24.4	39.6	45.3	49.4	50.9	49.5
Clomipramine	68.4	129.0	146.4	165.4	174.6	173.9

Appendix 7.2.3

Study 136: Mean Change from Baseline in YBOCS Total Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week											
	BL Mean		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X
Paroxetine	198	25.7	198	-4.2	198	-4.8	198	-5.6	198	-6.4	198	-6.9
Clomipramine	94	24.7	94	-4.5	94	-5.4	94	-6.1	94	-6.4	94	-6.9
PLACEBO	99	26.3	99	-3.2	99	-2.7	99	-3.3	99	-3.6	99	-3.9
2-sided p-values for pairwise comparisons												
Paroxetine vs PBO	0.294	0.501*	0.184	0.255*	0.005	0.032*	0.009	0.028*	0.002	0.010*	0.002	0.016*
CMI vs PBO	0.029	0.026*	0.118	0.088*	0.002	0.003*	0.005	0.001*	0.009	0.006*	0.008	0.007
Paroxetine vs CMI	0.137	0.058*	0.625	0.403*	0.440	0.186*	0.502	0.120*	0.945	0.515*	0.988	0.456*

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week											
	Baseline		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X
Paroxetine	198	25.7	180	-4.5	176	-5.1	167	-6.2	151	-7.9	147	-8.6
Clomipramine	94	24.7	80	-4.9	76	-6.1	72	-7.0	67	-8.2	64	-9.1
PLACEBO	99	26.3	85	-3.6	83	-3.6	76	-4.3	60	-5.9	62	-5.9
2-sided p-values for pairwise comparisons												
Paroxetine vs PBO	0.294	0.501*	0.185	0.270*	0.010	0.064*	0.038	0.137*	0.060	0.229*	0.022	0.366*
CMI vs PBO	0.029	0.026*	0.127	0.143*	0.002	0.005*	0.015	0.010*	0.071	0.102	0.022	0.072*
Paroxetine vs CMI	0.137	0.058*	0.638	0.534*	0.271	0.168*	0.413	0.114*	0.820	0.447*	0.680	0.190*

* Unweighted analysis

Appendix 7.2.3

Study 136: Mean Change from Baseline in NIMHOCS Total Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week											
	BL Mean		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X
Paroxetine	198	9.8	198	-1.1	198	-1.4	198	-1.7	198	-2.0	198	-2.2
Clomipramine	94	9.7	94	-1.1	94	-1.4	94	-1.8	94	-1.8	94	-2.2
PLACEBO	98	10.0	98	-0.8	98	-0.7	98	-0.9	98	-1.0	98	-1.1
2-sided p-values for pairwise comparisons												
Paroxetine vs PBO	0.230	0.324*	0.228	0.321*	0.006	0.030*	0.009	0.007*	0.002	0.007*	0.001	0.005*
CMI vs PBO	0.256	0.315*	0.225	0.207*	0.031	0.025*	0.015	0.007*	0.039	0.025*	0.007	0.007*
Paroxetine vs CMI	0.899	0.855*	0.834	0.638*	0.838	0.663*	0.628	0.411*	0.512	0.940*	0.926	0.718*

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week											
	Baseline		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X
Paroxetine	198	9.8	180	-1.2	176	-1.6	167	-2.0	151	-2.6	147	-2.8
Clomipramine	94	9.7	80	-1.3	76	-1.7	72	-2.1	67	-2.5	64	-3.0
PLACEBO	99	10.0	85	-0.9	83	-0.9	76	-1.2	60	-1.9	62	-1.7
2-sided p-values for pairwise comparisons												
Paroxetine vs PBO	0.230	0.324*	0.236	0.429*	0.015	0.103*	0.020	0.086*	0.073	0.398*	0.006	0.215*
CMI vs PBO	0.256	0.315*	0.232	0.306*	0.020	0.033*	0.021	0.021*	0.194	0.356*	0.007	0.068*
Paroxetine vs CMI	0.899	0.855*	0.772	0.685*	0.743	0.398*	0.673	0.319*	0.765	0.820*	0.683	0.340*

* Unweighted analysis

Appendix 7.2.3

Study 136: Mean Change from Baseline in CGI Severity of Illness Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week											
	BL Mean		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X
Paroxetine	194	5.0	194	-0.5	194	-0.7	194	-0.9	194	-1.0	194	-1.1
Clomipramine	94	4.9	94	-0.5	94	-0.7	94	-0.8	94	-0.9	94	-1.0
PLACEBO	99	5.1	99	-0.4	99	-0.3	99	-0.4	99	-0.5	99	-0.6
2-sided p-values for pairwise comparisons												
Paroxetine vs PBO	0.263	0.743*	0.409	0.415*	0.002	0.004*	0.002	0.002*	0.001	0.002*	0.003	0.004*
CMI vs PBO	0.178	0.243*	0.304	0.114*	0.004	0.002*	0.024	0.007*	0.048	0.019*	0.044	0.018*
Paroxetine vs CMI	0.657	0.321*	0.714	0.323*	0.834	0.514*	0.671	0.956*	0.376	0.657*	0.510	0.887*

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week											
	Baseline		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X
Paroxetine	194	5.0	177	-0.5	173	-0.8	165	-1.0	149	-1.2	147	-1.4
Clomipramine	94	4.9	79	-0.6	75	-0.9	71	-1.0	66	-1.1	63	-1.4
PLACEBO	99	5.1	85	-0.4	83	-0.3	76	-0.5	60	-0.9	62	-0.9
2-sided p-values for pairwise comparisons												
Paroxetine vs PBO	0.263	0.743*	0.358	0.474*	0.002	0.004*	0.002	0.002*	0.081	0.084*	0.017	0.056*
CMI vs PBO	0.178	0.243*	0.205	0.060*	0.002	0.001*	0.021	0.004*	0.277	0.076*	0.073	0.028*
Paroxetine vs CMI	0.657	0.321*	0.570	0.161*	0.519	0.279*	0.746	0.811*	0.617	0.744*	0.787	0.510*

* Unweighted analysis

Appendix 7.2.3

Study 136: Mean CGI Improvement Subscale Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X
Paroxetine	198	3.3	198	3.2	198	3.0	198	2.9	198	2.8
Clomipramine	95	3.2	95	3.1	95	2.9	95	2.8	95	2.7
PLACEBO	99	3.5	99	3.7	99	3.6	99	3.5	99	3.4
2-sided p-values for pairwise comparisons										
Paroxetine vs PBO	0.086	0.349*	<0.001	0.004*	<0.001	0.002*	0.001	0.005*	0.001	0.011*
CMI vs PBO	0.046	0.182*	<0.001	0.002*	<0.001	<0.001*	0.001	0.003*	0.001	0.004*
Paroxetine vs CMI	0.578	0.542*	0.494	0.397*	0.498	0.242*	0.723	0.511*	0.441	0.409*

OBSERVED CASES ANALYSIS

Treatment Groups	Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X
Paroxetine	180	3.2	176	3.1	168	2.8	151	2.6	147	2.5
Clomipramine	80	3.1	76	2.9	72	2.6	67	2.5	64	2.3
PLACEBO	85	3.4	83	3.6	76	3.4	60	3.0	62	2.9
2-sided p-values for pairwise comparisons										
Paroxetine vs PBO	0.276	0.416*	0.002	0.005*	0.002	0.005*	0.073	0.221*	0.013	0.011*
CMI vs PBO	0.099	0.127*	<0.001	0.001*	<0.001	<0.001*	0.021	0.076*	0.001	0.004*
Paroxetine vs CMI	0.496	0.342*	0.232	0.208*	0.163	0.064*	0.328	0.356*	0.151	0.409*

* Unweighted analysis

Appendix 7.2.3

Enumeration of NIMHOC Score by Level of Severity at Baseline versus Week 12 Study 136

	Baseline # of Patients	Normal n	Subclinical n	Clinical n	Severe n	Very Severe n
		Number of patients at week 12				
Paroxetine completers						
Normal	0	0	0	0	0	0
Subclinical	0	0	0	0	0	0
Clinical	75	17	29	26	3	0
Severe	72	10	19	20	19	4
Very Severe	4	1	2	0	0	1
Clomipramine completers						
Normal	0	0	0	0	0	0
Subclinical	0	0	0	0	0	0
Clinical	34	5	20	9	0	0
Severe	29	1	6	15	5	2
Very Severe	2	0	1	1	0	0
Placebo completers						
Normal	0	0	0	0	0	0
Subclinical	0	0	0	0	0	0
Clinical	75	3	6	12	4	0
Severe	31	4	4	11	12	0
Very Severe	4	0	1	0	1	2

Appendix 8.5.1.1

Adverse events occurring at a rate of 1% or greater in paroxetine treated patients	Paroxetine n=542 %	Clomipramine n=181 %	Placebo n=265 %
Body as a Whole			
Headache	25	21	29
Asthenia	22	24	14
Abdominal Pain	5	2	5
Infection	5	3	5
Chest Pain	3	2	2
Trauma	3	1	4
Back Pain	2	1	5
Chills	2	2	1
Fever	2	1	1
Pain	2	1	3
Cardiovascular			
Vasodilitation	4	5	1
Palpitation	2	1	<1
Migraine	1	1	<1
Postural Hypotension	1	5	<1
Digestive System			
Nausea	23	25	10
Dry Mouth	18	51	9
Constipation	16	27	6
Diarrhea	10	4	10
Decreased Appetite	9	7	3
Dypepsia	4	6	7
Increased Appetite	4	4	3
Flatulence	3	2	4
Liver Function Tests Abnormal	2	1	2
Vomiting	2	1	1
Gastrointestinal Disorder	1	1	2
Tooth Disorder	1	0	2
Ulcerative Stomatitis	1	1	1

Metabolic/Nutritional			
Weight Gain	2	5	3
Weight Loss	2	1	<1
Musculoskeletal			
Myalgia	3	3	4
Arthralgia	2	1	3
Nervous System			
Insomnia	24	26	13
Somnolence	24	24	17
Dizziness	12	29	6
Tremor	11	32	1
Nervousness	8	11	8
Libido Decreased	7	6	4
Abnormal Dreams	4	3	1
Anxiety	4	6	7
Concentration Impaired	3	3	2
Depersonalization	3	4	<1
Myoclonus	3	5	<1
Paresthesia	2	2	3
Agitation	2	3	2
Amnesia	2	3	1
Depression	2	3	8
Hyperkinesia	2	1	1
Emotional Lability	1	1	2
Hypertonia	1	1	1
Hypesthesia	1	1	<1
Thinking Abnormal	1	2	<1
Respiratory System			
Respiratory Disorder	8	4	12
Pharyngitis	4	2	5
Sinusitis	2	2	5
Yawn	2	3	<1
Cough Increased	1	0	2
Rhinitis	1	2	3
Skin/Appendages			

Sweating	9	25	3
Rash	3	1	2
Special Senses			
Abnormal Vision	4	4	2
Taste Perversion	2	4	0
Tinnitus	1	3	1
Urogenital System			
*Abnormal Ejaculation	23	18	1
*Impotence	8	9	1
*Female Genital Disorders	3	3	0
*Dysmenorrhea	1	0	2
Urinary Frequency	3	1	1
Urination Impaired	3	10	<1
Urinary Tract Infection	1	1	1
*Vaginitis	1	1	0

* Corrected for sex.

Appendix 8.5.1.2

Summary of common, drug-related adverse experiences by assigned dose group in fixed-dose study 116.

Daily Dose Paroxetine mg	Placebo	20	40	60
Body System Preferred Term	n=09 %	n*=88 %	n=86 %	n=85 %
DIGESTIVE SYSTEM				
Constipation	9	14	19	12
Dry mouth	7	17	23	15
Decreased Appetite	1	8	13	12
Nausea	8	20	26	18
NERVOUS SYSTEM				
Somnolence	10	25	23	33
Dizziness	8	15	8	12
Tremor	1	9	15	11
SKIN/APPENDAGES				
Sweating	2	5	8	8
UROGENITAL SYSTEM				
Abnormal ejaculation**	2	19	32	30
Impotence**	2	11	8	7

* n=number of patients receiving the specified paroxetine dose
**Corrected for sex.

Appendix 8.5.2.1

Mean Change from baseline to study endpoint for chemistry parameters in clinical OCD database.

Serum Chemistry Variable	Paroxetine		Placebo		Chlomipramine	
	Total Patients	Mean Change	Total Patients	Mean Change	Total Patients	Mean Change
Urea mmol/l	135	0.1	54	0.2	55	0.1
BUN mg/dl	245	0.5	124	0.5	54	-0.2
Creatinine mg/dl	379	-0.0	179	0.0	111	0.0
Total Bilirubin mg/dl	378	-0.0	178	-0.0	109	-0.1
SGOT (AST) u/l	380	4.0	179	1.7	111	-0.3
SGPT (ALT) u/l	378	3.8	177	-0.4	109	3.6
Alkaline Phosphatease u/l	380	2.5	63	-1.7	108	10.6
Total Protein g/dl	116	-0.1	44	-0.1	50	-0.1
Albumin g/dl	129	-0.1	51	-0.1	53	-0.1
Globulin	99	-0.0	36	-0.0	43	0.1

Number of Patients with Clinical (Blood) Chemistry Values of potential Clinical Concern by Parameter - all Studies

Parameter	PAROXETINE			CLOMIPRAMINE			PLACEBO		
	N	n	%	N	n	%	N	n	%
Urea	182	3	2	87	1	1	85	1	1
Blood Urea Nitrogen	312	4	1	72	1	1	154	2	1
Serum Creatinine	495	1	0	159	0	0	238	1	0
Total Bilirubin	493	4	1	157	1	1	239	2	1
AST (SGOT)	495	3	1	159	0	0	240	2	1
ALT (SGPT)	494	4	1	158	2	1	240	0	0
Alkaline	495	1	0	159	1	1	240	0	0
Phosphatase	158	0	0	76	0	0	74	0	0
Total Protein	179	0	0	83	0	0	80	0	0
Albumin	137	0	0	67	0	0	61	0	0

Appendix 8.5.2.2

Mean Change from baseline to study endpoint in clinical OCD database.

Hematology Variable	Paroxetine		Placebo		Chlomipramine	
	Total Patients	Mean Change	Total Patients	Mean Change	Total Patients	Mean Change
Hemoglobin g/dl	379	-0.1	179	-0.2	111	-0.3
Hematocrit (%)	377	-0.4	181	-0.5	108	-1.1
WBC($x10^9$/l)	384	-0.0	182	-0.1	111	-0.1
Neutrophils (%)	123	-0.8	51	0.3	52	2.4
Lymphocytes (%)	378	0.4	179	0.1	109	-0.2
Monocytes (%)	376	0.1	176	0.1	107	0.5
Basophils (%)	326	-0.0	157	0.1	103	0.1
Eosinophils(%)	335	0.1	165	0.0	105	0.4
Bands (%)	177	-0.1	98	0.0	55	0.1
Seg. Neut.(%)	252	-0.4	127	-0.5	58	-0.6
Plat ($x10^9$/l)	378	-0.9	182	-1.7	111	4.3

Number of Patients with Hematologic Values of Potential Clinical Concern by Parameter - all Studies Combined

	PAROXETINE			CLOMIPRAMINE			PLACEBO		
Parameter	N	n	%	N	n	%	N	n	%
Hemoglobin	483	0	0	158	0	0	235	0	0
Hematocrit	487	5	1	157	3	2	235	3	1
White Blood Cells	494	2	0	158	3	2	238	1	0
Neutrophils	171	0	0	81	0	0	78	0	0
Lymphocytes	493	1	0	158	0	0	238	0	0
Monocytes	492	4	1	158	4	3	237	4	2
Basophils	452	0	0	152	0	0	220	0	0
Eosinophils	455	9	2	155	4	3	227	4	2
Bands	245	0	0	76	0	0	132	1	1
Segmented Neutrophils	319	1	0	77	2	3	160	1	1
Platelets	490	1	0	158	0	0	239	0	0

Appendix 8.5.3

Number of Patients (%) with vital signs of potential clinical concern in the pooled OCD database

Vital Sign Parameter	Paroxetine N= 542	Placebo N=265	Clomipramine N=181
Diastolic BP	6 (1)	5 (2)	4 (2)
Systolic BP	6 (1)	3 (1)	5 (3)
Pulse	1 (<1)	3 (1)	7 (4)
Weight	44 (8)	15 (6)	11 (6)

Mean changes from baseline at endpoint in the combined OCD database*

	Paroxetine		Placebo		Clomipramine	
Vital Sign Parameter	Base-line	Mean diff. Wk 12	Base-line	Mean diff. Wk 12	Base-line	Mean diff. Wk 12
	n x	n x	n x	n x	n x	n x
Systolic lying	201 122	160 <1	99 123	67 -3	99 123	70 -<1
Diastolic lying	201 77	160 -<1	99 78	67 -2	99 77	70 2
Diastolic sitting	341 77	258 <1	166 78	134 -1	82 74	56 4
Systolic sitting	341 121	258 <1	166 121	134 -2	82 116	56 3
Diastolic standing	539 79	412 <1	264 80	196 -1	179 78	125 <1
Systolic standing	539 120	412 0	264 121	196 -3	179 118	125 -1
Pulse sitting BPM	341 73	257 <1	166 74	134 <1	82 72	56 10
Pulse standing	535 80	408 -<1	261 80	194 -2	178 78	124 10
Weight	519 75	418 <1	259 75	199 <1	179 70	126 <1

* n= number of patients; x= mean value at baseline or the mean change from baseline at Week 12.

Appendix 8.7

Serious adverse events judged not to be related to drug treatment among the 542 subjects randomized to paroxetine in the combined clinical trials data base. The patient who never received paroxetine is not included.

Study	Patient ID	Age	Sex	Daily Dose (mg/d)	Days to Onset	Adverse Experience-Result
116	010.0133	54	M	20 mg	57	Alcoholism-Hospitalized
118	008.0075	29	F	40 mg	40	Pulmonary embolus-lost to follow-up
136	035.0262	54	M	40 mg	42	Hepatitis A/jaundice-Lost to follow-up
136	043.0191	60	F	40 mg	47	Accidental burn-Hospitalized

Serious adverse events judged by the reviewer not to be related to drug treatment among subjects in the extended paroxetine treatment data base.

Study	Patient ID	Daily Dose (mg/day)		Adverse Experience-Result
126	003.0400	60 mg		Alcoholism-Detox hospitalization
126	004.0004	60 mg		Accidental fall/Alcohol & cocaine present on tox screen-hospitalized
126	008.0096	40 mg		Pneumonia-Hospitalized
126	009.0142	20 mg		Alcohol abuse-Hospitalized for detox
126	009.0245	60 mg		Cellulitis-Hospitalized
126	011.0035	50 mg		Toxic shock syndrome-Hospitalized
126	011.0039	20 mg		Chest pain-Drug d/ced awaiting surgery
126	013.0054	20 mg		Incisional hernia-Hospitalized for surgery
126	013.0338	60 mg		Fractured mandible/Hospitalized for open reduction.
126	014.0258	20 mg		Perianal abscess-Hospitalized for surgery
127	009.0226	60 mg		Infarcted lower bowel-Hospitalized

Patients in the placebo groups with serious adverse events that were not related to psychiatric symptoms related to the disease for which they were being treated.

Study	Patient ID	Days to Onset	Adverse Experience-Result
116	002.0115	67	Fracture left hip-Hospitalized
116	009.0109	15	Lumpectomy for right breast-Malignancy
118	006.0042	77	Auto accident head injury unconcious-not yet recovered.
118	013.9005	run-in	Chest pains-Hospitalized LV pathology
136	068.0408	31	Tetany crisis-Hospitalized and recovered

Memorandum

Department of Health and Human Services SEP 1 1995
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

SEP 1 1995

Date: August 31, 1995

From: David Hoberman, Ph.D., HFD-713

Thru: Satya Dubey, Ph.D. 8/31/95
Chief, Statistical Evaluation & Research Branch (HFD-713)

Subject: Paxil Supplement for Obsessive-Compulsive Disorder (NDA 20-031/SE1-007)

To: File (NDA 20-031)

Background

Study 116 conducted in the US has been accepted as one adequate and well-controlled trial supporting the proposed indication for Paxil. The sponsor's study report of the European study 136 reported only treatment effects based upon weighted ls means (over countries). The following results are the **unweighted** analyses and their contrast with those reported by the sponsor.

Results

Intent to Treat, All patients

There were 391 patients with data available for the all patients analyses: N=198 Paxil, N=94 Chlomipramine, N=99 placebo). The sponsor had stated in the analysis plan: "Note that due to the large number of centres [64] expected to contribute patients, centres may be grouped by country in the analysis". This was done with further groupings as follows: Belgium, France, Germany/Austria/Holland, Italy/Spain, Israel, Sweden, and Ireland/UK/Canada. The table below presents the numbers of patients of each cell of the modified design:

	Belgium	France	G/A/H	I/S	Israel	Sweden	I/UK/C
Chlomipramine	15	26	17	6	5	11	14
Paxil	30	54	35	14	9	23	33
Placebo	16	26	18	7	5	12	15

The table below presents the ls means and p-values for the unweighted analyses (over countries and investigator) for change from baseline for the YBOC and NIMH scales using the last observation carried forward to 12 weeks . A total of 17 investigators with at least 1 empty cell were grouped together.

	Grouped by Country		Investigator	
	YBOC	NIMH	YBOC	NIMH
Chlomipramine	7.43	2.30	8.59	2.87
Paxil	6.59	2.16	7.81	2.37
Placebo	3.89	1.05	5.39	1.69

The p-values for the Paxil-Placebo comparisons were .016 and .005 for YBOC and NIMH, respectively for the 'country' analysis and .036 and .09, respectively for the 'investigator' analysis. Thus the YBOC is statistically significant in both analyses.

