CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-427 / S-011

Trade Name: Cymbalta

Generic Name: Duloxetine hydrochloride / 20mg, 30mg, 40mg, and 60mg

Sponsor: Eli Lilly

Approval Date: February 23, 2007

Indications: For the addition of a new indication for the treatment of Generalized Anxiety Disorder (GAD).

However, we note that the enclosed labeling also includes changes proposed in your pending "Changes Being Effected" supplemental application [redacted], dated August 9, 2005, and amended on October 17, 2005, and October 4, 2006. This supplemental application proposes the following revisions:

[redacted]

[redacted]. We are currently evaluating the revisions and will comment on the changes in a separate action letter.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text/submitted labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, designate these submissions "FPL for approved supplement NDA 21-427/ S-009, S-011, S-013." Approval of these submissions by FDA is not required before the labeling is used.

Pediatric Research Equity Act (PREA) Requirements-Studies Deferred

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving studies for ages 0 to 7 years (neonates and young children). We are deferring submission of your pediatric studies for ages 7 to 17 years (children and adolescents) until 3 years from the date of approval of this NDA.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

Post Marketing Commitments

1. Deferred Pediatric Studies Under PREA

You are required to assess the safety and effectiveness of duloxetine hydrochloride as a treatment for Generalized Anxiety Disorder in pediatric patients ages 7 to 17 (children and adolescents). Both children (ages 7 to 11) and adolescents (ages 12 to 17) should be equally represented in the samples, and there should be a reasonable distribution of both sexes in these age strata.

Final Report Submission: by February 28, 2011

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated "**Required Pediatric Study Commitments**".

2. Long-term Efficacy Study in Generalized Anxiety Disorder

Since GAD is a chronic illness, you are required to assess longer-term effectiveness and safety of duloxetine hydrochloride in GAD. You have agreed in your email submission dated February 9, 2007, to submit the results of one adult clinical study of duloxetine in the longer-term treatment of GAD. We note that you have an ongoing study that is expected to meet the requirements of this commitment.

Final Report Submission: by August 31, 2007

Please submit your final study report to the IND, clearly marked as "**Postmarketing Study Final Report.**" If the study report is intended to support a change in labeling within this Division, please submit it to the NDA.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Psychiatry Product and two copies of both the promotional materials and the package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Felecia Curtis, Regulatory Project Manager, at (301) 796-0877.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
2/23/2007 01:13:54 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-427 / S-011

LABELING

A NL 3606 AMP

CYMBALTA®

(duloxetine hydrochloride) Delayed-release Capsules

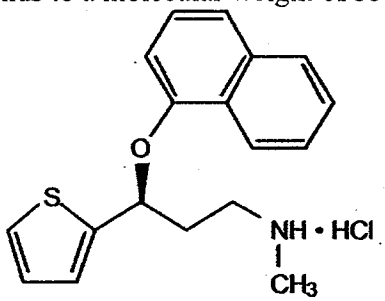
WARNING

Suicidality in Children and Adolescents — Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Cymbalta is not approved for use in pediatric patients. (*See* WARNINGS *and* PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Cymbalta® (duloxetine hydrochloride) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(*S*)-*N*-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride. The empirical formula is $C_{18}H_{19}NOS \cdot HCl$, which corresponds to a molecular weight of 333.88. The structural formula is:



Duloxetine hydrochloride is a white to slightly brownish white solid, which is slightly soluble in water.

Each capsule contains enteric-coated pellets of 22.4, 33.7, or 67.3 mg of duloxetine hydrochloride equivalent to 20, 30, or 60 mg of duloxetine, respectively. These enteric-coated pellets are designed to prevent degradation of the drug in the acidic environment of the stomach. Inactive ingredients include FD&C Blue No. 2, gelatin, hypromellose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate. The 20 and 60 mg capsules also contain iron oxide yellow.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS. Preclinical studies have shown that duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and GABA receptors *in vitro*. Duloxetine does not inhibit monoamine oxidase (MAO). Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of duloxetine.