Intent to Treat, Completers

There was a total of 273 completers: N=147 Paxil, N=64 Clomipramine, N=62 placebo. The table below presents those results while grouping by country, only:

	YBOC	NIMH
Chlomipramine	9.97	3.22
Paxil	8.06	2.72
Placebo	6.55	1.97

The p-values for the Paxil-Placebo comparisons are .37 and .22 for YBOC and NIMH, respectively. This result with a treatment difference of 1.51 on the YBOC is in contrast to that submitted by the sponsor at week 12, viz a p-value of .022 and a treatment difference of 2.7. This discrepancy is due to the gross imbalance of treatment allocations within and between countries. For the NIMH, the sponsor's p-value was .006 with a treatment difference of 1.2, while the unweighted analysis produces a treatment difference of 0.75.

The differences between the **unweighted** analyses for all patients and completers can be explained by the worse condition of placebo drop outs relative to those in the Paxil group. The ls means of the last observation before dropping out were 2.36 for Paxil and 0.39 for placebo on the YBOC while the respective ls means for the NIMH were .48 and .07. The **weighted** means resulted in more comparable groups. Thus, these analyses are highly dependent on the weights used to combine results over country. However, in this particular circumstance, the unweighted analysis would be preferred since it tests the null hypothesis of whether the population means of the two groups are the same.

Conclusions

Trial 136 produces a statistically significant difference utilizing the LOCF analysis between Paxil and placebo on the YBOC scale whether the strata are countries or investigator (the true design). In both cases, the treatment effect appears to be an average of approximately 2.5 points change from baseline. The results for the NIMH scale are less persuasive when the investigator is used as the stratifying factor.

These positive results appear to be highly dependent upon the worse condition of placebo drop outs relative to Paxil at the time of drop out.

David Hoberman, Ph.D.

concur: Dr. Nevius 5-1-95

cc: Arch NDA 20-031
HFD-120
HFD-120/Dr. Laughren, Dr. Andreason, Dr. Dubitsky, Mr. David
HFD-713/Dr Dubey [File: DRU 1.3.2]
HFD-713/Group 2 file
HFD-344/Dr. Lisook

This review consists of 3 pages of text

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Supplement SEI-009; Vol. 51.001

NDA 20-031

Reviewer:	Steven Sparenborg, Ph.D.
Dates:	Written Review - August 15, 1995 Approval Decision Due - March 29, 1996 Submission Dated - March 29, 1995
Sponsor:	SmithKline Beecham Pharmaceuticals
Drug:	PAXIL™ (paroxetine hydrochloride)
Category:	selective serotonin reuptake inhibitor
Indication:	panic disorder (already approved for treatment of depression)
Related IND's:	
Max. Recommended Dose	60 mg
Dosage Forms and Route of Administration	10, 20, 30, 40, 50 mg tablets for oral use

DRAFT

Summary

No pharmacology/toxicology studies were submitted with this supplement. All preclinical issues of concern with this supplement were dealt with in the original NDA and in the supplement for obsessive-compulsive disorder (S-007), except for the inclusion in labeling of rat pup deaths in reproductive studies. The following is a summary of rat pup survival results in peri- and post-natal rat studies submitted with the original NDA:

Two Segment I and two Segment III studies were performed in which dams had the opportunity to give birth and raise pups through weaning age. Drug-related decreases in pup survival were found in each study.

Doses of 5, 15 and 50 mg/kg were used in the first Segment I study. Maternal toxicity was present at the mid- and high-dose groups as evidenced by drastically reduced weight gains, but the low dose did not affect weight gain in the dams. At the low-dose,

only 3/12 dams had viable young after Day 9 pp. Survival in the higher dose groups was accordingly less than in the low-dose group. 13/14 control dams reared pups to weaning.

A second Segment I study used the dose of 1 mg/kg. There were no signs of maternal toxicity at this dose, but only 76.2% of treated pups survived until weaning. One of eleven treated dams suffered complete litter loss. All ten control dams raised some young to weaning age with a survival rate of 90.7% overall. Fetal weights were not lower than controls, but pup weights were not mentioned in a review of this study.

Doses of 1, 4, and 15 mg/kg were given to pregnant rats in a preliminary, modified, Segment III study. Dosing only took place on the last four days of gestation and the first four days of lactation. This study was only mentioned briefly in our review and the only results included were that the pup survival rates were 65 and 28% for the 4 and 15 mg/kg doses, respectively.

The final Segment III study also used a modified dosing regimen. The dose of 1 mg/kg was given to pregnant dams from Day 15 *post coitum* to Day 21 *post partum*. Doses of 3.3 and 10 mg/kg were given only on Days 5 to 24 *post partum*. These dosing regimens did not produce signs of maternal toxicity, but survival in the group treated with 1 mg/kg was significantly lower than in controls. The higher doses of 3.3 and 10 mg/kg did not affect survival. All four groups in this study had dams with reduced maternal mammary development, which apparently lowered survival in all groups in a non-drug-related manner. The survival rates on Day 25 were 83%, 71.4%, 93.5% and 88.2% for the C, L, M and H groups, respectively. The fact that the 3.3 and 10 mg/kg dose groups did not experience reduced survival strongly suggests that there is a critical period in which paroxetine exerts a lethal effect on the rat F_1 generation. That period lies within the range of 4 days before birth to 4 days after birth.

Recommendations

1. There are no toxicity findings that should clearly prevent the approval of this supplement. Human safety data may be more relevant for making a decision to approve or disapprove this request.

2. The recommended changes in the sponsor's draft labeling, taken from pp 176-77 of this supplement, are found below. Deletions from their labeling are marked with a line through the text and additions are highlighted with shading. The corrections in the multiples of maximum human dose are required by a new maximum human dose (60 mg) and by policy changes for CDER in computing body surface area put forth in a memo from Dr. J. DeGeorge dated October, 1993. All calculations are also based on a human body weight of 60 kg. The original labeling for this drug was based on a human weight of 50 kg.

Carcinogenesis: Two-year carcinogenicity studies were conducted in mice and rats given paroxetine in the diet at ~~1, 5 and 25 mg/kg/day (mice) and 1, 5 and 20 mg/kg/day (rats). The maximum doses in these studies were approximately 25 (mouse) and 20 (rat) times the maximum dose recommended for human use in the treatment of depression (50 mg/day) and approximately 21 (mouse) and 17 (rat) times the maximum recommended human dose for the treatment of OCD and Panic Disorder (60 mg/day) on a mg/kg basis. On a mg/m^2 basis, this is 2.5~~ doses up to 2.4 (mouse) and ~~5.8~~ 3.9 (rat) times the maximum recommended human dose (MRHD) for depression, on a mg/m^2 basis. Because the MRHD for depression is slightly less than that for OCD and Panic Disorder (50 mg vs. 60 mg), the doses used in these carcinogenicity studies were only ~~and 2.1~~ 2.0 (mouse) and ~~4.8~~ 3.2 (rat) times the MRHD for OCD and Panic Disorder. There was a significantly ...

Mutagenesis: no changes required

Impairment of Fertility

~~Serotonergic compounds are known to affect reproductive function in animals. Impaired reproductive function (i.e.,~~ A reduced pregnancy rate~~, increased pre- and post-implantation losses, decreased viability of pups)~~ was found in reproduction studies in rats at doses of paroxetine which were ~~15 or more times the highest recommended human dose for depression (50 mg/day) or 12.5 or more times the highest recommended dose of OCD and Panic Disorder (60 mg/day) on a mg/kg basis. These are 4.4~~ 2.9 times~~, 3.7~~ the MRHD for depression ~~times~~ or ~~3.7~~ 2.4 times the ~~maximum recommended human doses for depression and~~ MRHD for OCD and Panic Disorder, ~~respectively~~ on a mg/m^2 basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions, which consisted of vacuolation of epididymal tubular epithelium and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis occurred at doses which were ~~25, 21 and 21 times the highest recommended human dose for depression, OCD and Panic Disorder, respectively on a mg/kg basis. These are 7.3~~ 4.9 times the MRHD for depression ~~, 7.1 and 7.1~~ and 4.1 times the ~~maximum recommended doses for depression,~~ MRHD for OCD and Panic Disorder, ~~respectively~~ on a mg/m^2 basis.

NOTE: after studying the original NDA review, I have concluded that the finding of pre- and post-implantation loss was only marginal and was confounded by severe maternal toxicity and, therefore, need not be included in labelling.

Pregnancy

Teratogenic Effects - Pregnancy Category ~~B~~ C

Reproduction studies were performed in rats and rabbits at doses up to ~~50 and 6 times the maximum recommended human dose for depression (50 mg/day) and up to 42 and 5 times the maximum daily human dose for OCD and Panic Disorder (60 mg/day), respectively on a mg/kg basis. These are 10~~ 9.7 (rat) and ~~2~~ 2.2 (rabbit) times the maximum recommended human dose (MRHD) for depression (50 mg) and ~~8.3~~ 8.1 (rat) and ~~1.7~~ 1.9 (rabbit) times the ~~maximum recommended human dose~~ MRHD for OCD and Panic Disorder, on a mg/m^2

basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at 0.19 times (mg/m^2) the MRHD for depression and at 0.16 times (mg/m^2) the MRHD for OCD and Panic Disorder. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

TO THE SPONSOR:

As with other serotonin reuptake inhibitors, we find it necessary to request that the decreased survival of rat pups in reproduction toxicology studies receive more emphasis in labeling. Because it is not clear whether this finding was related to effects of the drug on the developing fetus *in utero* or was secondary to postnatal drug effects on the dams and/or pups, we have labeled PAXIL® pregnancy category C. If you were to conduct a cross-fostering study that clearly established that the adverse effect on pup survival occurred as a result of a postnatal effect rather than an *in utero* effect of drug on the fetus, the labeling may be changed from pregnancy category C to pregnancy category B. We recommend that you submit the protocol for this study for our concurrence before initiating it.

Steven Sparenborg

STEVEN SPARENBORG, Ph.D.

cc: NDA 20-031
HFD-120
HFD-120/GFitzgerald
/SSparenborg
/PDavid

DRAFT

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Supplement SEI-007; Vol. 49.013

NDA 20-031

Reviewer:	Steven Sparenborg, Ph.D.
Dates:	Written Review February 6, 1995 Approval Decision Due - December 7, 1995 Submission Received - December 7, 1994
Sponsor:	SmithKline Beecham Pharmaceuticals
Drug:	PAXIL™ (paroxetine hydrochloride)
Category:	selective serotonin reuptake inhibitor
Indication:	obsessive compulsive disorder (already approved for treatment of depression)
Related IND's:	
Max. Recommended Dose	60 mg
Dosage Forms and Route of Administration	10, 20, 30, 40, 50 mg tablets for oral use

Pharmacology

The sponsor submits two pharmacology studies to support its claim that there is preclinical evidence that PAXIL should be effective clinically for obsessive compulsive disorder. They argue that chronic SSRI treatment interferes with the ability of m-CPP to exacerbate OCD symptoms in humans. Furthermore, m-CPP induces repetitive mouth movements in rats. This repetitive exaggeration of a normal behavior is suggestive of a symptom of OCD. Chronic treatment with paroxetine reduced this behavior in rats. The sponsors target the 5-HT_{2c} receptor as the mechanism through which OCD symptoms may be ameliorated. m-CPP acts as an agonist at this site.

"The effect of 21 days administration of paroxetine, fluoxetine, desipramine (10 mg/kg, p.o.) and clomipramine (10, 20, 30 and 70 mg/kg p.o.) on m-CPP-induced hypolocomotion in rats."

Locomotion in a test box (the number of transits from one end to the other) and the number of rearings were reduced by m-CPP (4 and 6 mg/kg, i.p.) in male CD rats. Chronic paroxetine and fluoxetine and the highest dose of clomipramine partially blocked this reduction in locomotion and rearings. Desipramine, which primarily acts as an inhibitor of NE reuptake, did not affect them. Acute pre-treatment with these drugs did not affect the ability of m-CPP to reduce locomotion and rearings.

This study merely demonstrates that paroxetine can interfere with the effects of m-CPP. In the following study, the sponsor tries to link m-CPP with OCD by suggesting that m-CPP-induced mouth movements model compulsive, repetitive movements in humans.

"The effects of repeated (daily x 21 days) doses of paroxetine and fluoxetine (10 mg/kg, p.o.) and single doses of haloperidol (0.1 and 0.3 mg/kg i.p.), amphetamine (0.5 and 1 mg/kg i.p.), clonidine (0.1, 0.2 and 0.5 mg/kg i.p.), SB 206553 (10 mg/kg p.o.) and naloxone (5 and 10 mg/kg s.c.) on m-CPP-induced mouth movements in rats."

The drugs were given as acute pre-treatments one hour before m-CPP or as daily treatments for 21 days and then the m-CPP challenge. Paroxetine reduced the number of mouth movements in a 5 min period from 142 to 88. Fluoxetine was not effective. Both paroxetine and fluoxetine increased the amount of m-CPP in the brain by nearly five-fold. The drugs given acutely, namely amphetamine, clonidine, SB 206553, and haloperidol, but not naloxone, reduced m-CPP-induced mouth movements, also. Naloxone increased them. The fact that fluoxetine did not act just as paroxetine did is unexplained. It calls into question the real mechanism of action of paroxetine in this model. It also calls into question the appropriateness of the model. We have recently approved fluoxetine for OCD.

Toxicology

The only toxicity study submitted with this supplement was the following:

"BRL 29060: Mutation tests with escherichia coli, WP2 pKM101 and WP2 uvrA pKM101."

Conducted in Welwyn, UK by SKB. Paroxetine was toxic to the cells at concentrations of 540 µg/plate and greater. 400 µg was the highest concentration used in the mutagenicity test. There was no evidence of increased revertants with or without S-9 in either strain of bacteria. The positive controls acriflavine, mitomycin and MMS, all increased the numbers of revertants. No evidence of a mutagenic effect by paroxetine.

Summary

The pharmacology studies reviewed here suggest that this drug may be useful in OCD, but with no more significance than does the general view held by most people that SSRI's should be effective for this indication. There is no data to support the argument that pharmacological intervention in OCD is mediated through 5-HT_{2c} receptors. Binding studies or functional assays of the 5-HT_{2c} receptor have not been done with paroxetine. The addition of the Ames *E. coli* assay does not affect our interpretations of the mutagenicity of this drug. This test was negative, as were all the other mutagenicity tests previously performed.

The most significant issue for pharmacology/toxicology is the request for an increased clinical dose. PAXIL for depression has a recommended dose of 50 mg, but for OCD, the proposed recommended dose is 60 mg. Preclinical toxicity studies generally do not have the resolution to predict an increased risk of a relatively small dose change, such as is requested here. There are no toxicity studies with paroxetine that obviously warn against the dose increase from 50 mg to 60 mg.

The use of a higher dose necessitates re-calculation of the dose multiples used in carcinogenicity and reproductive sections of package insert labeling.

Recommendations

1. There are no toxicity findings that should clearly prevent the approval of this supplement. Human safety data may be more relevant for making a decision to approve or disapprove this request.

2. The following changes should be made in the labeling for this product:

Carcinogenesis: simply change the multiples of the mg/m^2 from 2.5 to 2.0 for the mouse and from 5.8 to 3.2 for the rat.

Mutagenesis: no changes required

NOTE: the changes recommended for the reproductive sections incorporate changes I have proposed elsewhere based on the mortality of rat pups in post-natal studies and also include the necessary recalculations of dose multiples required by the dose increase requested in this supplement.

Impairment of Fertility

~~Serotonergic compounds are known to affect reproductive function in animals. Impaired reproductive function (i.e.,~~ A reduced pregnancy rate~~,~~ and increased pre- and post-implantation losses~~, decreased viability of pups) was~~ were found in reproduction studies in rats at doses of paroxetine which were 15 or more times the highest recommended human dose on a mg/kg basis, or ~~4.4~~ 2.4 times on a mg/m^2 basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions, which consisted of vacuolation of epididymal tubular epithelium and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis occurred at doses which were 25 times the highest recommended human dose on a mg/kg basis or ~~7.3~~ 4 times on a mg/m^2 basis.

Pregnancy

Teratogenic Effects - Pregnancy Category ~~B~~ C

Reproduction studies performed in rats and rabbits at doses up to 50 and 6 times the maximum recommended human dose on a mg/kg basis or ~~10~~ 8 and ~~2~~ 1.9 times on a mg/m^2 basis, respectively, have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation. This effect occurred at 1 times (mg/kg) or 0.16 times (mg/m^2) the maximum human daily dose. The no effect dose for rat pup mortality was not determined. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Steven Sparenborg

STEVEN SPARENBORG, Ph.D.

cc: NDA 20-031
HFD-120
HFD-120/GFitzgerald gf 2/13/98
/SSparenborg
/PDavid

SENSITIVE

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-031 S-007

PAXIL® TABLETS (20-mg)

(Paroxetine Hydrochloride)

CENTER FOR DRUG EVALUATION AND RESEARCH

HFD-120 REVIEW DIVISION

DATE COMPLETED 26/07/95

The sponsor provides an updated Environmental Assessment for S-007. The assessment includes the information summarized below.

1. Date: October 28, 1994

2. Name of applicant/petitioner: SmithKline Beecham Pharmaceuticals

3. Address: Four Falls Corporate Center
Route 23 and Woodmont Avenue
P.O.Box 1510
King of Prussia
PA 19406

4. Description of the proposed action:

The sponsor indicates that the purpose of the proposed action is to add a new indication, Obsessive-Compulsive Disorder to the currently approved application for Paxil ® 20-mg tablets(NDA 20-031, November 29, 1989).

The Chemistry and manufacturing Controls for the supplement are the same as described in the approved NDA and subsequent amendments and supplements. No change is reported for the manufacturing sites of the drug substance or products. Updated documentation for disposal firms is provided.

5. Identification of chemical substances that are the subject of the proposed action:

Adequately described. No change from approved NDA.

6. Introduction of substances into the environment: For the site(s) of production:

Adequately described. Estimates of the maximum expected concentration (MEEC) of the major metabolite of paroxetine are provided. These reflect an increase of less than 5% to the MEEC in the approved NDA.

7. Fate of emitted substances in the environment:

Adequately described. No change from approved NDA.

8. Environmental effects of released substances:

Adequately described. No change from approved NDA.

9. Use of resources and energy:

Adequately described. No change from approved NDA.

10. Mitigation measures:

Adequately described.

11. Alternatives to the proposed action:

No potential adverse environmental impacts have been identified for the proposed action.

12. List of preparers:

The sponsor includes a list of preparers with a brief description of their qualifications.

13. Certification:

The sponsor submits adequate certification signed by James R Hagan, P E., Vice President & Director, Corporate Environment & Safety, SmithKline Beecham (October 31, 1994).

14. References:

Adequate.

15. Appendices:

Adequate.

Conclusions and Recommendations: A FONSI was prepared for the approved NDA (December 29, 1992). We recommend the same action for S-007 since the supplement has indicated no change in CMC, manufacturing locations, or usage patterns that would necessitate a different action and the increase in the MEEC due to increased usage of the drug is insignificant and is not expected to be toxic.

Reviewed by: Mona Zarifa

Mona Zarifa, Ph.D., HFD-120

Review Completed: July 26, 1995

Concurrence:

Stanley W. Blum, Ph.D., HFD-120 Environmental Scientist, CDER

cc: Orig: NDA 20-031
HFD-120/Division File
HFD-120/MZarifa
HFD-120/SBlum
HFD-120/PDavid

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

[PAXIL® TABLETS]
[Paroxetine Hydrochloride]

[20-mg]

NDA 20-031 S007

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION HFD-120

Finding of NO Significant Impact
NDA 20-031 S007
Paroxetine hydrochloride Tablets

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decision maker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their efficacy supplement S007 for the approved NDA 20-031 for Paroxetine Hydrochloride, SmithKline Beecham has conducted a number of environmental studies and prepared environmental assessments (21 CFR 25.31a(a); ~~See attached Environmental Assessment Review~~) which evaluates the potential environmental impacts of the manufacture, use and disposal of the drug product. See the attached Environmental Assessment ~~Review~~.

A new indication is introduced for Paroxetine HCl, the treatment of Obsessive-Compulsive Disorder. The drug is intended for use as 20 mg tablets to be taken orally once daily by male and female adults.

The drug substance and the drug product are manufactured at the same sites as in the approved NDA. Updated documentation for disposal firms is provided in the Environmental Assessment. The maximum expected environmental concentration (MEEC) for the new indication is also provided. For details on the environmental effects of paroxetine hydrochloride see the FONSI of the approved NDA.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are

expected to minimize occupational exposures and environmental release. The increase in the MEEC of the substance due to increased usage is insignificant and is not expected to be toxic. Any residues of paroxetine hydrochloride or its major metabolite entering the environment as a result of administering the drug to humans are expected to rapidly degrade.

7/26/95
DATE

PREPARED BY
Mona Zarifa, Ph.D.
Review Chemist
HFD-120

8/17/95
DATE

DIVISION CONCURRENCE
Stanley W. Blum, Ph.D.
Supervisory Chemist
HFD-120

8/30/95
DATE

Approved
Environmental Scientist
Center for Drug Evaluation and Research

8/24/95
DATE

Concurred
Robert A. Jerussi, Ph. D.
Associate Director for Chemistry
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachments: Environmental Assessment

CC: Original NDA 20-031/HFD-120
Division File
FONSI File NDA 20-031/HFD-004
Docket File NDA 20-031/HFD-004
FOI Copy/HFD-019

ENVIRONMENTAL ASSESSMENT

Paroxetine OCD

16 June 1995

Prepared By:
Corporate Environmental Research Laboratory
SmithKline Beecham
709 Swedeland Road
Swedeland, PA 19479

ENVIRONMENTAL ASSESSMENT

Paxil ™(Paroxetine Hydrochloride) Tablets

June 16, 1995

REDACTIONS MADE BY APPLICANT

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Paxil ™(Paroxetine Hydrochloride) Tablets

June 16, 1995

ENVIRONMENTAL ASSESSMENT

***Paxil*™(Paroxetine Hydrochloride) Tablets**

June 16, 1995

1. **DATE:** June 16, 1995

2. **NAME OF APPLICANT:** SmithKline Beecham Pharmaceuticals

3. **ADDRESS:** Four Falls Corporate Center
Route 23 and Woodmont Avenue
P.O. Box 1510
King of Prussia, PA 19406

4. DESCRIPTION OF THE PROPOSED ACTION:

4.1 Description of the Requested Approval

SmithKline Beecham Pharmaceuticals is requesting approval to register, manufacture, package and market paroxetine hydrochloride (NDA # 20-031) as an ethical pharmaceutical for the treatment of Obsessive-Compulsive Disorder (OCD). Paroxetine is intended for use by males and females as tablets to be taken orally.

4.2 Need for the Proposed Action

Paroxetine hydrochloride is a novel phenylpiperidine compound with antidepressant activity. The apparent mechanism of action is by specific inhibition of 5-hydroxytryptamine uptake in the central nervous system.

This Environmental Assessment reflects the effluent discharges based on the current maximum marketing estimates of production of drug substance and product (in 1998), and describes the waste treatment and disposal processes at SmithKline Beecham Pharmaceuticals facilities at SmithKline Beecham (Manufacturing) Limited in Cork (Ireland), Irvine Scotland (U.K.), and Cidra (Puerto Rico). It also includes all of the fate and effects data and results which have been obtained to date for paroxetine itself and for its major human metabolite.

The manufacture of paroxetine substance and tablets will employ the same environments and utilize existing plants that are also currently manufacturing other pharmaceutical products.

ENVIRONMENTAL ASSESSMENT

***Paxil*™(Paroxetine Hydrochloride) Tablets**

June 16, 1995

REDACTIONS MADE BY APPLICANT

4.3 Location where Product will be Produced

Paroxetine, the drug substance in the product which is the subject of the proposed action, is manufactured at the following facilities:

Stages 1-3 of the drug substance process are carried out at:

SmithKline Beecham (Manufacturing) Limited
Currabinny
Carrigaline
County Cork
Ireland

SmithKline Beecham (Manufacturing) Limited, Cork (Ireland) is located approximately twelve miles south of Cork City on the southern shores of Cork Harbor. There is a total landbank of 130 acres, but the facility occupies only 28 acres. The immediate area is rural, with some farms and dwellings within a half mile radius of the boundary fence. The site discharges an aqueous waste into Cork Harbor after on-site biological treatment.

Stages 4-7 of the drug substance process are carried out at:

SmithKline Beecham Pharmaceuticals
Shewalton Road
Irvine, Ayrshire, KA11 5AP
Scotland

The Irvine facility is located on the southwest coast of Scotland, on a site of approximately 360 acres on flatlands approximately 1.5 miles inland from the coast of the Clyde River estuary in Irvine, Scotland (U.K.). The site has a small 150 foot hill to the southern boundary. The site also borders a farm, a wooded area, and a river. The area between the plant and the sea is open flatlands.

Paroxetine drug product will be prepared at the following facility:

SB Pharmco Puerto Rico Inc.
Road 172, Km 9.1
Puerto Rico 00739

The Cidra facility for the drug product manufacture is a site of approximately 52 acres located in an agricultural/urban/industrial area on the central mountainous ridge of the island of Puerto Rico. Details on the environmental characteristics of the Cidra community are given in Appendix V.

4.4 Locations where Product will be Used

Paroxetine drug product will be used in the United States of America, with predominant use coinciding with areas of greatest population density.

4.5 Locations where Product will be Disposed of

Paroxetine drug product returned goods will be collected at the following site:

Division KENCO Group Inc.
1704 Mid Park Drive
Knoxville, Tennessee 37291

From this site, the materials will be shipped to one or more of the following licensed outside waste disposal firms for destruction by high temperature incineration:

SmithKline Beecham Pharmaceuticals
Bristol Industrial Park
Weaver Pike
Bristol, Tennessee 37620

Rollins Environmental Services (NJ), Inc.
Rt. 322 & I-95
Bridgeport, NJ 08014

Environmental Healthcare Incorporated
Delray Beach,
Florida 33447

Documentation for these disposal firms is provided in Appendix I.

ENVIRONMENTAL ASSESSMENT

Paxil ™(Paroxetine Hydrochloride) Tablets

June 16, 1995

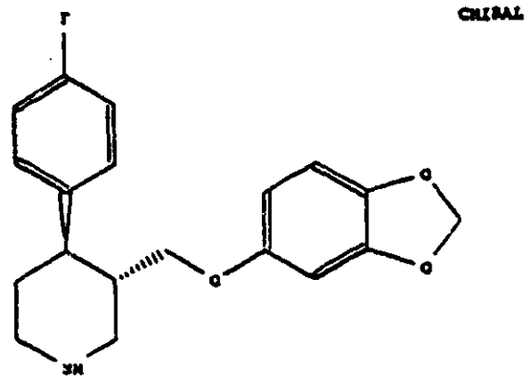
5. DESCRIPTION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION:

5.1 Complete Nomenclature

British Approved Name (BAN):	Paroxetine*
INN:	Paroxetine*
USAN:	Paroxetine*
Chemical Name:	(-)Trans-4-(4'-fluorophenyl)-3-(3',4'-methylenedioxyphenoxy methyl) piperidine hydrochloride hemihydrate

*The dosage form contains paroxetine hydrochloride

5.2	CAS Number: (hemihydrate)	110429-35-1
	CAS Number: (hydrochloride)	78246-49-8
5.3	Laboratory Code:	BRL 29060A (hydrochloride)
		BRL 29060 (free base)
5.4	Molecular Formula:	$C_{19}H_{20}NO_3F \cdot HCl \cdot \frac{1}{2}H_2O$
5.5	Molecular Weight (salt-hemihydrate):	374.8
	Molecular Weight (hydrochloride):	365.8
	Molecular Weight (free base):	329.3
5.6	Structural Formula (free base):	



	Description:	White to off-white solid
	Additives:	Not applicable
5.9	Impurities:	

Organic impurities arising from the synthesis are determined by GC and HPLC. Solvent content is measured by GC and the inorganic impurities (heavy metals and sulfated ash) are also monitored. Identification is included on the drug substance specification. The compound is stable, and no degradants are likely to arise under normal conditions.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 Introduction from Production of Drug Substance

6.1.1 Introduction from Drug Substance Production at SmithKline Beecham (Manufacturing) Limited, Cork, Ireland

Stages 1-3 of paroxetine drug substance production will be carried out at SmithKline Beecham (Manufacturing) Limited, Cork, Ireland. Environmental evaluations of the impacts from drug substance production follow.

Stages 1-3 of paroxetine drug substance production will utilize the same facilities currently being used for the production of other pharmaceuticals. The following evaluations of the anticipated environmental impact of paroxetine production are based on estimates of maximum yearly production and on existing waste treatment systems at SmithKline Beecham (Manufacturing) Limited, Cork, Ireland. Engineering estimates are used to predict anticipated discharge levels; however, the evaluations do not reflect changes in treatment process operations or technology which might be implemented before actual approval of the application.

SmithKline Beecham (Manufacturing) Limited, Cork, Ireland is expected to remain in compliance with applicable waste effluent permits throughout the production of paroxetine drug substance.

6.1.1.1 Waste Stream Summary and Disposition

The types of waste streams generated at SmithKline Beecham (Manufacturing) Limited, Cork (Ireland) will be disposed of such that release into the environment (gaseous and aqueous waste) will not exceed plant permit levels for the Cork facility (see Appendix II).

6.1.1.2 Material Balance

Material balance information for the chemical inputs, process intermediates and effluents was determined for stages 1-3, thus accounting for all materials and amounts used in or produced by these stages. Waste outputs include leftover material resulting from production, assay solutions sampled before and after filtration, and floor and equipment washings.

6.1.1.3 Controls Exercised on Wastes

6.1.1.3.1 Air and Off-Gases

Off-gas waste streams produced during stages 1-3 of the process are incinerated. If the incinerator is off-line, the gaseous wastes are passed through caustic scrubbers before venting to the atmosphere. A solvent recovery stack vents into a standby incinerator if the main incinerator goes off-line; it does not vent directly to the atmosphere.

Fugitive emissions are monitored if there is reason to suspect a gaseous leak. Air from the buildings where chemical processes are performed is filtered through two chemical absorbers. Air is automatically monitored every half hour by gas chromatography for several compounds, depending on the processes being performed, as it is discharged to the atmosphere. The production site buildings (2) at SmithKline Beecham (Manufacturing) Limited, Cork (Ireland) vent a total of 102,500 m^3 of air per hour (102,000 and 500 m^3).

6.1.1.3.2 Aqueous Wastes

Most process waste streams produced during paroxetine production at Cork are incinerated. Process effluents are stored prior to incineration, which is performed by three incinerators. After incineration, the effluent gas is passed through an absorber for the scrubbing of acidic compounds before discharge to the environment through a stack.

This scrubber unit consists of a caustic solution circulating through a packed bed. Incinerator scrubber liquors are sent to the on-site wastewater treatment facility.

At discharge, incinerator gases are continuously monitored for CO, SO_2, HCl, NO_x and total organic carbon (TOC). The amount of organic material remaining after incineration is calculated using a 99.99% incineration destruction efficiency, based upon the known removal efficiencies for mercaptan and methylethyl ketone (MEK). Regulations governing the operation of the incinerators are administered by the Cork County Council of Cork, Ireland. The facility is operating under Air Pollution Register Number A.P. 9/89.

Review of the measured and calculated levels of affected incineration effluent components, and a comparison with their permitted levels resulted in the determination that the Cork facility will be in compliance with their incinerator permits during the disposal of incinerated waste streams produced by paroxetine stages 1-3 for the paroxetine OCD indication.

Solvents from several aqueous waste streams are recovered either on-or off-site, with the unrecovered portions of the on-site recovered streams disposed of by incineration. All SB disposal contractors are audited by SmithKline Beecham.

6.1.1.3.3 Biotreatment System

None of the paroxetine process waste streams are treated in the on-site wastewater biotreatment facility. Scrubber liquors from the incinerators, however, are sent for aerobic biological treatment before being discharged.

The biotreatment facility operates under wastewater license W.P. (W) 8/91, issued in December 1991. This facility incorporates a 3000 m^3 basin of activated sludge, which has a retention time of 10 days. The waste to be biotreated (including sanitary effluents, floor washes, incinerator quench streams, and scrubber and environmental spent liquors) is sent to a balancing tank prior to neutralization in a second tank. The wastes are then sent to a stripping tank, prior to passing to an aeration tank to reduce biological oxygen demand (BOD). After aeration, some of the waste is aerated a second time in another tank, while the remaining waste is sent to a clarifier. The twice-aerated effluent is passed

to another clarifier. Both clarifiers are dosed with polyelectrolytes, and effluent wastes are sent to the final holding tank (300 m^3) prior to discharge.

Several parameters of the effluent are monitored on a daily basis at three stages of the treatment process. The flow rate, pH, COD, total dissolved solids and load (kg of COD per day) are monitored at the input stage, and the pH, dissolved oxygen, MLSS and F/M are monitored at the sludge plant. At the final holding tank, the pH, COD, suspended solids, ammonia and flow rate are also monitored. In addition to normal testing, effluent liquors are sampled if a problem (e.g., equipment malfunction) is discovered. Treatment of effluents results in >80% reduction in BOD.

6.1.1.3.4 Solid Waste

As of October 1 1994, all treatment plant sludge is mechanically dewatered to not less than 15% solids prior to off-site disposal, with the extracted liquid returned to the effluent treatment unit (wastewater license W.P. (W) 8/91). Sludge wastes are scheduled to be tested for the presence of heavy metals, organohalogens and other micropollutants at regular intervals; sludge waste regarded as non-hazardous is then disposed of in a lined landfill designated for non-hazardous materials, with leachate monitoring.

Spent solid waste from paroxetine process stages 1-3 is sent off-site for disposal. All SB disposal contractors are audited by SmithKline Beecham. There are currently no limits as to the amount of solid wastes disposed of off-site.

6.1.1.4 Certification of Compliance

SmithKline Beecham (Manufacturing) Limited, Cork (Ireland) is committed to environmental control and will operate within its permits during paroxetine drug substance process stages 1-3. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix II.

6.1.2 Drug Substance Production at Irvine

Paroxetine process stages 4-7 will be performed at Irvine, a SmithKline Beecham Pharmaceuticals' facility in Ayrshire, Scotland (U.K.). Environmental evaluations of the impacts from drug substance production follow.

6.1.2.1 Waste Stream Summary and Disposition

During stages 4-7, waste is comprised of several waste streams. The wastes generated at Irvine will be disposed of using appropriate procedures, such that their disposal will not violate applicable regulations.

6.1.2.2 Material Balance

Material balance information for the chemical inputs, process intermediates and effluents was determined for stages 4-7, thus accounting for all materials and amounts used in or produced by these stages. Waste outputs include leftover material resulting from production, assay solutions sampled before and after filtration, and floor and equipment washings.

6.1.2.3 Controls Exercised on Wastes

The Irvine plant is registered under the Alkali & Works Regulations 1906 as an Amines Works, a Bisulphite Works, a Bromine Works, a Chlorine Works, a Hydrochloric Acid Works and a Sulphuric Works.

6.1.2.3.1 Air and Fugitive Emissions

Gases produced during the process stages are generated at levels permitted to be emitted directly to the atmosphere. Permission to operate certain chemical processes at Irvine is given by the H.M. Industrial Pollution Inspectorate for Scotland (HMIPIS); processes that require such permission are clearly defined by Government Regulations. Permission to operate any of these processes is granted only after prior discussion with HMIPIS inspectors. Typical discussions include levels of gaseous emissions versus scrubber design, and evidence is often required to show that excessive gaseous emissions (after scrubbing) are not occurring. Sampling of post-scrubbed gases is performed by Draeger tube measurement.

6.1.2.3.2 Aqueous Waste Disposal

Several aqueous waste streams are disposed of on-site as effluent. These aqueous wastes are equalized with other Irvine plant wastes and fresh water (from a nearby river), and pumped to two storage tanks prior to discharge to a sea outfall in the Clyde Estuary. Aqueous effluent from the Irvine plant is diluted with fresh water in the storage tanks.

Consent (permit) levels for chemicals discharged by the Irvine plant were established through negotiation with the local water authority; the limits are reviewed and revised regularly. Consent to discharge is granted by the Clyde River Purification Board (CRPB) under the Control of Pollution Act 1974. To continue discharge consent, the water effluent must comply with stated consent levels for several materials. The consent levels are reviewed and revised regularly by the CRPB. The Irvine facility permit levels are presented in Appendix III.

Aqueous wastes not suitable for solvent recovery or discharge are currently sent off-site to a licensed waste disposal company for incineration. These aqueous wastes, based on results of treatability data and after the planned commissioning of a full-scale biological wastewater treatment plant in 1995, may be considered for on-site treatment.

6.1.2.3.3 Solid Waste Disposal

Solid waste produced during process stages 4-7 is sent off-site for disposal. Disposal of any wastes not suitable for discharge is controlled by the Control of Pollution (Special Wastes) Regulations 1980. These wastes are held in a licensed storage area at Irvine prior to release to licensed waste disposal companies. The license for the Irvine storage area is granted by the Cunninghame District Council. Waste disposal companies currently employed have been audited by SmithKline Beecham personnel for competence, as documented in the Waste Management Audit 1990. There are no limits or restrictions placed on the quantities of materials that may be sent to the licensed disposal facilities.

6.1.2.3.4 Regulated Aqueous Effluent Components

Review of the measured and calculated concentrations of affected aqueous effluent components and a comparison with their permit levels resulted in the determination that the Irvine facility is in compliance with their aqueous effluent permits. The effluent is routinely monitored by the Irvine QA department, and the water authority also takes samples for comparison and to ensure adherence to consent levels.

6.1.2.4 Environmental Legislation

The main piece of legislation governing the disposition of wastes is the Environmental Protection Act, especially the Prescribed Processes and Substances Regulations 1991. In association with these regulations is the Environmental Protection (Applications, Appeals and Registers) Regulations 1991.

The statutory instruments for the United Kingdom that may be applicable to the Irvine site and the production of paroxetine are listed in Appendix IV.

6.1.2.5 Emergency Response Plan

The initial response to any emergency is under the control of the appropriate plant supervisor (Incident Controller). The fire alarm or toxic gas alarm results in the evacuation of the area and the immediate response of the Irvine site's Special Duty Team. Members of the Team (Irvine employees) are trained in a wide range of emergency duties, including firefighting, search and rescue, first aid treatment and spill control measures. Special Duty Team members are either Production or Engineering employees, from all shifts and all site production areas.

The fire alarm automatically initiates a response from the external fire brigade. The first arrival of the external services occurs approximately 4 minutes after the alarm is sounded, with additional firemen assisting in accordance with the external emergency service response plan for the Irvine site.

In emergencies, communications are coordinated at the main gatehouse, which is continuously manned by security personnel. Communication systems include radio communications to each site area, a site-wide personnel address system and emergency telephones.

Emergency equipment immediately available to the Incident Controller and Special Duty Teams includes fire hoses, fire extinguishers, water monitors, breathing apparatus, protective clothing, a Special Duty Team transport vehicle, First Aid/oxygen equipment, a stretcher, spill containment booms and absorbents.

In the event of a serious escalation of an emergency situation, the major emergency plan for the site will be implemented, which results in mobilization of senior managers and technical specialists.

6.1.2.6 Spill Control

All storage vessels are contained within spillage bunds (dikes), in accordance with U.K. Health and Safety Executive guidelines on the storage of flammable liquids and other materials.

All production plant and material storage areas are served by the site effluent drainage system, which carries waste waters to the sea outfall. Consequently, spills in these areas are prevented from entering local surface waters.

Minor spills in production plants are handled by process staff, following appropriate spill procedures described for each type of material. Larger spills may either be retained in storage tank bunds, or otherwise drained to the site effluent system with waste water. The first action by process staff is to shut off the source of the spill, if possible, and alert supervisory staff and the Special Duty Team.

The Special Duty Team will use spill booms and absorbents to contain spilled material as much as possible, and then pump it into suitable containers. If necessary, substantial quantities of material that enter the site effluent system can be intercepted before release by holding the effluent in one of the balance/equalization tanks at the effluent outfall, where it may be treated appropriately.

If a spill occurs outside the areas served by the site effluent system, (e.g., during transport on site), storm water outfalls can be plugged to limit the movement of material to surface water courses outside the site boundary, in addition to the Special Duty Team's efforts to contain the spill.

6.1.2.7 Certification of Compliance

SmithKline Beecham Pharmaceuticals, Irvine, Scotland (U.K.) will operate within its permits during the production of paroxetine drug substance. A citation of and statement of compliance is provided in Appendix III.

6.2 Introduction from Production of Drug Product at Cidra

Paroxetine OCD will be prepared as a 20 mg tablet formulation. The paroxetine OCD tablets will be produced in a continuous process that consists of granulation, drying and blending, compression and coating, and packaging at SmithKline Beecham Pharmaceuticals Co. in Cidra, Puerto Rico. The manufacture of 20 mg tablets will

employ the same environment and utilize the existing plants that are currently used to manufacture other pharmaceutical products.

6.2.1 Waste Stream Summary and Disposition

Waste streams are produced during the production of paroxetine tablets due to rejection of inspected product, sampling, handling and cleaning operations. Effluent chemicals consist of an estimated loss of 3% of the input chemicals.

Waste generated at the Cidra facility will be disposed of using appropriate procedures, such that release into the environment (gaseous and aqueous waste) will not exceed Cidra permit levels (Appendix V). Information on the types of waste streams follows.

6.2.2 Material Balance

Material balance information for the chemical inputs, process intermediates and effluents was determined, thus accounting for all materials and amounts used in or produced during the drug product process. Waste outputs include material resulting from: filling adjustments; residual bulk drug at the end of production; inspection operations (rejects are discarded); sample assay solutions before and after filtration; and floor and equipment washes. For the purposes of this evaluation, the production campaign is assumed to use all of the drug substance, which is based on projected paroxetine production in 1998.

6.2.3 Controls Exercised on Wastes from Production

6.2.3.1 Air emissions

Dryer water vapor consists of water evaporated during drying processes. This stream is filtered before venting to the environment and should contain no hydrocarbons or particulates. The water collected is sent to the on-site wastewater treatment facility for biotreatment (see below).

Air emissions from the process fall under the State Rules and Regulations for Air Pollution Control. The regulations are administered by the Environmental Quality Board of the Commonwealth of Puerto Rico. The facility is operating under Permit No. PFE-21-0590-0477-I-III-0 and PFF-21-1089-0929-I-II-III-0, and is not considered to be a major pollutant source.

6.2.3.2 Aqueous Waste

Other aqueous waste streams consist of residual product formulation and coatings from equipment and floor washings. All drug product waste streams are sent to the on-site wastewater treatment facility. The aqueous stream is first pumped through a series of sand filters and an activated carbon adsorption system. The waste stream is then discharged into an equalization holding tank for aeration. The combined sanitary wastewater, process streams and digester supernatant are aerated to reduce oxygen demand, and blended with nutrients (phosphoric acid) for biotreatment in the activated sludge system.

The pH of the effluent stream is adjusted with sodium hydroxide prior to entering the activated sludge system, where it undergoes aerobic biotreatment. The residence time of effluent in the activated sludge basin is 24 hours, and the average volume maintained is 80,000 gallons. The treatment facility is designed for a 85,000 gallon per day flow, with a maximum capacity of 130,000 gallons per day. The biotreatment waste stream then enters a clarifier, where the sludge is allowed to settle and separate from the biotreated aqueous effluent.