Pharmacokinetics

Duloxetine has an elimination half-life of about 12 hours (range 8 to 17 hours) and its pharmacokinetics are dose proportional over the therapeutic range. Steady-state plasma concentrations are typically achieved after 3 days of dosing. Elimination of duloxetine is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP1A2.

Absorption and Distribution — Orally administered duloxetine hydrochloride is well absorbed. There is a median 2-hour lag until absorption begins (T_{lag}), with maximal plasma concentrations (C_{max}) of duloxetine occurring 6 hours post dose. Food does not affect the C_{max} of duloxetine, but delays the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (AUC) by about 10%. There is a 3-hour delay in absorption and a one-third increase in apparent clearance of duloxetine after an evening dose as compared to a morning dose.

The apparent volume of distribution averages about 1640 L. Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and α_1-acid glycoprotein. The interaction between duloxetine and other highly protein bound drugs has not been fully evaluated. Plasma protein binding of duloxetine is not affected by renal or hepatic impairment.

Metabolism and Elimination — Biotransformation and disposition of duloxetine in humans have been determined following oral administration of ^{14}C-labeled duloxetine. Duloxetine comprises about 3% of the total radiolabeled material in the plasma, indicating that it undergoes extensive metabolism to numerous metabolites. The major biotransformation pathways for duloxetine involve oxidation of the naphthyl ring followed by conjugation and further oxidation. Both CYP2D6 and CYP1A2 catalyze the oxidation of the naphthyl ring *in vitro*. Metabolites found in plasma include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate. Many additional metabolites have been identified in urine, some representing only minor pathways of elimination. Only trace (<1% of the dose) amounts of unchanged duloxetine are present in the urine. Most (about 70%) of the duloxetine dose appears in the urine as metabolites of duloxetine; about 20% is excreted in the feces.

Special Populations

Gender — Duloxetine's half-life is similar in men and women. Dosage adjustment based on gender is not necessary.

Age — The pharmacokinetics of duloxetine after a single dose of 40 mg were compared in healthy elderly females (65 to 77 years) and healthy middle-age females (32 to 50 years). There was no difference in the C_{max}, but the AUC of duloxetine was somewhat (about 25%) higher and

the half-life about 4 hours longer in the elderly females. Population pharmacokinetic analyses suggest that the typical values for clearance decrease by approximately 1% for each year of age between 25 to 75 years of age; but age as a predictive factor only accounts for a small percentage of between-patient variability. Dosage adjustment based on the age of the patient is not necessary (*see* DOSAGE AND ADMINISTRATION).

Smoking Status — Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers.

Race — No specific pharmacokinetic study was conducted to investigate the effects of race.

Renal Insufficiency — Limited data are available on the effects of duloxetine in patients with end-stage renal disease (ESRD). After a single 60-mg dose of duloxetine, C_{max} and AUC values were approximately 100% greater in patients with end-stage renal disease receiving chronic intermittent hemodialysis than in subjects with normal renal function. The elimination half-life, however, was similar in both groups. The AUCs of the major circulating metabolites, 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate, largely excreted in urine, were approximately 7- to 9-fold higher and would be expected to increase further with multiple dosing. For this reason, Cymbalta is not recommended for patients with end-stage renal disease (requiring dialysis) or severe renal impairment (estimated creatinine clearance [CrCl] <30 mL/min) (*see* DOSAGE AND ADMINISTRATION). Population PK analyses suggest that mild to moderate degrees of renal dysfunction (estimated CrCl 30-80 mL/min) have no significant effect on duloxetine apparent clearance.

Hepatic Insufficiency — Patients with clinically evident hepatic insufficiency have decreased duloxetine metabolism and elimination. After a single 20-mg dose of Cymbalta, 6 cirrhotic patients with moderate liver impairment (Child-Pugh Class B) had a mean plasma duloxetine clearance about 15% that of age- and gender-matched healthy subjects, with a 5-fold increase in mean exposure (AUC). Although C_{max} was similar to normals in the cirrhotic patients, the half-life was about 3 times longer (*see* PRECAUTIONS). It is recommended that duloxetine not be administered to patients with any hepatic insufficiency (*see* DOSAGE AND ADMINISTRATION).