The pH of the aqueous effluent is adjusted to 11.0 with hydrated lime and sent to a second clarifier, where solids are precipitated out of solution and removed by flocculation. The clarifier's precipitated solids are sent to the aerobic digester for further processing. The wastewater effluent is recarbonated and neutralized with carbon dioxide prior to passing through a second series of sand and carbon filters. The wastewater effluent from filters is then chlorinated. This stream then passes through a Reverse Osmosis (RO) unit. The RO unit permeate is then aerated and monitored for pH, temperature and dissolved oxygen before entering Quebrada Las Quebradillas (Las Quebradillas Creek). The RO unit reject goes to a tank from where part of it goes to the digester and the other part is discharge off-site to PRASA. Rainwater runoff from the grounds of the Cidra facility are also discharged to this creek, which empties into the Turabo River and flows into Carraizo Lake (the water source for the metropolitan area of San Juan). Prior to the discharge of the rainwater into the Creek, the influent can be diverted into a holding tank, which will hold any major spill or contaminated water.

The quality of the effluent discharge meets Puerto Rico's water quality standards. The treatment facility operates under National Pollutant Discharge Elimination System

(NPDES) Permit PR 0021997. In Puerto Rico, the NPDES Permit Program is administered by the U.S. Federal Environmental Protection Agency.

The facility is also regulated by the Puerto Rico Water Pollution Law, which is administered by the Assistant Secretary of Health for Environmental Health and Consumer Protection. Additional regulations include the Puerto Rico Harmful Spills Law, the Puerto Rico Public Policy Environmental Act, and the Puerto Rico Water Quality Standards, each administered by the Board of Environmental Quality. Permit limits for the wastewater discharge are stated in the NPDES permit. The discharge limits are presented in Appendix V.

Final effluent levels were calculated using the following equation:

$$(A \times 10^6/B/C)D = E$$

where:
- A = total quantity (kg) of component to waste/batch of paroxetine product;
- B = number of days over which discharge is made (1);
- C = site effluent discharge rate;
- D = removal efficiency, based on 1990 yearly average;
- E = concentration of component in effluent in mg/L.

For developing the discharge level data, it is assumed that no volatilization or bioadsorption of these materials occurs during treatment, and that biodegradation and filtration are the only operative removal mechanism for all stream components with the exception of paroxetine. This compound is expected to be removed essentially completely through the site's activated carbon adsorption system.

Review of the measured and calculated concentrations of affected aqueous effluent components and a comparison with their permit levels resulted in the determination that the Cidra facility is in compliance with their aqueous effluent permits.

Paroxetine tablet formulation wastewaters will not cause any impact on the waste treatment plant performance standards.

6.2.3.3 Solid Waste

The activated carbon from the biotreatment filters is replaced approximately every three months, and spent carbon is returned to the manufacturer for regeneration. Settled

sludge from the first clarifier in the biotreatment process is divided into two streams: sludge waste to an aerobic digester and sludge returned to the system. Within the digester the sludge waste is concentrated by settling and decanting the water. More water is then removed from the concentrated sludge slurry by means of a wedge filtration system and solar drying beds. The decanted water is recycled back to the feed of the wastewater treatment system. Dried sludge removed from the beds is disposed of at a municipal landfill, after testing using the Toxicity Characteristic Leaching Procedure (TCLP).

6.2.3.4 Environmental Legislation

The following partial list of federal legislation may affect operation of the wastewater treatment facility.

Federal Water Pollution Control Act, as amended
Clean Water Act, as amended
Resource Conservation and Recovery Act
Safe Drinking Water Act
Toxic Substances Control Act
National Environmental Policy Act

6.2.3.5 Safety

The Cidra facility has adopted personnel safety procedures in all areas of plant activity, including procedures and information on electrical hazards, tool use, fire hazards, chemical handling and first aid.

6.2.3.6 Certification of Compliance

SmithKline Beecham Pharmaceuticals Co. (Cidra) is committed to environmental control and will operate within its permits during the production of paroxetine drug product. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix V. A Material Safety Data Sheet for paroxetine hydrochloride is also given in Appendix V.

6.3 Introduction from Use of Drug Product

The environmental fate and effects of BRL 36610A (which is considered to be the major metabolite of paroxetine from an environmental perspective (see Item 7.1 below)) are discussed in Items 7 and 8, respectively.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

The experimental program undertaken to provide data for paroxetine fate assessment focused initially on paroxetine parent. Physical property data and depletion mechanism studies were carried out on paroxetine parent with the intent that the results could be extrapolated to the more polar major metabolite (BRL 36610A); see below. However, when results indicated that paroxetine itself was likely to be recalcitrant to ready microbiological degradation, samples of BRL 36610A were obtained and selected pivotal studies carried out on this compound as well, since it is the chemical actually excreted into the environment from use.

7.1 Metabolism

Drug metabolism studies and identification of the major metabolites of paroxetine [1] indicate that the compound is eliminated from the body by oxidative metabolism. Metabolism is initiated by oxidation at the methylenedioxyphenyl carbon atom by the liver, a well know metabolic process for compounds containing this moiety. Identification of metabolic end products in the urine of mice, Rhesus monkeys, and man indicated that this is the primary metabolic process for all species. The catechol intermediate resulting from the initial oxidation was too unstable to isolate. It is further metabolized, in part, by methylation at the meta-position (BRL 36610A), followed by conjugation of the free phenolic group with glucuronic acid or sulfate to produce the major metabolites in plasma, urine, and bile. Some methylation at the para position and cleavage of the ether linkage also occurs. The proposed metabolic pathway is illustrated in Scheme 1 below.

All of the species studied utilized the metabolic pathway depicted in Scheme 1. In human subjects, 68% of the urine radioactivity (equivalent to 40% of the dose) was identified as the metabolites shown. The very low percentage of dose excreted unchanged in the urine and feces of rats, monkeys and humans indicated that metabolism was the major determinant in the elimination of paroxetine hydrochloride. Because of its high lipophilicity, paroxetine is not excreted by the kidneys in significant amounts. Rather, the compound is eliminated by metabolism to a range of polar analogs and conjugates. The routes of excretion of metabolites depended upon the species studied; urine and feces were the predominant routes in man.

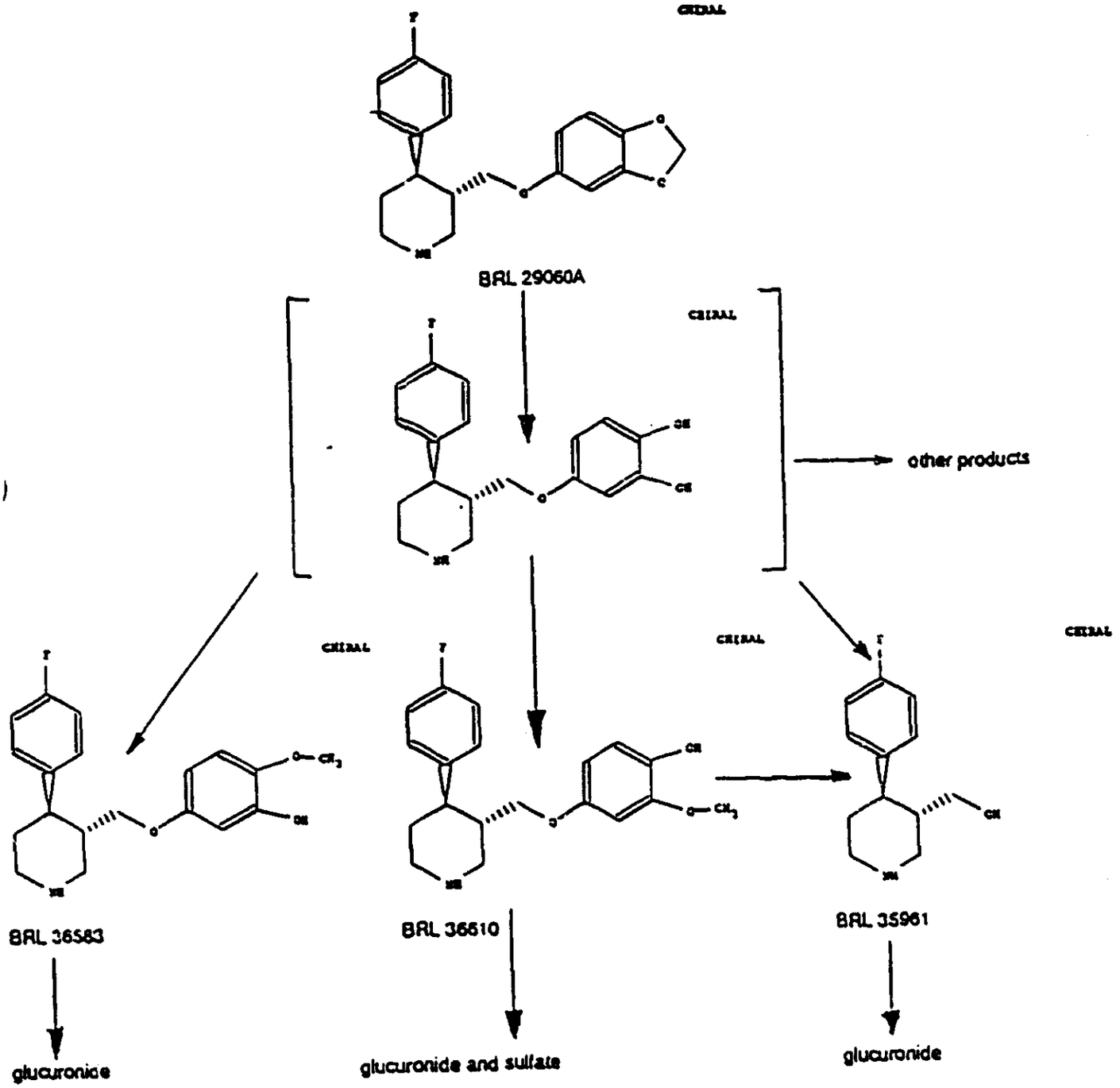
ENVIRONMENTAL ASSESSMENT

***Paxil*™(Paroxetine Hydrochloride) Tablets**

June 16, 1995

REDACTIONS MADE BY APPLICANT

Scheme 1: Proposed Metabolic Pathway for BRL 29060A



Given that glucuronide and sulfate conjugates would undergo rapid cleavage back to BRL 36610A in a waste water treatment plant environment, this compound was considered the major metabolite of paroxetine from an environmental prospective. BRL 36583, the minor metabolite, would be expected to behave in the environment in a manner similar to BRL 36610A. Therefore, no studies were carried out on BRL 36583. Rather, environmental fate and effects predictions are based on data on paroxetine parent and on paroxetine major metabolite, BRL 36610A.

7.2 Physical Properties of Paroxetine Hydrochloride

Physical properties were determined for paroxetine hydrochloride or its free base as appropriate. The data are summarized below for selected determinations. The details of each test follow, and a data summary sheet including results of environmental fate studies on paroxetine is given in Appendix VI. The analytical method and validation studies are listed as references [2, 3, 4]. All concentrations are reported in terms of the free base of paroxetine.

Property	Value	Comment
H_2O Solubility	1165 ± 22.6 mg/L (pH 7)	See 7.2.1
pK_a	9.6	See 7.2.2
Log K_{ow}	1.30 (pH 7)	See 7.2.3
Vapor Pressure (estimate)	<8.25E-6 torr (free base)	See 7.2.4
UV/Vis	Sign. abs. > 290 nm	See 7.2.5
Log K_{oc} (estimate)	0.8	See 7.2.6

7.2.1 Water Solubility

The water solubility of paroxetine hydrochloride as a function of pH was determined [6] using the under- and oversaturation method [5]. An anomaly was observed in the deionized water and pH 5 buffer systems, where the undersaturated and oversaturated solutions did not come within 5% of each other (indicating equilibrium), but rather differed by 22-29% and 24-37%, respectively. The pH 7 buffer system gave satisfactorily close results from both undersaturation and oversaturation studies; however, the pH 9 studies showed varying degrees of spread between results from the two procedures, as well as evidence of degradation of the paroxetine. See Item 7.4.1 for discussion of paroxetine hydrolysis. For use in fate prediction, the water solubility at pH 7 is used as the least subject to experimental anomalies and the most meaningful in

environmental terms. The equilibrium value for paroxetine hydrochloride hemihydrate in pH 7 buffer is 1165 ± 22.6 mg/L. BRL 36610A would be expected to be somewhat more soluble.

7.2.2 Dissociation Constant

Previous determinations of the paroxetine pK_a were carried out by SmithKline Beecham R&D in 50% aqueous dimethylsulfoxide (DMSO) and gave a pK_a of 9.9 [7]. Definitive determination of the pK_a for paroxetine in deionized water by SmithKline Beecham Environmental Research Laboratory [8] gave a value of 9.6. An abnormality observed with the results is the non-symmetric behavior of the titration curve at pH levels greater than the pK_a. While the compound started to precipitate out at pH levels >9, this should not have caused the non-symmetric behavior, although the pK_a values calculated from data points above pH 9 cannot be used. In a saturated solution, the concentration of free base is no longer free to vary but is constant at the solubility limit, thus invalidating the pK_a calculation.

It is more likely that the non-symmetry is due to the hydrolysis of the compound that starts to appear at pH levels around 9, and that this reaction rate is increased by the increase in base concentration brought about by the titration of the solution with NaOH. This is consistent with the observations during the water solubility studies discussed above, suggesting hydrolysis of paroxetine in the pH 9 buffer system. The failure of the system pH to rise once an equivalent of NaOH was added suggests that the hydroxide ion is being consumed by the hydrolysis reaction.

The above factors are thought to explain why preliminary determinations of the paroxetine pK_a gave a value of 7.3, previously reported in an earlier version of the environmental assessment. The real pK_a was missed because of the lack of a symmetric curve above pH 9.

The pK_a of BRL 36610A would be expected to be almost exactly the same as paroxetine parent, as the ionizable group and its chemical structural environment in the molecule is the same in both parent and metabolite.

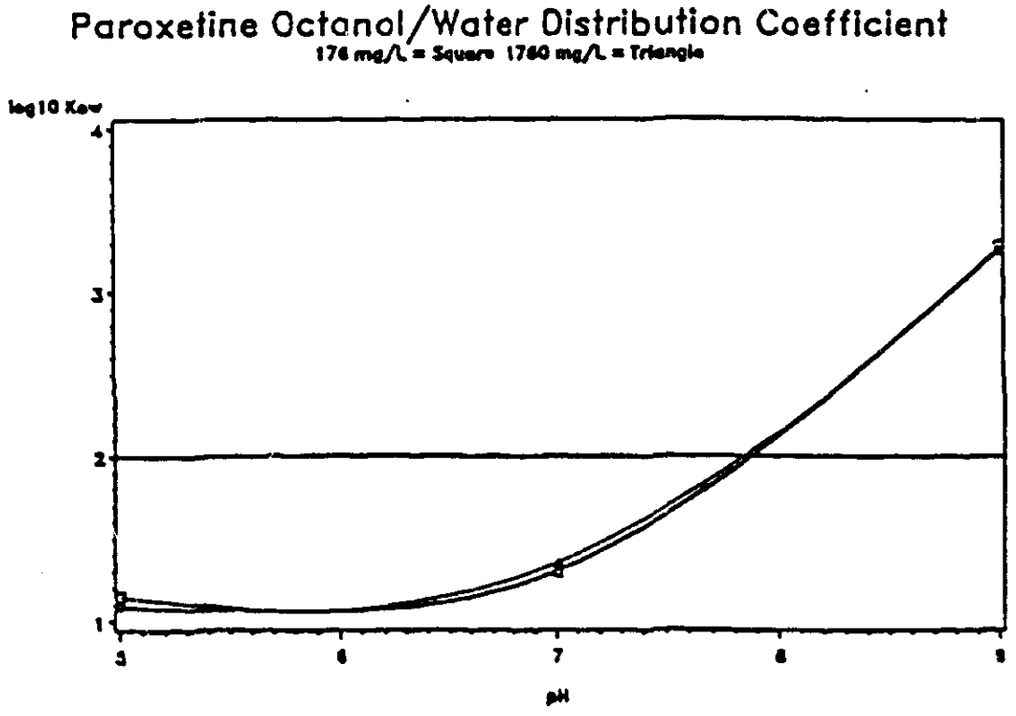
7.2.3 Octanol/Water Distribution Coefficient

The octanol/water distribution coefficients (K_{OW}) for paroxetine were determined [9] in triplicate at 25°C at three pH levels: 5, 7 and 9, and at two concentrations. The results are summarized below.

pH	Concentration 1 (176 mg/L) K_{ow} (%RSD)	$log_{10}K_{ow}$	Concentration 2 (1769 mg/L) K_{ow} (%RSD)	$log_{10}K_{ow}$
5	14.1 (3.5)	1.15	12.2 (3.3)	1.09
7	20.0 (1.8)	1.30	22.2 (1.2)	1.35
9	1930 (14.2)	3.29	1800 (4.2)	3.26

A plot of these results, shown in Figure 1, indicates that the log K_{ow} should not exceed 2 until a pH of about 7.9. Consequently, at typical environmental pH levels, the log K_{ow} will be such that no significant bioconcentration should occur. For the purposes of fate evaluations, a log K_{ow} of 1.32 will be used. Given its structural similarity to paroxetine, a similar value may be used for BRL 36610A.

Figure 1



7.2.4 Vapor Pressure

Because it is a relatively high molecular weight salt, paroxetine hydrochloride would be expected to have an extremely low vapor pressure. However, both the cationic protonated form and the neutral free base form will exist in the environment. Although the latter form will be at very low concentrations at environmental pH levels, it would be expected to be more volatile than the cationic form. Since the cationic form and the free base form are in equilibrium, the loss of the free base form by volatilization will cause the generation of more free base form by conversion of cationic form in order to restore the equilibrium. Thus, significant losses could occur, especially during aeration processes in wastewater treatment plants, were paroxetine free base to have an appreciable vapor pressure. In light of its low water solubility, the vapor pressure would not need to be very high to yield a relatively high Henry's constant. The vapor pressure of the free base of paroxetine was estimated using a volatility limit test, which represents a "worst case" scenario since all loss of compound is attributed to volatilization losses [10].

The vapor pressure was estimated to be less than 8.25×10^{-6} torr. This estimated vapor pressure, when coupled with the water solubility determinations, gives an estimated Henry's constant of $<10^{-8}$ to $<10^{-10}$ atm-m^3/mol. Based on these estimates, volatilization will not be a significant transport process in the environment for paroxetine. BRL 36610A would be expected to exhibit similar behavior.

7.2.5 UV/Vis Spectrum

The UV/Vis spectra of aqueous solutions of paroxetine hydrochloride were determined at pH 5, 7 and 9 [11]. Absorbance maxima of 234 and 292 nm were observed for all three pH values; another maximum at 210 nm was observed at pH 7 and 9, but not at pH 5. The molar extinction coefficients(e|) of 3736, 3827, and 3811 in L mol^{-1} cm^{-1} were calculated for pH 5, 7, and 9, respectively. The absorbance spectrum did not appear to be affected by the pH of the aqueous solution, and the significant absorption of light above 290 nm suggests that paroxetine hydrochloride may undergo direct photochemical degradation in the environment (see Item 7.4.3).

7.2.6 Soil Sorption/Desorption (K_{OC})

No soil sorption/desorption isotherm study to generate a K_{OC} value for BRL 36610A (the major metabolite of paroxetine) was performed. A preliminary estimate of the K_{OC} value for BRL 36610A may be made, however, based on data obtained on the adsorption of paroxetine itself to biomass. That some adsorption would occur was apparent from early studies on paroxetine biodegradability, where rapid depletion of some of the

paroxetine from solution occurred over the first day of the studies, followed by no further depletion despite culture acclimations, enrichments, etc. [12]. A controlled paroxetine biomass adsorption study was then carried out [13], monitoring depletion of paroxetine as a function of initial biomass concentration (as measured by total suspended solids (TSS)) and of time. The data were fit to a Freundlich equation

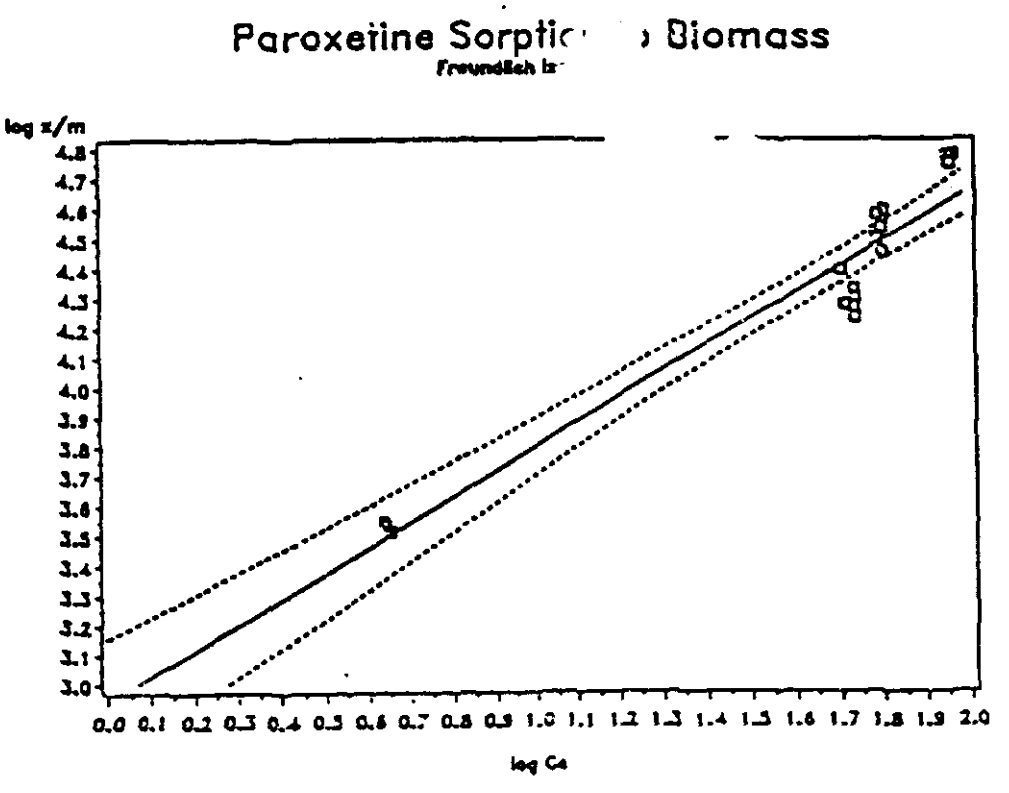
$$\text{Log } x/m = \log K + (1/n) \log C_e$$

where

Log x/m	=	logarithm of the amount of chemical sorbed per amount of adsorbent at equilibrium;
Log C_e		logarithm of the amount of chemical in solution at equilibrium;
K	=	Freundlich adsorption coefficient;
n	=	a constant describing the degree of nonlinearity of the isotherm. When n ≅ 1, the K_f Freundlich constant can be used as an adsorption distribution coefficient, K_d.

If a plot of Log x/m vs Log C_e gives a straight line, the slope of the line is the (1/n) linearity term and the intercept is the log K. The plot for paroxetine is given in Figure 2.

Figure 2



The data were subjected to the SAS General Linear Models Procedure [14] to give the linear regression results shown below:

PAROXETINE SORPTION TO BIOMASS

GENERAL LINEAR MODELS PROCEDURE

DEPENDENT VARIABLE: LOGCSORB

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE
MODEL	1	2.56453608	2.56453608	199.81
ERROR	13	0.20536048	0.01283503	PR > F
CORRECTED TOTAL		14	2.76989656	0.0001

R-SQUARE	C.V.	ROOT MSE	LOGCSORB MEAN
0.925860	2.6200	0.11329179	4.32404502

SOURCE	DF	TYPE I SS	F VALUE	PR > F
LOGCSOLN	1	2.56453608	199.81	0.0001

SOURCE	DF	TYPE III SS	F VALUE	PR > F
LOGCSOLN	1	2.56453608	199.81	0.0001

PARAMETER	ESTIMATE	T FOR H0: PARAMETER=0	PR > |T|	STD ERROR OF ESTIMATE
INTERCEPT	2.94109574	29.00	0.0001	0.10141504
LOGCSOLN	0.86121117	14.14	0.0001	0.06092614

The intercept term above shows that the estimated log $K_{biomass}$ for paroxetine is 2.94. See discussion on paroxetine metabolite and bioadsorption in Item 7.6.

7.3 Environmental Partitioning Estimates for Paroxetine Hydrochloride

Based on the physical property data generated for paroxetine hydrochloride and/or its free base, predictions of environmental distribution in the air, water, ground, and hydrosoil can be made. For this assessment, a simple fugacity equilibrium model is used to estimate the percent of the compound which would be expected to distribute in each compartment at steady-state, assuming no depletion mechanisms. For this evaluation, the QSAR system supplied by Technical Database Services was used [15].

This model appears to apply reasonably well to the paroxetine chemical structure. A comparison of the predicted physical properties with those actually determined for the free base (pH 9) is shown below.

Property	Predicted Value	Actual Value
Water Solubility- mg/L	203	318-485
Log P	3.25	3.27
pK_a	9.66	9.6

Used in the QSAR Environmental Partitioning Model, the actual data at pH 9 yielded the following prediction:

<<<< QSAR >>>>
Institute for Process Analysis
Montana State University

Name: Paroxetine Free Base

Smiles: O(-c(c(-O1)ccc2-OCC(C(-c(ccc(-F)c3)c3)CCN4)C4)c2)C1

QSAR Estimates for Exposure Assessment

LOG(Water Solubility) = -2.83 Mol/L
Log(BCF) = 2.19 BCF = 155.31
Absorption Coef. Log(Koc) = 3.12 (See Lyman et al. 1990) [16]
Hydrolysis Half Life = 1000 Days
Hydrolysis is not likely to be an important transformation mechanism for this chemical.

Henrys law Constant and Environmental Partitioning

Log10 (Henrys Constant) = -10.15 atm-m**3/mole
Lyman et al. 1990. [16] would conclude that a chemical with these properties is non-volatile. See p15-15.

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NEELY 100 Day Partitioning Pattern

Air	=	0.00 %
Water	=	70.11 %
Ground	=	15.46 %
Hydrosoil	=	14.43 %

However, the pH 9 data represent the lower limit of water solubility and the upper limit of log P. Using the actual physical property data generated in-house at pH 7, the environmental partitioning is as follows:

<<<< QSAR >>>>
Institute for Process Analysis
Montana State University

Name: Paroxetine Hydrochloride

Smiles: O(-c(c(-O1)ccc2-OCC(C(-c(ccc(-F)c3)c3)CCN4)C4)c2)C1

QSAR Estimates for Exposure Assessment

LOG(Water Solubility) = -2.51 Mol/L

Log(BCF) = 0.65 BCF = 4.47

Absorption Coef. Log(Koc) = 2.06 (See Lyman et al. 1990) [16]

Hydrolysis Half Life = 1000 Days

Hydrolysis is not likely to be an important transformation mechanism for this chemical.

Henrys law Constant and Environmental Partitioning

Log10 (Henrys Constant) = -9.47 atm-m**3/mole

Lyman et al. 1990. [16] would conclude that a chemical with these properties is non-volatile. See p15-15.

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NEELY 100 Day Partitioning Pattern

REDACTIONS MADE BY APPLICANT

Air	=	0.00 %
Water	=	99.52 %
Ground	=	0.25 %
Hydrosoil	=	0.23 %

Therefore, based on this model using data generated at pH 7, any paroxetine hydrochloride emitted into the environment from production or accident is predicted to partition predominantly in the aquatic (water) compartment [17]. No losses to atmosphere are anticipated, and only a small percentage of material is expected to enter the ground or hydrosoil compartments. At pH levels greater than 7, as more paroxetine free base is present, more partitioning into ground and hydrosoil would be expected. However, even at pH 9, predominant partitioning is to the aquatic compartment.

7.4 Transformation and Depletion Mechanisms of Paroxetine Hydrochloride

7.4.1 Hydrolysis

The hydrolytic stability of paroxetine hydrochloride was determined at 50°C in deionized water and aqueous buffer solutions at pH 5, 7, and 9 over a five day period [18]. No appreciable hydrolysis was found to occur in deionized water or at pH levels of 5 and 7; for pH 9, a 6.95% loss was determined after 5 days. No rate determination was carried out since less than 10% of the initial concentration hydrolyzed over the 5 day period. However, as discussed above, even this slow rate of hydrolysis was significant enough to interfere with water solubility studies and pK_a studies at $pH \geq 9$. In the environment, there is little potential for paroxetine to experience pH levels > 9, and no evidence of hydrolysis was observed in any tests at pH levels < 9. Hydrolysis per se is therefore unlikely to be a significant transformation or depletion process for paroxetine in the environment.

7.4.2 Aerobic Biodegradation

Extensive aerobic biodegradability studies were carried out using paroxetine hydrochloride and a variety of microorganisms sources. These included seed from both domestic and industrial biotreatment plants and soils. Extensive work was carried out in attempts to acclimate, adapt, and enrich cultures for organisms with a propensity to degrade paroxetine as both a sole carbon source and as a co-metabolic substrate [19]. None of these studies was successful. After some decrease in paroxetine concentration

due to bioadsorption [20], the concentration of paroxetine in all studies remained essentially constant and no by-products were observed in the HPLC chromatograms used to monitor the studies. One in-house definitive study is given as reference [21]. A contract laboratory study which followed the aerobic biodegradation by both CO_2 evolution and HPLC assays for parent was also unsuccessful in demonstrating biodegradability [22].

7.4.3 Aqueous Photolysis

Given the recalcitrance of paroxetine to microbial biodegradation, and its significant absorption of light at wavelengths >290 nm, an evaluation was made of the potential of aquatic photolysis as a degradative pathway for paroxetine in the environment. The maximum direct aqueous photoreaction rate constant and minimum half-life were estimated using standard methods based on UV/visible spectra and solar irradiance data [23].

The results indicate estimated half-lives for paroxetine in natural sunlight of 0.01 days to 0.004 days depending on season and latitude. Because of this favorable preliminary estimate, an aquatic photolysis study was carried out to determine definitive experimental values.

Studies were carried out in deionized water and in pH 7 buffer in natural sunlight [24]. The results gave initial first order photolysis rate constants for paroxetine of 0.29 hr^{-1} and 0.27 hr^{-1} respectively. The rate constants were derived from linear regressions of initial data, as illustrated in Figure 3 for the reaction in pH 7 buffer.

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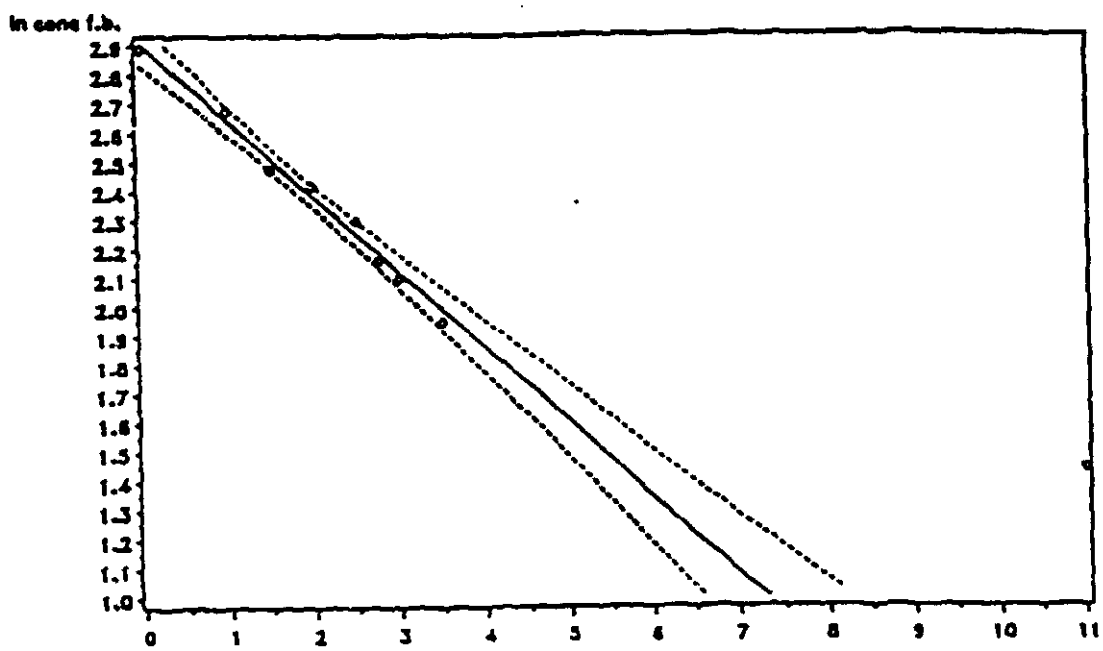
Figure 3

Aqueous Photolysis of Paroxetine in pH 7 Buffer



The rate constant corresponds to a half-life of 2.4 hours. HPLC analysis of the photolyzed solution, which contained no residual paroxetine, did not show any major UV active degradants. See Item 8.2.2 for a discussion of the toxicity of the photolysis by-products.

7.5 Physical Property Determinations for Paroxetine Metabolite (BRL 36610A)

No physical property determinations were carried out for paroxetine metabolite (BRL 36610A). However, its very close similarity to paroxetine itself makes the use of paroxetine physical property data adequate for evaluation of the fate of metabolite.

7.6 Environmental Partitioning Estimates for Paroxetine Metabolite (BRL 36610A)

Since paroxetine metabolite (BRL 36610A) is the predominant species resulting from use of the product, its fate in conventional wastewater treatment plants is first considered. Based on its structural similarity to paroxetine parent, BRL 36610A would be expected to have similar physical properties and to partition in similar ways. Thus the $K_{biomass}$ determined for paroxetine is relevant to estimating the sorption of BRL 36610A to the sludge during waste treatment. The implications of this sorption to biomass can be assessed using a distribution calculation based on a "worst case" situation:

The maximum recommended dose of paroxetine hydrochloride OCD will be 60 mg/day/patient. Assuming that the average person discharged 600 L/day into a wastewater treatment plant, this corresponds to a maximum emitted concentration (C_T) of

$$\frac{60\text{ mg} \times 331\text{ (MW metabolite)}}{600\text{ L} \times 374\text{ (MW parent)}} = 8.85\text{E-}02\text{ mg/L/day}$$

$$C_T = C_{sorbed} + C_{soln}$$

$$C_{sorbed} = C_T - C_{soln}$$

$$K_{biomass} = \frac{C_{sorb}\text{(mg/L)/biomass(mg/L)}}{C_{soln} \times 10^{-6}\text{ (mg/mg)}}$$

$$8.71\text{E}02 = \frac{(8.85\text{E-}02 - C_{soln})/2500}{C_{soln} \times 10^{-6}\text{ (mg/mg)}}$$

$$8.71\text{E}02 \times C_{soln} \times 10^{-6} = 3.54\text{E-}05 - 4.00\text{E-}04 C_{soln}$$

$$1.27\text{E-}03 \times C_{soln} = 3.54\text{E-}05$$

$$C_{soln} = 2.79\text{E-}02\ (31.5\%)$$

$$C_{sorb} = 8.85\text{E-}02 - 2.79\text{E-}02$$

$$= 6.06\text{E-}02\ (68.5\%)$$

Thus, in a wastewater treatment plant, 68.5% of the compound should sorb to the biomass, with 31.5% remaining in solution.

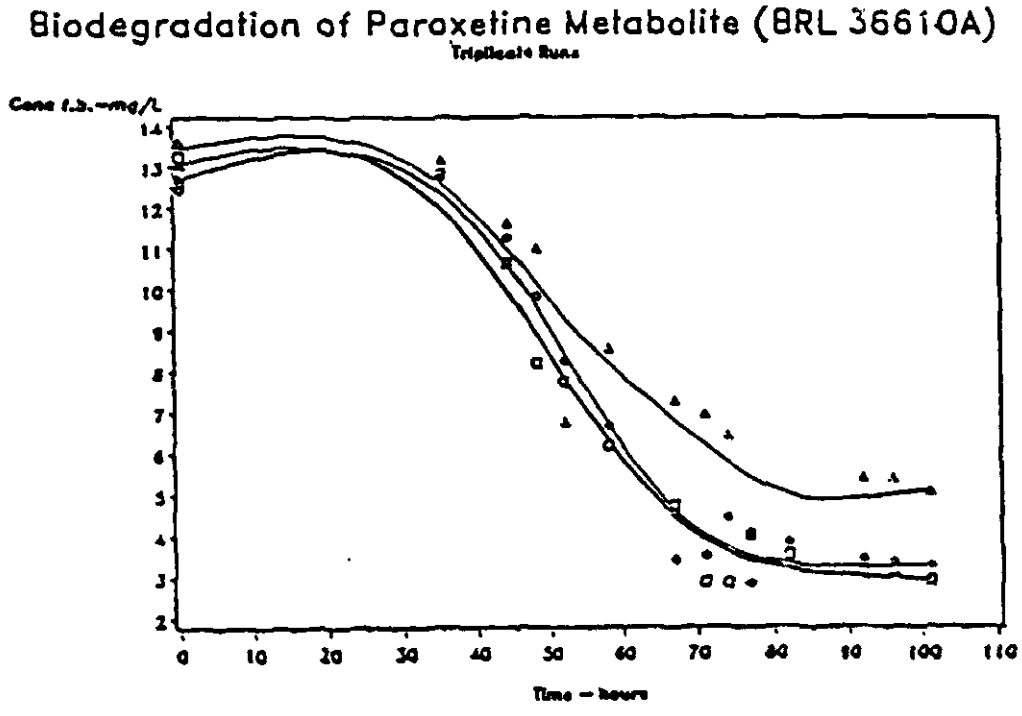
7.7 Transformation and Depletion Mechanisms of Paroxetine Metabolite (BRL 36610A)

7.7.1 Aerobic Biodegradation

Aerobic biodegradation studies were carried out on paroxetine metabolite (BRL 36610A) since it is the major compound excreted into the environment from use. BRL 36610A was found to degrade to less than detectable levels within 5 days. Although adsorption to biomass occurs, the compound should still be available for degradation, since the adsorption is reversible. As the compound is biodegraded, more will desorb from the biomass until complete degradation is accomplished. The results of preliminary and definitive in-house studies are given in references [25] and [26]. A contract laboratory aerobic biodegradation study was also completed, but has not been included in this assessment due to non-compliance issues. However, a memo describing the preliminary results of the non-compliant study is provided [27].

A plot of the data from the definitive in-house study is shown in Figure 4.

Figure 4



A natural log transformation of the averaged data gave the results shown in Figure 5. Here, the early lag, the active biodegradation, and the die-off portions of the study are clearly apparent.

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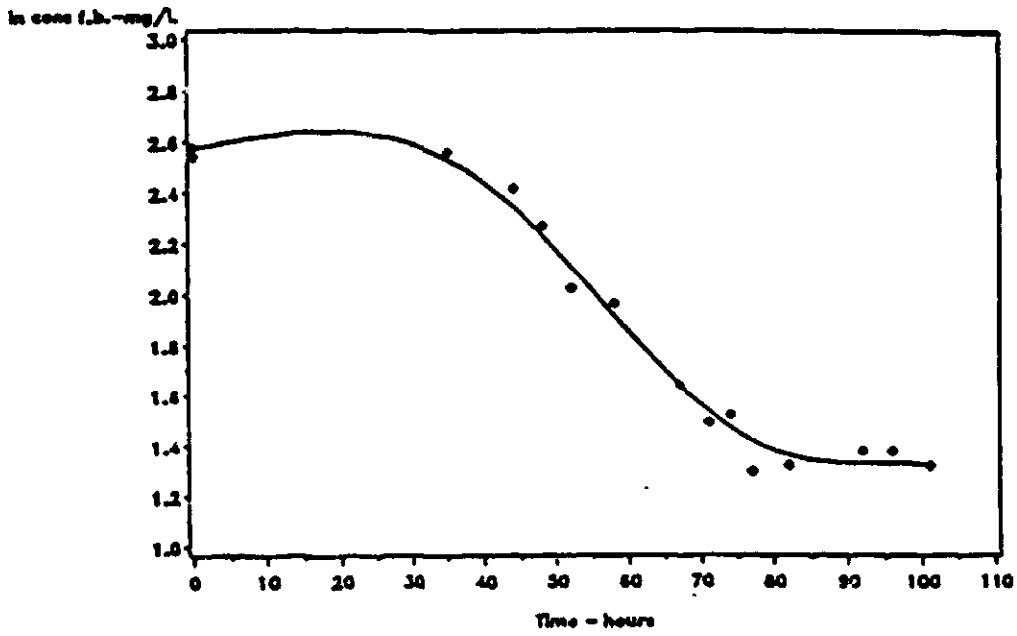
Figure 5

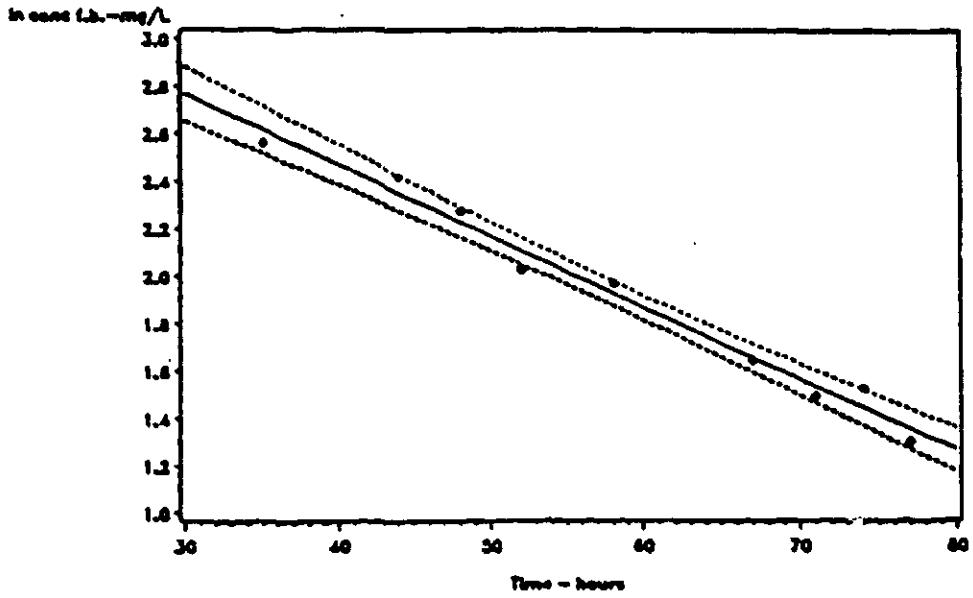
Biodegradation of Paroxetine Metabolite (BRL 36610A)



The linear regression and 95% confidence limits for the data from days 35-77 are shown in Figure 6.

Figure 6

Biodegradation of Paroxetine Metabolite (BRL 36610A)



The data were subjected to the SAS General Linear Models Procedure [14] to give the linear regression results shown below:

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BIODEGRADATION OF PAROXETINE METABOLITE (BRL 36610A)

GENERAL LINEAR MODELS PROCEDURE

DEPENDENT VARIABLE: LNCAV

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE
MODEL	1	1.56088461	1.56088461	380.24
ERROR	7	0.02873512	0.00410502	
CORRECTED TOTAL	8	1.58961973		

R-SQUARE	C.V.	ROOT MSE	LNCAV MEAN
0.981923	3.3549	0.06407041	1.90972871

SOURCE	DF	TYPE I SS	F VALUE	PR > F
TIME	1	1.56088461	380.24	0.0001

SOURCE	DF	TYPE III SS	F VALUE	PR > F
TIME	1	1.56088461	380.24	0.0001

PARAMETER	ESTIMATE	T FOR H0: PARAMETER=0	PR > |T|	STD ERROR OF ESTIMATE
INTERCEPT	3.66716780	39.59	0.0001	0.09262232
TIME	-0.03007025	-19.50	0.0001	0.00154209

The intercept term above shows that the ln K, the first order rate constant for biodegradation of paroxetine metabolite (BRL 36610A), is 0.03 hr^{-1}.

7.8 Environmental Transport Issues

In addition to estimation of the distribution and transformation of a chemical in the environment, Item 7 of the Environmental Assessment requires some evaluation of the likely mobility of the chemical in the environment by means of air, water, and other environmental transport mechanisms. However, given data supporting the distribution of paroxetine and paroxetine metabolite (BRL 36610A) essentially completely in the aquatic compartment, and the rapid depletion of paroxetine parent by photolysis and paroxetine metabolite (BRL 36610A) by biodegradation at expected environmental discharge concentrations, further consideration of environmental transport issues is not considered

necessary. Neither compound should not persist in the environment long enough for significant transport to occur.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

8.1 Human and Mammalian Health Effects Summary

8.1.1 Acute Toxicity Studies

8.1.1.1 Oral Toxicity [28]

The oral and intravenous acute toxicity of paroxetine free base has been examined in the mouse and in the rat. The approximate oral LD_{50} was similar for both species (mouse 341 and rat 374 mg/kg pfb). Intravenously, the compound was approximately ten times as toxic as by the oral route. In both species, the central nervous system (CNS) was apparently the target organ as physical signs of CNS stimulation were evident. Paroxetine hydrochloride was found to be less toxic, with acute oral LD_{50} values of >630 mg/kg pfb in both male and female rats.

8.1.1.2 Skin Irritation [29]

Paroxetine hydrochloride was classified as a non-irritant to rabbit skin based on studies that showed no signs of irritation up to 3 days after direct application for 4 hours in rabbits.

8.1.1.3 Eye Irritation [29]

Paroxetine hydrochloride was classified as a very severe to extremely severe irritant to rabbit eyes. Severe irritation occurred immediately after direct application and animals were immediately destroyed.

8.1.1.4 Sensitization [29]

Paroxetine hydrochloride was classified as a non-sensitizer to guinea pig skin. No irritation or adverse skin reactions occurred in guinea pigs used to test for sensitization or allergic skin reaction (modified Maguire/Split Adjuvant Test).

8.1.2 Chronic Toxicity Studies [28]

8.1.2.1 Carcinogenicity

Studies were carried out in Sprague-Dawley rats and an outbred CD1 strain of mice from the same suppliers. The conclusions reached were that paroxetine has no apparent carcinogenic potential. The predicted carcinogenic risk for man following long term administration of paroxetine is therefore very low.

8.1.2.2 Reproduction toxicology

The rat and rabbit were used to assess the potential of paroxetine to cause embryo toxicity. These studies did not indicate any adverse effect on the embryo or fetus, and in neither species was there any teratogenicity. In addition, the effects of paroxetine on fertility were assessed in the rat and there were no indications from the general toxicity studies that the female reproductive system has been adversely affected.

8.1.2.3 Mutagenicity studies

The tests carried out for examining the effects on the gene were the bacterial Ames and mouse lymphoma tests, both of which are *in vitro* tests. In neither system (with and without a metabolic activating system) were significant increases in mutation frequency observed. The potential to cause chromosomal aberrations was studied by examining the bone marrow cells for micronuclei following the administration of paroxetine to mice at the very high doses of 75 and 150 mg/kg. There was no evidence for any chromosomal damage. Human lymphocytes were also studied *in vitro* with and without a metabolic activating system, and again no damage to the chromosomes of these cells was observed.

8.2 Aquatic Toxicity Studies

8.2.1 Acute Aquatic Toxicities of Paroxetine Hydrochloride and its Major Metabolite (BRL 36610A)

Acute aquatic toxicity studies were carried out on microorganisms (Microtox® ([30] and [31]) and Microbial Respiration Inhibition [32], *Daphnia magna*, [33, 35] and bluegill sunfish (*Lepomis macrochirus*) [34, 36], for paroxetine parent and on microorganisms [39] and *Daphnia magna* [37, 38] for paroxetine metabolite BRL 36610A.

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The results are summarized below and in the data summary sheet (Appendix VI), which summarizes the results of environmental effects studies on both paroxetine and its metabolite.

Toxicity Test	Paroxetine HCl (mg/L)	BRL 36610A (mg/L)
Microtox® - EC_{50}	8.2	33.0
Respiration Inhibition - EC_{50}	25 to 26	80 to 83
Daphnia magna - LC_{50}	2.5	35.3
Bluegill Sunfish - LC_{50}	1.6	No study performed

From the data above, paroxetine metabolite appears to be less toxic to aquatic organisms than paroxetine itself. This, coupled with its ready biodegradability, indicates that paroxetine metabolite will not have an adverse impact on the environment.

8.2.2 Acute Aquatic Toxicity of Paroxetine Photolysis By-Products

Paroxetine itself, although more toxic, is rapidly degraded in the presence of sunlight to simpler by-products. These by-products can be assumed to be less toxic than paroxetine based on the results of a Microtox® test carried out on samples of paroxetine solutions that had been exposed to sunlight [40]. No EC_{50} could be determined for the degraded solutions as compared to the control solutions which showed an EC_{50} of 9.1 mg fb/L, comparable to the independently determined EC_{50} of paroxetine hydrochloride of 8.2 mg fb/L shown above. Any paroxetine which might enter the environment from production or accident will rapidly photodegrade into innocuous polar by-products.

8.2.3 Acute Aquatic Toxicity of BRL 36610A Biodegradation By-Products

BRL 36610A, the major metabolite of paroxetine, will be readily biodegraded in municipal wastewater treatment plants. Although the compound is not mineralized, it does appear to be transformed into simpler, more polar by-products. These by-products can be assumed to be less toxic than BRL 36610A itself based on the results of a Microtox® test carried out on samples of BRL 36610A solutions after laboratory biodegradation experiments. No EC_{50} could be determined for the degraded solutions [41]. Any compounds entering the environment after biotreatment of paroxetine metabolite should be innocuous polar by-product which should not exert any toxic effects.

Thus the production and use of paroxetine will not have any adverse impacts on the environment.

9. USE OF RESOURCES AND ENERGY TO PRODUCE DRUG SUBSTANCE

9.1 Use of Resources And Energy At Cork

To produce the drug substance required for the paroxetine OCD product at maximum estimated yearly production levels (in 1998), it is estimated that < 0.5% of total yearly Cork plant usage of electricity, fuel and water will be used to perform stages 1-3 of the drug substance process.

The effects on the use of resources and land for the production of paroxetine drug substance are minimal because of the low production volumes and associated wastes, and the existing treatment units that will be used.

9.1.1 Effect Upon Endangered Species And Historic Places

The production of paroxetine substance and the disposal of associated wastes should have no impact on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by paroxetine substance production or waste disposal activities since the production is taking place outside of the United States.

9.2 Use of Resources And Energy At Irvine

To produce the drug substance required for the paroxetine OCD product at maximum estimated yearly production levels (in 1998), it is estimated that < 0.05% of total yearly plant usage of electricity and water will be used to perform drug substance stages 4-7 at Irvine.

9.2.1 Effect Upon Endangered Species And Historic Places

The production of paroxetine substance and the disposal of associated wastes should have no impact on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by paroxetine substance production or waste disposal activities since the production is taking place outside of the United States.

9.3 Use of Resources And Energy At Cidra

The drug product will be produced in the SmithKline Beecham Pharmaceuticals' facility in Cidra, Puerto Rico, which also produces other pharmaceutical products. The facility is located on a 52 acre site. The effects on the use of resources and land for the production of paroxetine drug product are minimal because of the relatively low production volumes and associated wastes, and the existing treatments units which will be used. Manufacture of this product uses only a small percentage of the resources and energy available at this site and of resources and energy required for transport.

To produce the paroxetine OCD product at maximum estimated yearly production levels (in 1998), it is estimated that < 0.1% of total yearly plant usage of electricity and water will be used at Cidra.

9.3.1 Effect Upon Endangered Species And Historic Places

The production of paroxetine product and the disposal of associated wastes should have no effect on threatened or endangered species. Details on the environmental characteristics of the Cidra community are given in Appendix V. Property listed in or eligible for listing in the National Register of Historic Places will also not be impacted by paroxetine product production or waste disposal activities.

10. MITIGATION MEASURES

10.1 Mitigation At Cork

Plans to minimize waste output were considered and implemented at the outset of paroxetine development, as well as during substance production. Potential environmental impacts associated with drug substance production at SmithKline Beecham (Manufacturing) Limited, Cork (Ireland) are minimized by the following:

Most waste streams are incinerated, and the gases scrubbed before being discharged. Scrubber liquors are biotreated in the on-site wastewater treatment facility before discharge; see Item 6 for details on treatment processes.

Biotreated effluent streams are checked before discharge, with ample capacity for emergency storage in the event that effluent criteria are not met.

Airstreams from the process buildings are filtered prior to venting to the atmosphere.

10.2 Mitigation At Irvine

Plans to minimize waste output were considered and implemented at the outset of paroxetine development, as well as during substance production. A nitrogen generating plant was built at the facility to meet the plant's nitrogen requirements, thus eliminating the need for external sources of nitrogen.

10.2.1 Energy

Approximately 10% of steam energy is saved, through the use of boiler economisers and spray recuperations.

10.2.2 Effluents

The amounts of regulated components discharged in effluent is regularly monitored by the Irvine facility's QA department and the local water authority of Irvine, to ensure compliance with established consent levels. Additional details on the mitigation and disposal of aqueous wastes are provided in Item 6 of this assessment.

10.2.3 Resource Recovery

Components discharged to effluent are monitored by the Irvine facility's QA department and the local water authority of Irvine, to ensure compliance with established consent levels. Additional details on the mitigation and disposal of aqueous wastes are provided in Item 6 of this report.

10.2.4 Spill Control

The SmithKline Beecham Pharmaceutical's facility at Irvine, Scotland (U.K.), has established adequate spill control and clean up procedures, as described in Item 6 of this assessment.

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10.3 Mitigation [illegible]ra

Potential adverse [illegible] tal impacts associated with the proposed action are minimized at the [illegible] facili[illegible] by the following:

The activated carb[illegible] f [illegible]he biotreatment filters is returned to the manufacturer for regeneration approx[illegible] every three months.

No waste or exhaust st[illegible]ns are directly discharged. All streams are directed to major treatment units. Treated effluent streams are checked before discharge, with ample capacity for emergency storage in the event that effluent criteria are not met;

Airstrea[illegible] from the pro[illegible]ess are small and directed to dust collectors, which minimize the effects of the emissions by at least 99.9%;

A holding tank is designed to allow for the capture and treatment of any spills or oil contaminated water before any major environmental effects could result. Also, the adopted spills prevention, control and contingency plans have been demonstrated to be effective in the prevention of such emergencies.

11. ALTERNATIVE TO THE PROPOSED ACTION:

No potential adverse environmental impacts have been identified for the proposed action. The only alternative to the proposed action is that of no action, thus depriving patients an important therapy. The approval of paroxetine OCD will provide an important benefit to patients requiring its administration with no known adverse environmental risk.

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13. CERTIFICATION:

The undersigned official certifies that the information presented is true, accurate, and complete to the best knowledge of the SmithKline Beecham Environmental Research Laboratory.

Date: June 26, 1995

Signature: James Hagan

James R. Hagan, P.E.
Vice President & Director
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SmithKline Beecham

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15. APPENDICES

ENVIRONMENTAL ASSESSMENT

***Paxil*™(Paroxetine Hydrochloride) Tablets**

June 16, 1995

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SmithKline Beecham
Pharmaceuticals

Penn Chemicals B.V. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Paroxetine at its facilities in Currabinny, Carrigaline, Co. Cork, Ireland.

Declan Ryan 14/10/91

NAME: DATE:

TITLE: Manager Engineering / Environmental

[redacted] 14/10/91

NAME: DATE:

TITLE: Director of Manufacturing

PENN CHEMICALS B.V., Currabinny, Carrigaline, Co. Cork, Ireland.
Tel. 021-371384, Fax 021-372302, Telex 75855 Int'l Dialing +353-21-371781

SMITHKLINE BEECHAM (MANUFACTURING) LIMITED EMISSIONS LIMITS

CONSTITUENT	UNITS	TREATED EFFLUENT
pH	-	6 - 9
Total Heavy Metals	mg/L	0.5
Oils, Fats & Greases	-	no visible film
COD	kg/day	2000
BOD_5	kg/day	750
*Total Suspended Solids	mg/L	250*
Total N (kjeldahl)	mg/L	700
Nitrates	mg/L	100
**Ammonia	mg/L	400
Orthophosphates	mg/L	25
Organohalogens	mg/L	0.5 (as chlorine)
Toxic units	T.U.	25
Temperature	°C	30

*From October 1st, 1994 through September 30th, 1995
**Ammonia must be < 50 mg/L by Oct. 1995.

6/15/94
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SMITHKLINE BEECHAM (MANUFACTURING) LIMITED EMISSIONS LIMITS

CONSTITUENT	UNITS	INCINERATOR #3	INCINERATORS #1,4&5
Carbon Disulfide	mg/m3	N/A	N/A
Carbon Monoxide	mg/m3(kg/hr)	100	100
Chlorine	mg/m3	N/A	N/A
Class I Solvents	mg/m3	N/A	N/A
Class II Solvents	mg/m3(kg/hr)	N/A	N/A
Class III Solvents	mg/m3(kg/hr)	N/A	N/A
Cyclohexane	mg/m3	N/A	N/A
Dimethyl Sulfate	mg/m3	N/A	N/A
Dusts	mg/m3	N/A	N/A
Epichlorohydrin	mg/m3	N/A	N/A
Hydrochloric Acid	mg/m3(kg/hr)	N/A	30
Hydrogen Sulfide	mg/m3	N/A	N/A
Isopropanol	mg/m3	N/A	N/A
Methyl Mercaptan	mg/m3	N/A	N/A
Monomethylamine	mg/m3	N/A	N/A
NOx (as NO2)	mg/m3	500	500
ORM #1	mg/m3	N/A	N/A
Sulfur Dioxide	mg/m3	500	500
Total Organics (as C)	mg/m3	20	20

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SMITHKLINE BEECHAM (MANUFACTURING) LIMITED EMISSIONS LIMITS

CONSTITUENT	UNITS	BOILER #1	BOILER #2	VENT #7
Carbon Disulfide	mg/m3	N/A	N/A	100
Carbon Monoxide	mg/m3(kg/hr)	200(1.7)	200(1.5)	N/A
Chlorine	mg/m3	N/A	N/A	15
Class I Solvents	mg/m3	N/A	N/A	N/A
Class II Solvents	mg/m3(kg/hr)	N/A	N/A	N/A
Class III Solvents	mg/m3(kg/hr)	N/A	N/A	N/A
Cyclohexane	mg/m3	N/A	N/A	N/A
Dimethyl Sulfate	mg/m3	N/A	N/A	1.0
Dusts	mg/m3	N/A	N/A	N/A
Epichlorohydrin	mg/m3	N/A	N/A	N/A
Hydrochloric Acid	mg/m3(kg/hr)	N/A	N/A	100(<0.3) & 30(>0.3)
Hydrogen Sulfide	mg/m3	N/A	N/A	N/A
Isopropanol	mg/m3	N/A	N/A	N/A
Methyl Mercaptan	mg/m3	N/A	N/A	1.0
Monomethylamine	mg/m3	N/A	N/A	N/A
NOx (as NO2)	mg/m3	500(4.1)	500(11.5)	N/A
ORM #1	mg/m3	N/A	N/A	5.0
Sulfur Dioxide	mg/m3	500(4.1)	500(11.5)	N/A
Total Organics (as C)	mg/m3	N/A	N/A	N/A
Dimethyl Disulfide	mg/m3	-	-	1.0

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SMITHKLINE BEECHAM (MANUFACTURING) LIMITED EMISSIONS LIMITS

CONSTITUENT	UNITS	VENT #8	VENT #9	VENT #10
Carbon Disulfide	mg/m3	100	100	N/A
Carbon Monoxide	mg/m3(kg/hr)	N/A	N/A	N/A
Chlorine	mg/m3	5	15	N/A
Class I Solvents	mg/m3	20	N/A	20
Class II Solvents	mg/m3(kg/hr)	100	N/A	300(<0.1)
Class III Solvents	mg/m3(kg/hr)	150	N/A	500(<1.0)
Cyclohexane	mg/m3	N/A	N/A	N/A
Dimethyl Sulfate	mg/m3	N/A	N/A	N/A
Dusts	mg/m3	N/A	N/A	N/A
Epichlorohydrin	mg/m3	N/A	5	N/A
Hydrochloric Acid	mg/m3(kg/hr)	30	100(<0.3) & 30(>0.3)	N/A
Hydrogen Sulfide	mg/m3	0.3	N/A	N/A
Isopropanol	mg/m3	N/A	N/A	N/A
Methyl Mercaptan	mg/m3	1	N/A	N/A
Monomethylamine	mg/m3	N/A	N/A	N/A
NOx (as NO2)	mg/m3	N/A	N/A	N/A
ORM #1	mg/m3	N/A	N/A	N/A
Sulfur Dioxide	mg/m3	N/A	N/A	N/A
Total Organics (as C)	mg/m3	N/A	N/A	N/A
Dimethyl Disulfide	mg/m3	1.0	-	-
Ammonia	mg/m3	-	75	-

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SMITHKLINE BEECHAM (MANUFACTURING) LIMITED EMISSIONS LIMITS

CONSTITUENT	UNITS	VENT #12	VENTS #13-15
Carbon Disulfide	mg/m3	N/A	N/A
Carbon Monoxide	mg/m3(kg/hr)	N/A	N/A
Chlorine	mg/m3	N/A	N/A
Class I Solvents	mg/m3	20	N/A
Class II Solvents	mg/m3(kg/hr)	300(<0.1)	N/A
Class III Solvents	mg/m3(kg/hr)	500(<1.0)	N/A
Cyclohexane	mg/m3	N/A	N/A
Dimethyl Sulfate	mg/m3	N/A	N/A
Dusts	mg/m3	N/A	1.0
Epichlorohydrin	mg/m3	N/A	N/A
Hydrochloric Acid	mg/m3(kg/hr)	N/A	N/A
Hydrogen Sulfide	mg/m3	N/A	N/A
Isopropanol	mg/m3	N/A	N/A
Methyl Mercaptan	mg/m3	N/A	N/A
Monomethylamine	mg/m3	N/A	N/A
NOx (as NO2)	mg/m3	N/A	N/A
ORM #1	mg/m3	N/A	N/A
Sulfur Dioxide	mg/m3	N/A	N/A
Total Organics (as C)	mg/m3	N/A	N/A

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ENVIRONMENTAL ASSESSMENT

***Paxil*™(Paroxetine Hydrochloride) Tablets**

June 16, 1995

ITEM **PAGE**

SmithKline Beecham
Pharmaceuticals

PAROXETINE ENVIRONMENTAL ASSESSMENT

GENERAL COMPLIANCE STATEMENT

SMITHKLINE BEECHAM states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of PAROXETINE HYDROCHLORIDE at its facilities in IRVINE, SCOTLAND, U.K. as currently interpreted and applied by the relevant environmental enforcing authorities.

D McCurry 15/10/91

NAME: Mr. D. McCurry DATE:
TITLE: Plant Manager

R H Leckie 11.10.91

NAME: Dr. R.H. Leckie DATE:
TITLE: Safety and Environmental Manager

Shewalton Road, Irvine, Ayrshire, KA11 5AP, Scotland. Telephone: 0294-74200. Telex: 779171. Fax: 0294-73738

EFFLUENT CONSENT LEVELS AT IRVINE, SCOTLAND

CONSTITUENT	PARAMETER (mg/L)
BOD_5	7000
Suspended Solids	5000
Methyl isobutyl ketone	700
Isopropyl alcohol	350
Acetone	300
Methanol	500
Methylene dichloride	80
Phenol	30
Ethanol	200
Triethylamine	5
Toluene	60
Butanol	100
Tertiary butyl amine	40
Dimethylformamide	20
Tetrahydrofuran	20
Pyridine	5
Zinc	2
Copper	1.5
Ammonia (as NH_3-N)	200
pH	4 - 12

The volume of the discharge in any one day shall not exceed 6000 m^3 and the rate of discharge shall not exceed 400 m^3 per hour.

Reference: Clyde River Purification Board
Glasgow, Scotland
Consent No.: CP8750 (N2)

ENVIRONMENTAL ASSESSMENT

Paxil ™(Paroxetine Hydrochloride) Tablets

June 16, 1995

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SB

SmithKline Beecham

Environmental Research Laboratory

22/October/1991

TO: Dr. Virginia Cunningham

cc: ERL Files
C&C Files

FROM: W. Tirado

SUBJECT: Summary of the Environmental Characteristics of the Cidra Community

Attached you will find an abstract and translation of the following Environmental Evaluation Reports from the Cidra community in Pueno Rico:

Environmental Evaluation Report for the Residential Project Sabanera Estates & Country Club

Environmental Evaluation Report for the Expanded Operations of SKF Lab Co. (Actually SB Pharmaceuticals)

Environmental Evaluation of the Proposed Cidra Industrial Park

The abstract provides a description of the physical and biotic characteristics of the Cidra community.

Abstract

The Cidra community is located within the subtropical humid forest zone, more specifically within a transition zone between the Humid Coastal Forest and the Lower Mountain Forest. The area has been extensively deforested due to farming activities and for this reason the natural vegetation was reported as being in an extinction phase by 1926 (See Table I). By 1988 there were few representatives of the tree species common to this climatic zone. Within this area is also found grasslands associations and small secondary vegetation associations (See Table II for dominant species reported by 1988).

SB Cidra plant is specifically located in a 50.4 acre lot owned by SmithKline Beecham (Road 172 Km 9.1) and it is surrounded by Cidra Lake (North), by Road 172 (South) and by two semi-urban development projects (east and west). The area is located at 425 meters above the sea level. The annual average precipitation recorded during a twenty (20) year period, and reported in 1989, was 66.98 inches. The average temperature for the same period of time was 72.6 F. Wind direction is from east to west at an average speed of 10 knots.

There are three types of soils reported for this area:

a) "Arcilla Aceituna"
b) "Arcilla Humatas"
c) "Arcilla Daguey"

All these soils have good drain characteristics and moderate permeability.

Cidra is not included in the inventory of areas with potential to exceed the air limits for sulfur oxides and particulate matter. This is mainly due to the fact that Puerto Rico is located within a permanent air current which maintains a constant renovation of the atmospheric air. Persistent progressive acumulation of atmospheric contaminants are not observed.

The fauna that it is present in Cidra is usually restricted to the tree zones where adequate humidity and temperature conditions for the fauna are found. Table III presents a list of the species reported in our reference report from 1988.

No endangered species were reported in our reference reports for Cidra. Nevertheless, it has been reported in other references that the Cidra Lake is a protected area for the endangered specie known as Columba inornata wetmorei ("Paloma Sabanera"). This specie gets its food mainly from fruits and seeds. It breeds in trees such as Bambusa vulgaris, Syzygium jambos, Spathodea campulata, and Didimopanax morototonis (See Table IV). It's breed peak period is between winter and spring and its characteristic habitat is tree zones associated with water bodies.

The main factors contributing to its extinction are the destruction of their habitat and the uncontrolled intervention of man mainly through hunting. The recent increase in their number within the Cidra area may be associated to the decrease in agricultural activities.

Abstract (Continued)

The total population of Cidra was estimated to be 28,365 by 1980 Census. The projection for year 2000 is an increase of 7736 habitants (See Table V).

References:

Evaluacion Ambiental Sabanera Estates and Country Club, Barrio Bayamon, Cidra, Puerto Rico, 1988

Evaluacion Ambiental Para La Expansion de SKF Lab, Co., Cidra, Puerto Rico, Proyecto UNIPRO num. 88053, 1989

Evaluacion Ambiental Para Proyecto Parque Industrial de Cidra, Barrio Bayamon, Cidra, Puerto Rico, 1991

TABLE I

Natural Tree Species From the Transition Zone Between The Coastal Forest Zone and The Lower Mountain Forest Zone.*

	Common Name	Scientific Name
I. Humid Coastal Forest		
1.	Corazo	Acrocomia media
2.	Mago	Hernandia sonora
3.	Moca	Andira inermis
4.	Tortugo Amarillo	Sideroxilum sp.
5.	Maria	Calophyllum brasiliense
6.	Asubo	Manilkara bidentata
7.	Roble Blanco	Tabebuia heterophylla
II. Lower Mountain Forest		
1.	Yagrumo Hembra	Cecropia peltata
2.	Laurel Geo	Ocotea leucoxylon
3.	Nuez Moscada	Ocotea moschata
4.	Guama	Inga laurina
5.	Moca	Andira inermis
6.	Tabonuco	Dacryodes excelsa
7.	Capa Prieto	Cordia alliodora
8.	Yagrumo Macho	Didymopanax Morototoni

* No source for an English translation was available for the common name of these species.

TABLE II

Dominant Vegetation Species From Cidra Reported By 1968.*

	Common Name	Scientific Name
I. Grasslands		
1.	Yerba Pangola	Digitaria decumbes
2.	Markiki	Mimosa pudica
3.	La Escobilla	Vernonia saricea
4.	Bejuco de Puerco	Ipomea setifera
5.	Cohitre Falso	Ichnanthus pallens
II. Secondary Vegetation Associations		
1.	Tulipan Africano	Spathodea campanulata
2.	Pomarrosa	Syzygium jambos
3.	Guabe	Inga vera
4.	Yagrumo Macho	Didymopanax morototoni
5.	Yagrumo Hembra	Cecropia peltata
6.	Guaraguao	Guarea guidonia
7.	Teca	Tectonia grandis
8.	Palma real	Roystonea borinquena
9.	Bamboo	Bambusa vulgaris

* No source for an English translation was available for the common name of these species.

TABLE III
Fauna From Bo. Bayamon, Cidra Reported By 1988

A. Birds

	Common Name Spanish	Common Name English	Scientific Name	Family
1.	Guaraguao	Red-tailed hawk	Buteo jamaicensis	Accipitridae
2.	Garza ganadera	Cattle egret	Bubylcus ibis	Ardeidae
3.	Martinete	Green heron	Butorides striatus	Ardeidae
4.	Reinita comun	Banaquit	Coereba flaveola	Coerebidae
5.	Paloma turca	Scaly-naped pigeon	Columba squamosa	Columbidae
6.	Tortola cardosantera	Zenaida dove	Zenaida aurita	Columbidae
7.	Pajaro bobo menor	Mangrove cuckoo	Coccyzus minor	Cuculidae
8.	Diablito	Bronze manniquin	Lonchura cucullata	Estrildidae
9.	Gorrion barba amarilla	Yello-faced grassquit	Tiaris olivacea	Fringilidae
10.	Golondrina de cuevas	Cave swallow	Petrochelidon fulva	Hirundinidae
11.	Chango	Greater Antillean grackle	Quiscalus niger	Icteridae
12.	Ruisenor	Mockingbird	Mimus poglottos	Mimidae
13.	Gallinazo americano	American coot	Fulica americana	Rallidae
14.	Gallareta comun	Common gallinule	Gallinula chloropus	Rallidae
15.	San Pedrito	Puerto Rican tody	Todus mexicanus	Todidae

TABLE III (Continued)

16.	Zumbadorcito de Puerto Rico	Puerto Rican emerald	Chlorostilbon maugeys	Trochilidae
17.	Zorzal de patas coloradas coloradas	Red-legged trush	Mimocichla plumbea	Turdidae
18.	Pitirre	Gray kingbird	Tyrannus dominicensis	Tyrannidae

B. Gastropoda

	Scientific Name	Family
1.	Caracollus caracolla	Camaenidae
2.	Polydontes acutangula	Camaenidae
3.	Nenia tridens	Clausilidae
4.	Megalomastoma croceum	Cyclophoridae
5.	Austroselenites alticola	Haplotrematidae
6.	Alcadia striata	Helicinidae
7.	Alcadia alta	Helicinidae
8.	Varicella terebraiformis	Oleacinidae
9.	Subulina octona	Subulinidae
10.	Obeliscus terebraster	Subulinidae

TABLE III (Continued)

C. Amphibians*

	Common Name	Scientific Name	Family
1.	Sapo Comun	Bufo marinus	Bufonidae
2.	Coqui	Eleutherodactylus coqui	Leptodactylidae
3.	Coqui Antillensis	Eleutherodactylus antillensis	Leptodactylidae
4.	Coqui Grillus	Eleutherodactylus grillus	Leptodactylidae
5.	Rana Leptodactila	Leptodactylus albilabris	Leptodactylidae
6.	Sapo Yure	Rana catesbeiana	Ranidae

* No source for an English translation was available for the common name of these species.

D. Reptiles*

	Common Name	Scientific Name	Family
1.	Lagartija Comun	Anolis cristatellus	Iguanidae
2.	Lagartija de las Yerbas	Anolis pulchellus	Iguanidae
3.	Lagartija de los Arboles	Anolis stratulus	Iguanidae
4.	Gekko	Sphaerodactylus klauberi	Gekkonidae
5.	Iguana	Ameiva exsul	Teiidae

* No source for an English translation was available for the common name of these species.

TABLE IV

Vegetation Used for Feeding Purposes by Genus Columba and Other Related genus.*

Common Name	Scientific Name	Family	Columba species
1. Achiotillo	Alchornea latifolia	Euphorbiaceae	Zenaida aurita
2. Adelia	Bernaidia dichotoma	Euphorbiaceae	Columba leucocephala
3. Adormidera	Croton rigidus	Euphorbiaceae	Columbina passerina
4. Arroz	Oryza sativa	Gramineae	Columba squamosa Zenaida aurita
5. Bejuco de Puerco	Ipomoea tiliacea	Convolvulaceae	Zenaida aurita
6. Berenjena Cimarrona	Solanum torvum	Solanaceae	Columba squamosa C. inornata wetmorei
7. Bledo	Amaranthus dubius	Amaranthaceae	Columbina passerina Zenaida aurita
8. Bretonica Prieta	Melochia nodiflora	Sterculiaceae	Columbina passerina
9. Cadillo	Urena lobata	Malvaceae	Zenaida aurita
10. Camasey	Miconia prasina	Melostomataceae	Geotrygon montana
11. Cardo Santo	Argenome mexicana	Papaveraceae	Columbina passerina Zenaida aurita
12. Carrucillo	Olyra latifolia	Gramineae	Columbina passerina Geotrygon montana Zenaida aurita
13. China	Citrus sinensis	Rutaceae	Columbina passerina Geotrygon montana Zenaida aurita
14. Cohitre Azul	Gibasus geniculata	Commelinaceae	Columbina passerina
15. Coqui	Hypoxis decumbens	Hypoxidaceae	Columbina passerina

TABLE IV (Continued)

	Common Name	Scientific Name	Family	Columba species
16.	Coqui Blanco	Rhynchospora miliacea	Gramineae	Columbina passerina
17.	Cortadora	Paspalum millegrana	Gramineae	Columbina passerina
18.	Cortadora de Altura	Scleira secans	Cyperaceae	Columbina passerina Zenaida aurita
19.	Escoba	Sida acuta	Malvaceae	Columbina passerina Zenaida aurita
20.	Espino Rubial	Zanthoxylum caribaeum	Rutaceae	Zenaida aurita
21.	Fresa	Rubus rosaefolius	Rosaceae	Columbina passerina
22.	Guaraguao	Trichilia hirta	Meliaceae	Columba squamosa
23.	Habichuela Para	Macroptilium lathyroides	Papilionoideae	Columbina passerina Zenaida aurita
24.	Hedionda	Cassia occidentalis	Caesalpinioideae	Zenaida aurita
25.	Hicaco	Chrysobalanus icaco	Chrysobalanaceae	Columba leucocephala
26.	Higuillo	Piper aduncum	Piperaceae	Zenaida macroura
27.	Jacana	Pouteria multiflora	Sapotaceae	Zenaida macroura
28.	Jaguey Blanco	Ficus citrifolia	Moraceae	Columbina passerina Columba squamosa
29.	Junquito	Fimbristylis dichotoma	Cyperaceae	Columbina passerina
30.	Laurel de Paloma	Ocotea portoricensis	Lauraceae	Columba squamosa
31.	Laurel Geo	Ocotea leucoxylon	Lauraceae	Zenaida macroura
32.	Leche Vana	Euphorbia heterophylla	Euphorbiaceae	Columbina passerina Zenaida aurita

TABLE IV (Continued)

	Common Name	Scientific Name	Family	Columba species
33.	Lechecilla	Chamaesyce hirta	Euphorbiaceae	Columbina passerina Geotrygon montana
34.	Llanten	Plantago major	Plantaginaceae	Columbina passerina Zenaida aurita
35.	Maiz	Zea mays	Gramineae	Columba squamosa
36.	Manzanillo	Hippomane mancinella	Euphorbiaceae	Geotrygon montana
37.	Maricao	Byrsonima spicata	Malpighiaceae	Zenaida macroura
38.	Matagallina	Solanum americanum	Solanaceae	Columba squamosa Zenaida aurita
39.	Moral	Cordia sulcata	Boraginaceae	Geotrygon montana Columba squamosa Columba leucocephia Zenaida aurita
40.	Morivivi Bobo	Aeschynomene americana	L-Papilionoideae	Zenaida aurita
41.	Naranja	Citrus aurantium	Rutaceae	Geotrygon montana
42.	Palma de Abanico	Coccothrinax argentea	Palmaceae	Columba leucocephala Columba squamosa
43.	Palma de Sierra	Prestoea montana	Palmaceae	Columba squamosa
44.	Palma Real	Roystonea borinquena	Palmaceae	Columba squamosa Columba leucocephala
45.	Palo Blanco	Drypetes glauca	Euphorbiaceae	Columba leucocephala
46.	Palo de Jazmin	Styrax portoricensis	Styracaceae	Columba squamosa
47.	Pata de Gallina	Eleusine indica	Gramineae	Columbina passerina

TABLE IV (Continued)

	Common Name	Scientific Name	Family	Columba species
48.	Paxote	Chenopodium ambrosioides	Chenopodiaceae	Zenaida aurita Columbina passerina
49.	Penduta	Citharexylum trulcoeum	Verbenaceae	Columba fvia
50.	Pomarrosa	Syzygium jambos	Myrtaceae	Columba inornata wetmorei
51.	Tagua-Tagua	Passiflora foetida	Passifloraceae	Zenaida aurita
52.	Toronja	Citrus maxima	Rutaceae	Geotrygon montana
53.	Tua-Tua	Jatropha gossypiofia	Euphorbiaceae	Zenaida aurita Columbina passerina
54.	Verdolaga	Portulaca oleracea	Portulacaceae	Zenaida aurita Columbina passerina
55.	Verdolaga de Abrojo	Kallstroemia maxima	Zygophyllaceae	Zenaida aurita Columbina passerina
56.	Verdolaguilla	Talinum triangulare	Portulacaceae	Columbina passerina
57.	Vinagrillo	Oxalis corniculata	Oxalidaceae	Columbina passerina
58.	Yagrumo Macho	Didymopanax morototoni	Araliaceae	Zenaida macroura Columba inornata wetmorei
59.	Yerba de Hicotea	Polygonum glabrum	Polygonaceae	Zenaida aurita Columbina passerina
60.	Yuca	Manihot esculenta	Euphorbiaceae	Zenaida aurita

* No source for an English translation was available for the common name of these species.

REDACTIONS MADE BY APPLICANT

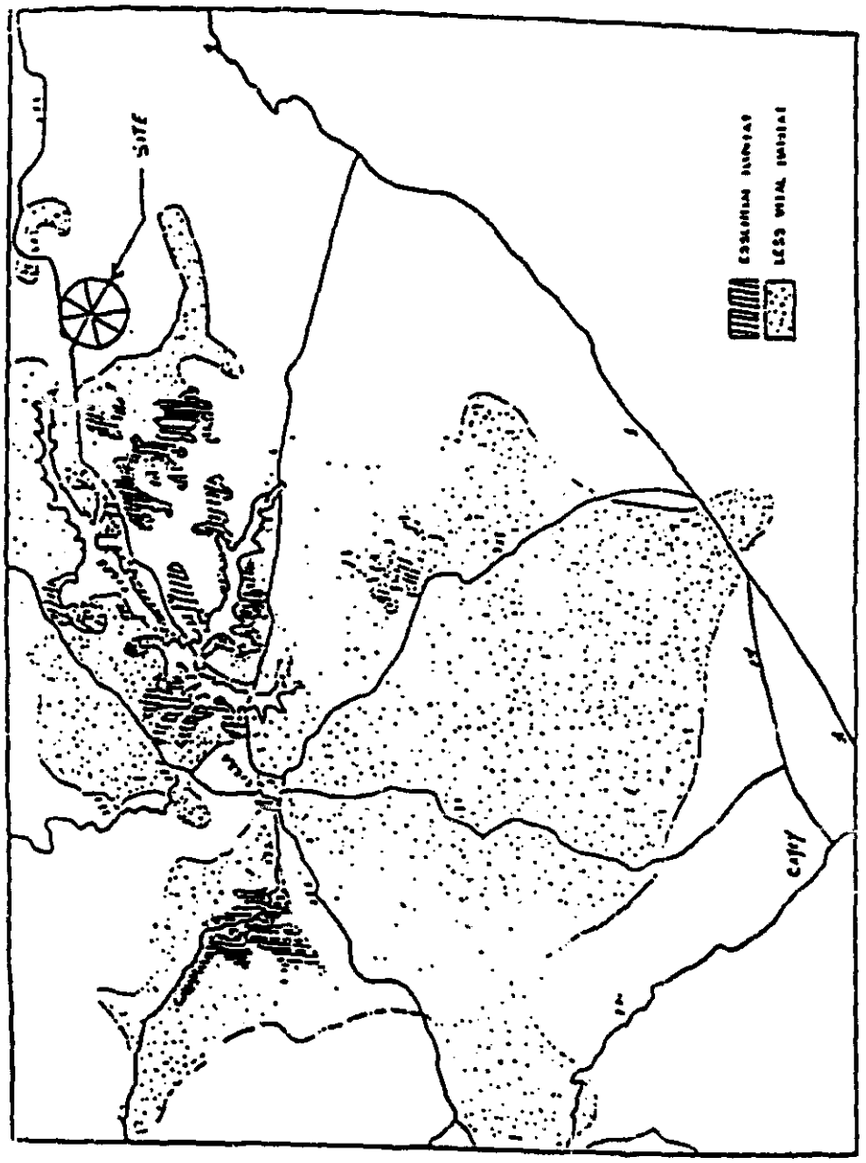
TABLE V

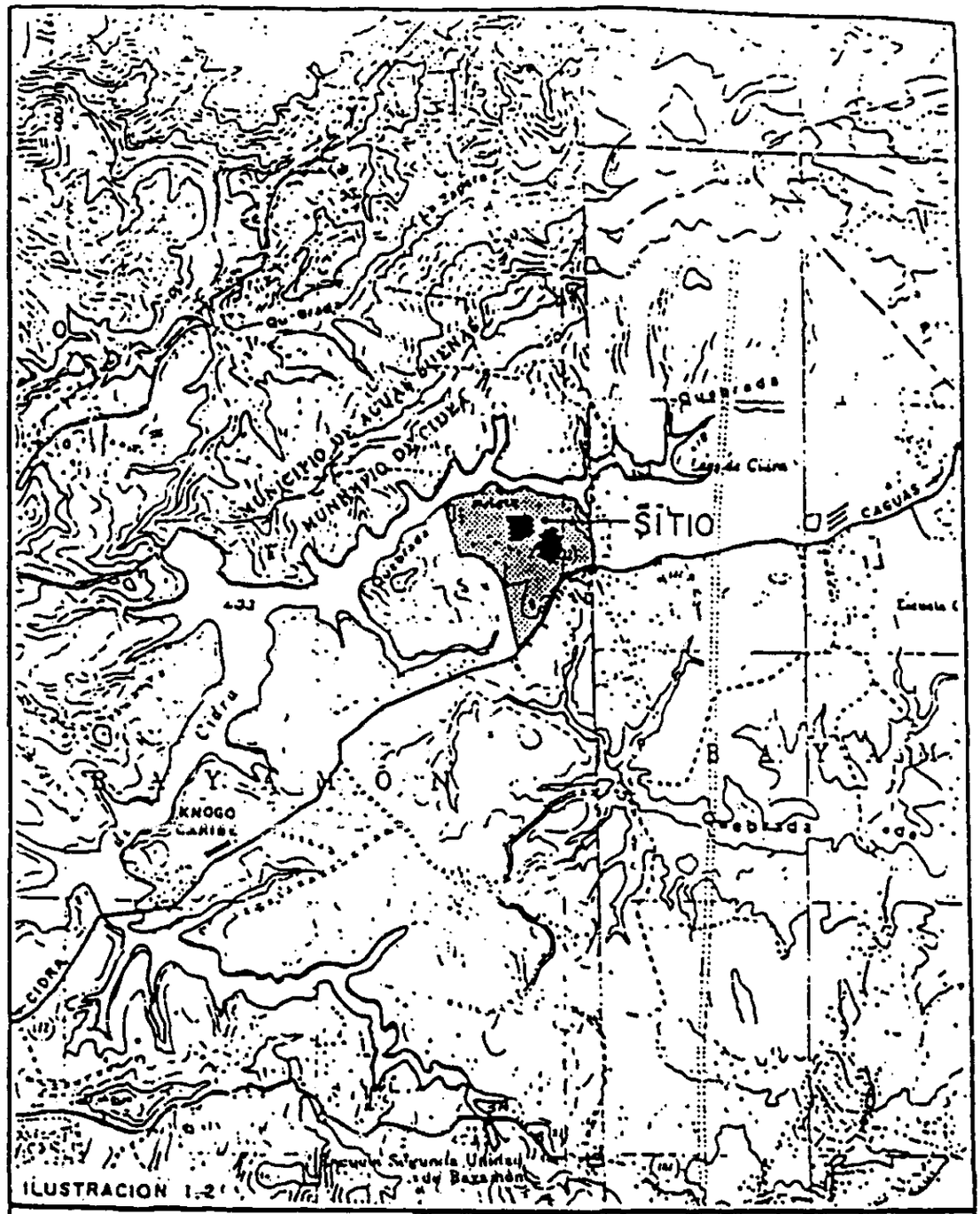
Projected Population per Municipality

MUNICIPIO	1980	1985	1990	1995	2000	2005
ADJUNTAS	18784.	18144.	17608.	17156.	16821.	16417.
AGUADA	31567.	33723.	34147.	35679.	37262.	38674.
AGUADILLA	54606.	54936.	55555.	56325.	57322.	57975.
AGUAS BUENAS	22429.	22652.	23089.	23556.	24103.	24538.
AIBONITO	22167.	22231.	22620.	23134.	23747.	24182.
ANASCO	23274.	23952.	24673.	25457.	26333.	27072.
ARECIBO	86766.	89101.	91449.	93905.	96832.	99246.
ARROYO	17014.	18328.	20014.	22072.	24534.	27116.
BARCELONETA	18942.	19729.	20540.	21385.	22355.	23254.
BARRANQUITAS	21639.	20908.	20158.	19925.	19559.	19066.
BAYAMON	196206.	207629.	219780.	232567.	245809.	257613.
CABO ROJO	34045.	35805.	37683.	39776.	42200.	44498.
CAGUAS	117959.	123325.	129231.	135603.	142551.	149236.
CAMUY	25922.	27668.	29488.	31300.	33312.	35256.
CANOVANAS	31850.	34287.	37189.	40387.	43895.	47175.
CAROLINA	165954.	171119.	176194.	181561.	187582.	192122.
CATANO	26243.	26336.	26691.	27377.	27808.	28113.
CAYEY	41079.	42040.	45157.	46700.	49618.	51841.
CEIBA	14944.	16537.	18377.	20542.	22984.	25673.
CIALES	16211.	16657.	16888.	17406.	18001.	18686.
CIDRA	28365.	29251.	30530.	31912.	33451.	34813.
COAMO	30822.	31587.	32709.	34071.	35662.	37100.
COMERIO	18212.	17587.	17023.	16547.	16138.	15634.
COROZAL	28221.	28757.	29670.	30718.	31807.	32716.
CULEBRA	1265.	1417.	1598.	1806.	2064.	2348.
DORADO	25511.	28824.	32641.	36965.	41992.	47376.
FAJARDO	32087.	33497.	35182.	37192.	39545.	41683.
FLORIDA	7237.	8008.	8916.	9947.	11133.	12606.
GUANICA	18799.	19452.	20079.	20625.	21301.	22065.
GUAYAMA	40183.	39788.	40013.	40150.	40331.	40527.
GUAYANILLA	21050.	20703.	20367.	19953.	19598.	19223.
GUAYNABO	80742.	85152.	90229.	95154.	100289.	104665.
GURABO	23574.	25268.	27196.	29284.	31609.	33849.
HATILLO	28958.	30437.	32117.	34020.	36223.	38315.
HORMIGUEROS	14030.	15141.	16287.	17503.	18870.	20158.
HUMACAO	46134.	48931.	52176.	55851.	60117.	64220.
ISABELA	37435.	38829.	39978.	41459.	43175.	44686.
JAYUYA	14722.	14459.	14321.	14241.	14229.	14163.
JUANA DIAZ	43505.	43363.	43515.	43646.	43976.	44184.
JUNCOS	25397.	25751.	26160.	26546.	27064.	27386.
LAJAS	21236.	22798.	24411.	26051.	27920.	29790.
LARES	26743.	26265.	25903.	25624.	25462.	25139.
LAS MARIAS	8747.	8894.	9073.	9263.	9493.	9685.
LAS PIEDRAS	22412.	23518.	24754.	25987.	27337.	28621.
LOIZA	20867.	22367.	24162.	26188.	28516.	30820.

BEST POSSIBLE COPY

Fig. 1 Areas of Essential Habitat and Less Vital Habitat for the Specie Columbo Innonata watanabei.





SB Pharmaceuticals
Cidra, Puerto Rico
Plant Location

SmithKline Beecham
Pharmaceuticals

GENERAL COMPLIANCE STATEMENT

SmithKline Beecham Pharmaceuticals Co. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of 'Paroxetine' at its facilities in Cidra, Puerto Rico.

10/23/91

NAME: Ismael Guzmán DATE:
TITLE: Director of Engineering Services

10/23/91

NAME: Betsy Rodriguez DATE:
TITLE: Production Director

SmithKline Beecham Pharmaceuticals Co.
PO Box 11975, Road 172, KM 9.1
SO Cantanezza, Cidra, Puerto Rico 00639-1975
Telephone: (809) 786 4000

New NPDES Permit
English Translation from Spanish Original

Parameter	Limit	Frequency	Type of Sample
1. Flow	130,000 gal/day	Continuous	Continuous
2. BOD_5	10.0 mg/L average 15.0 mg/l daily max.	Monthly	Composite
3. Suspended Solids	None		
4. Dissolved Oxygen	> 5.0	Daily	Grab
5. Total coliform	10,000 col/100 mL	Monthly	Grab
6. Fecal coliform	2000 col/100 mL	Monthly	Grab
7. Residual chlorine	That will not affect receiving water	Daily	Grab
8. pH	>6.0 to <9.0	Daily	Grab
9. Color	10.0 Pt/Co SU	Dec & June	Grab
10. Turbidity	50.0 NTU	Mar & Sept	Grab
11. Cadmium	1.03 µg/L	Weekly./Monthly	Grab
12. Oil & grease	10.0 average	Monthly	Grab
13. Temperature	<32.2 °C	Daily	Grab
14. Phenol	Limit of detection (10.0 µg/L)	Mar & Sept	Grab
15. Lead	2.7 µg/L	Weekly/Monthly	Grab
16. Silver	1.0 µg/L	Dec & June	Grab
17. Zinc	50 µg/L	Monthly	Grab
18. Fluoride	700 µg/L	Monthly	Grab
19. Chloride	250 mg/L	2/Month	Grab
20. Copper	10.6 µg/L	Weekly/Monthly	Grab
21. Boron	1.0 mg/L	Monthly	Grab
22. Total Chromium	50 µg/L	Monthly	Grab
23. Cyanide	20 µg/L	Monthly	Grab
24. Mercury	1.0 µg/L	Monthly	Grab
25. Selenium	10 µg/L	Monthly	Grab
26. Surfactants	0.100 mg/L	Monthly	Grab
27. Sulfide	Limit of Detection (2.0 µg/L)	Monthly	Grab
28. TDS	500.0 mg/L	Monthly	Grab
29. Phosphorus	1.0 mg/L	Weekly/Monthly	Grab
30. NO3 + NO2	10.0 mg/L	Monthly	Grab
31. TSS	60.0 mg/L	Monthly	Composite
32. COD	126.0 mg/L	Monthly	Composite
33. Color & Taste	None	-	-
34. Floating solids	None	-	-

REDACTIONS MADE BY APPLICANT

SmithKline Beecham

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MATERIAL SAFETY DATA SHEET

1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND OF THE COMPANY/UNDERTAKING

SUBSTANCE:
PAROXETINE HYDROCHLORIDE
CHEMICAL FAMILY:
Substituted phenylpiperidine
MOLECULAR FORMULA:
C19-H20-F-N-O3 . H-Cl
MOLECULAR WEIGHT:
365.5
EINECS NUMBER:
NOT ASSIGNED
ELINCS NUMBER:
NOT ASSIGNED
COMPANY:
SMITHKLINE BEECHAM CORPORATION
CORPORATE ENVIRONMENT AND HEALTH AND SAFETY
709 SWEDELAND ROAD
KING OF PRUSSIA, PA 19406
PHONE: (215)270-7855

2.COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENTS	CAS REGISTRY NO	PERCENT
PAROXETINE HYDROCHLORIDE	78246-49-8	99

CONTAMINANTS:
No significant hazardous contaminants present.

3. HAZARDS IDENTIFICATION

PRIMARY ROUTES OF EXPOSURE:
Avoid breathing dust, skin contact, eye contact.
SKIN CONTACT:
Irritation after direct contact and allergic skin reaction are not expected, based on animal studies. However, skin contact should be avoided.
EYE CONTACT:
Irritation can occur following direct contact. Symptoms might include redness, swelling, blurred vision, pain, lachrymation or permanent eye damage.
INHALATION:
This material is a potent pharmaceutical agent, small amounts of dust can produce pharmacologic effects. Symptoms after breathing dust might include weakness, dizziness, insomnia, tremor, agitation, nervousness, nausea, dry mouth, diarrhea, constipation or loss of appetite.
INGESTION:
Symptoms after over exposure might include weakness, dizziness, insomnia, tremor, agitation, nervousness, nausea, dry mouth, diarrhea, constipation or loss of appetite.
CONDITIONS AGGRAVATED BY EXPOSURE:
Individuals taking other medications, including monoamine oxidase inhibitors, might be sensitive to the effects of this material. In cases of over exposure, seek medical assistance concerning possible drug interactions.

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4. FIRST-AID MEASURES

SKIN CONTACT:
Remove contaminated clothing and wash exposed area with soap and water. Obtain medical assistance if unusual symptoms occur.

NOTE TO PHYSICIAN:
None

EYE CONTACT:
Wash eyes with water for at least 15 minutes then obtain medical assistance.

NOTE TO PHYSICIAN:
Because of the possibility for long lasting damage following eye contact, refer all such cases to an ophthalmologist.

INHALATION:
Move exposed subject to fresh air. Refer to a physician if subject experiences difficulty breathing.If breathing has stopped, perform cardiopulmonary resuscitation (CPR) and seek immediate medical assistance.

NOTE TO PHYSICIAN:
Effects on the nervous system are of prime concern in cases of over exposure. Treatment should be symptomatic and supportive. For additional information consult the most recent Physicians Desk Reference for treatment of overdosages by serotonin uptake inhibitors.

INGESTION:
In the event of swallowing this material, a trained person should induce vomiting, if subject is fully conscious, then seek medical assistance. Gastric lavage can also be considered.

NOTE TO PHYSICIAN:
Effects on the nervous system are of prime concern in cases of over exposure. Treatment should be symptomatic and supportive. For additional information consult the most recent Physicians Desk Reference for treatment of overdosages by serotonin uptake inhibitors.

ANTIDOTES:
None

5.FIRE-FIGHTING MEASURES

FIRE CONTROL:
Use water, carbon dioxide, foam or dry chemical suitable for surrounding fire.

SPECIAL FIREFIGHTING PROCEDURES:
Toxic or corrosive gases including oxides of carbon, nitrogen and fumes of chlorine or fluorine are expected in fires of this material. Self contained breathing apparatus and full protective equipment are recommended for firefighters.

6. ACCIDENTAL RELEASE MEASURES

SPILLS:
For large spills, isolate the spill area, restrict access and post the area for hazards present (potent pharmaceutical agent, harmful if swallowed, eye irritant) and necessary precautions. Wear appropriate protective equipment to avoid (ingestion, eye contact, breathing dust. Avoid creating excessive dust clouds when cleaning up spills. Scoop or shovel spilled material into a suitable, properly labeled container for recovery or disposal. If present in a liquid mixture, mix with sand or

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MATERIAL SAFETY DATA SHEET

absorbent material and scoop or shovel into a suitable, properly labeled container for recovery or disposal.

DECONTAMINATION PROCEDURES:

Water based detergents should be useful in clean up operations.

7. HANDLING AND STORAGE

HANDLING:

Enclosure is recommended to routinely control airborne dust levels.

STORAGE:

Store in a cool, dry, secure area. Use conductive or anti static liners for storage. Avoid contact with direct sunlight.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

EXPOSURE CONTROLS:

PAROXETINE HYDROCHLORIDE:

SmithKline Beecham(PEL/PC):

0.2 MG/M3 (8 HR TWA) PEL

United Kingdom(HSE):

No Exposure Limit Established.

United States(ACGIH):

No Exposure Limit Established.

United States(OSHA):

No Exposure Limit Established.

INDUSTRIAL HYGIENE METHOD:

For SmithKline Beecham operations, contact the site Occupational or Industrial Hygienist or regional Corporate health and safety group, as appropriate, for advice on suitable monitoring methods.

For other operations, industrial hygiene monitoring advice may be obtained from the health and safety group identified in section 1.

PERSONAL PROTECTION:

RESPIRATORS:

If dust is greater then 0.2 mg/cubic meter a laboratory fume hood or approved respirator should be used. The type of respirator will depend on air levels present. In the US, OSHA 1910.134 must be followed when respirators are used in the workplace.

GLOVES:

Wear impervious gloves.

EYE PROTECTION:

Wear chemical splash goggles when handling this material. In addition, a face shield is recommended.

HYGIENE PRACTICES:

Wash hands and arms thoroughly after handling this material. Clean up spills immediately.

OTHER PROTECTIVE EQUIPMENT:

An eye wash station should be available. Wear lab coat or other protective clothing with long sleeves.

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE:

White to off white powder. Will discolour on exposure to light.

FLASH POINT:

Greater than 55 degrees C

AUTOIGNITION TEMP:

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Not determined

LOWER EXPLOSIVE LIMIT:
Not applicable

UPPER EXPLOSIVE LIMIT:
Not applicable

MELTING POINT:
120 to 129 degrees C.

BOILING POINT:
Not applicable

SPECIFIC GRAVITY:
Not determined

EVAPORATION RATE/VAPOR PRESSURE:
Not determined

PH OF AQUEOUS SOLUTIONS:
Neutral

SOLUBILITY:
Soluble in water (8 g/l), ethyl alcohol (200 g/l) and methyl alcohol (200 g/l).

10. STABILITY AND REACTIVITY

CONDITIONS TO AVOID:
Avoid generating dust clouds. Avoid using plastic materials when handling or storing this material.

INCOMPATIBILITY:
None known.

STABILITY:
Stable but decomposes at elevated temperatures (greater than 130 degrees C).

HAZARDOUS POLYMERIZATION:
Will not occur.

HAZARDOUS DECOMPOSITION PRODUCTS:
None known.

FIRE AND EXPLOSION HAZARDS:
Paroxetine is non combustible in the train fire test and is therefore considered to be non flammable in bulk quantities. However, it is combustible if dispersed as a dust cloud and care should be taken to avoid dust dispersion. It is moderately sensitive to electrostatic ignition and all plant equipment and operators should be earthed (grounded) to minimize this risk. Plastic materials should be avoided when handling this material and conductive or anti static liners should be used for storage or handling.

11. TOXICOLOGY INFORMATION

ORAL TOXICITY:
Moderate doses are required to produce lethality following a single ingestion. Oral LD50 values were 378 mg/kg in mice and 415 mg/kg in rats.

INHALATION TOXICITY:
Not determined

SKIN IRRITATION:
This material was classified as a non irritant to rabbit skin. No signs of irritation occurred up to 3 days after direct application for 4 hours in rabbits.

EYE IRRITATION:
This material was classified as a very severe to extremely severe

SmithKline Beecham

irritant to rabbit eyes. Water irrigation reduced irritation after direct application of a reduced volume of this material.

SENSITIZATION:
This material was classified as a non sensitizer to guinea pig skin. No irritation or adverse skin reactions occurred in guinea pigs used to test for sensitization or allergic skin reaction (modified Maguire/Split Adjuvant Test).

MUTAGENICITY:
This material was not mutagenic in bacteria (Ames test) or other laboratory tests.

CARCINOGENICITY:
This material is not listed as a carcinogen by IARC, NTP, UK HSE or US OSHA. It was not carcinogenic in studies with rats or mice.

REPRODUCTIVE EFFECTS:
No teratogenic (birth defects) or embryotoxic effects resulted in rats or rabbits. Fertility in female rats was reduced at relatively low dose levels.

OTHER EFFECTS:
This material is an anti-depressant agent that selectively blocks serotonin reuptake and can affect the nervous system.

12. ECOLOGICAL INFORMATION

ACUTE AQUATIC EFFECTS:
Not determined.

BIODEGRADATION:
Not determined.

ACTIVATED SLUDGE RESPIRATION INHIBITION (OECD 209 PROTOCOL):
Not determined.

SOIL ADSORPTION:
Not determined.

OTHER EFFECTS:
Not determined.

13. DISPOSAL CONSIDERATIONS

Dispose of waste on site in a chemical incinerator if allowed by the incinerator permit. If no on-site incinerator is available, dispose of waste in a licensed chemical incinerator.

14. TRANSPORT INFORMATION

FOR AIR TRANSPORT (IATA REQUIREMENTS):
Proper Shipping Name: OTHER REGULATED SUBSTANCES
Technical Name (for n.o.s.,not otherwise specified): Not applicable
UN/Identification Number: ID8027
Class/Division: 9
Sub Risk: Not applicable
Packing Group: Not applicable
RQ (Reportable Quantity): Not applicable
Emergency Response Guide Number: 11

FOR MARITIME TRANSPORT (IMDG REQUIREMENTS):
Proper Shipping Name: NOT RESTRICTED
Technical Name (for n.o.s., not otherwise specified): Not applicable
UN/Identification Number: Not applicable
Class: Not applicable
Sub Risk: Not applicable

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Packing group: Not applicable
IMDG page number: Not applicable
NFAG number: Not applicable
EMS number: Not applicable
Marine Pollutant: Not applicable
Emergency Response Guide Number: Not applicable

FOR UNITED STATES GROUND TRANSPORT (DOT REQUIREMENTS):

Proper Shipping Name: NOT RESTRICTED
Technical Name (for n.o.s., not otherwise specified): Not applicable
UN/Identification Number: Not applicable
Class/Division: Not applicable
Sub Risk: Not applicable
Packing Group: Not applicable
RQ (Reportable Quantity): Not applicable
Emergency Response Guide Number: Not applicable

FOR EUROPEAN GROUND TRANSPORT (ADR/RID/ROAD/RAIL REQUIREMENTS):

Not determined. Hazards according to ADR/RID requirements not identified.

EMERGENCY INFORMATION:

HAZCHEM code: Not identified.
TREMCARD Number: Not identified.

15. REGULATORY INFORMATION

FOR EC CLASSIFICATION, PACKAGING AND LABELLING REQUIREMENTS:

FIRE RISK CLASSIFICATION

NO FIRE HAZARD IDENTIFIED

HEALTH RISK CLASSIFICATION

HARMFUL IRRITANT

RISK PHRASES:

HARMFUL IF SWALLOWED. (R22)
RISK OF SERIOUS DAMAGE TO EYES.(R41)

SAFETY PHRASES:

AVOID CONTACT WITH EYES. (S25)
IN CASE OF CONTACT WITH EYES, RINSE IMMEDIATELY WITH PLENTY OF WATER AND SEEK MEDICAL ADVICE. (S26)
WEAR EYE/FACE PROTECTION. (S39)

SYMBOL:

ST. ANDREW'S CROSS(Xn) & ST. ANDREW'S CROSS(Xi)

16. OTHER INFORMATION

HAZARD LABEL:

**** NO FIRE HAZARD IDENTIFIED ****
**** HARMFUL AND IRRITANT ****
** HARMFUL IF SWALLOWED.
** RISK OF SERIOUS DAMAGE TO EYES.
** AVOID CONTACT WITH EYES.
** IN CASE OF CONTACT WITH EYES, RINSE IMMEDIATELY WITH PLENTY OF WATER AND SEEK MEDICAL ADVICE.
** WEAR EYE/FACE PROTECTION.
** TARGET ORGAN-TO BE DETERMINED

IF HMIS RATINGS ARE USED AT YOUR SITE, USE THE FOLLOWING:
HEALTH = 3 FIRE= 1 REACTIVITY = 0

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REFERENCES:
SB HAZARD DETERMINATION

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ENVIRONMENTAL ASSESSMENT

***Paxil*™(Paroxetine Hydrochloride) Tablets**

June 16, 1995

ITEM **PAGE**

SMITHKLINE BEECHAM ENVIRONMENTAL RESEARCH LABORATORY

SUMMARY OF ENVIRONMENTAL FATE AND EFFECT STUDIES

compound - BRL 29060A (PAROXETINE HCl)
concentrations given as free-base

summary prepared by - Scott Ziegenfuss revised as of 3/23/95

ENVIRONMENTAL FATE

Water Solubility

	mg/L
pH 5 -	5696 to 7881
pH 7 -	1132 to 1133
pH 9 -	318 to 341 (426 to 430 in repeat)
DI water -	5050 to 6804

Octanol/Water Distribution Coefficient (Kow)

	176 mg/L		1760 mg/L	
pH	Kow	log Kow	Kow	log Kow
5	14.1	1.15	12.2	1.09
7	20.0	1.30	22.2	1.35
9	1930	3.29	1800	3.26

Sludge Adsorption log K-biomass = 2.94 (y intercept of log x/m vs. log Ce plot)

Vapor Pressure < 8.25E-6 torr

UV/vis Spectrum

pH 5		pH 7		pH 9	
lambda	E	lambda	E	lambda	E
234	3732	234	3823	234	3806
292	3828	292	3817	292	3797

Dissociation Constant (pKa) 9.6

Aerobic Biodegradation none observed for BRL 29060A
metabolite (BRL 36610A)
* degraded at k=0.03/hr to < detection limit in 5 days (in-house), t1/2 = 23 hrs

Photolysis k = 0.29/hr in DI H2O and 0.27/hr in pH 7 buffer
t1/2 = 2.4 hours in DI H2O and 2.6 hrs in pH 7 buffer

ENVIRONMENTAL EFFECTS

		BRL 29060A	BRL 36610A
D. magna 48-hr acute	EC50 =	2.5 mg/L	35 mg/L
	NOEC =	0.49 mg/L	14 mg/L
	slope =	4.4	15
Bluegill 96-hr acute	EC50 =	1.6 mg/L	-
	NOEC =	0.18 mg/L	-
	slope =	8.5	-
Microbics Microtox	EC50 =	8.2 mg/L	29 mg/L
photodegraded solution		non-toxic	-
biodegraded solution		-	non-toxic
Activated Sludge Respiration Inhibition (OECD 209)	EC50 =	25 to 26 mg/L	80 to 83 mg/L

END

MD

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