Nursing Mothers — The disposition of duloxetine was studied in 6 lactating women who were at least 12-weeks postpartum. Duloxetine 40 mg BID was given for 3.5 days. Lactation did not influence duloxetine pharmacokinetics. Like many other drugs, duloxetine is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7 µg/day while on 40 mg BID dosing. The excretion of duloxetine metabolites into breast milk was not examined. Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended. (*see* DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions (also *see* PRECAUTIONS, Drug Interactions)

Potential for Other Drugs to Affect Duloxetine

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2 — When duloxetine 60 mg was co-administered with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to male subjects (n=14) duloxetine AUC was increased approximately 6-fold, the C_{max} was increased about 2.5 fold, and duloxetine $t_{1/2}$ was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin.

Inhibitors of CYP2D6 — Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does,

result in higher concentrations (on average 60%) of duloxetine (*see* PRECAUTIONS, Drug Interactions).

Dual Inhibition of CYP1A2 and CYP2D6 — Concomitant administration of duloxetine 40 mg BID with fluvoxamine 100 mg, a potent CYP1A2 inhibitor to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6 fold increase in duloxetine AUC and C_{max}.

Studies with Benzodiazepines

Lorazepam — Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by co-administration.

Temazepam — Under steady-state conditions for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

Potential for Duloxetine to Affect Other Drugs

Drugs Metabolized by CYP1A2 —*In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline, caffeine) resulting from induction is not anticipated, although clinical studies of induction have not been performed. Duloxetine is an inhibitor of the CYP1A2 isoform in *in vitro* studies and in two clinical studies the average (90% confidence interval) increase in theophylline AUC was 7% (1%-5%) and 20% (13%-27%) when co-administered with duloxetine (60 mg BID).

Drugs Metabolized by CYP2D6 — Duloxetine is a moderate inhibitor of CYP2D6 and increases the AUC and C_{max} of drugs metabolized by CYP2D6 (*see* PRECAUTIONS). Therefore, co-administration of Cymbalta with other drugs that are extensively metabolized by this isozyme and that have a narrow therapeutic index should be approached with caution (*see* PRECAUTIONS, Drug Interactions).

Drugs Metabolized by CYP2C9 — Duloxetine does not inhibit the *in vitro* enzyme activity of CYP2C9. Inhibition of the metabolism of CYP2C9 substrates is therefore not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP3A — Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction or inhibition is not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP2C19 — Results of *in vitro* studies demonstrate that duloxetine does not inhibit CYP2C19 activity at therapeutic concentrations. Inhibition of the metabolism of CYP2C19 substrates is therefore not anticipated, although clinical studies have not been performed.

Studies with Benzodiazepines

Lorazepam — Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of lorazepam were not affected by co-administration.

Temazepam — Under steady-state conditions for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of temazepam were not affected by co-administration.

Drugs Highly Bound to Plasma Protein — Because duloxetine is highly bound to plasma protein, administration of Cymbalta 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.

CLINICAL STUDIES

Major Depressive Disorder

The efficacy of Cymbalta as a treatment for depression was established in 4 randomized, double-blind, placebo-controlled, fixed-dose studies in adult outpatients (18 to 83 years) meeting DSM-IV criteria for major depression. In 2 studies, patients were randomized to Cymbalta 60 mg once daily (N=123 and N=128, respectively) or placebo (N=122 and N=139, respectively) for 9 weeks; in the third study, patients were randomized to Cymbalta 20 or 40 mg twice daily (N=86 and N=91, respectively) or placebo (N=89) for 8 weeks; in the fourth study, patients were randomized to Cymbalta 40 or 60 mg twice daily (N=95 and N=93, respectively) or placebo (N=93) for 8 weeks. There is no evidence that doses greater than 60 mg/day confer any additional benefit.

In all 4 studies, Cymbalta demonstrated superiority over placebo as measured by improvement in the 17-item Hamilton Depression Rating Scale (HAMD-17) total score.

Analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics.

Diabetic Peripheral Neuropathic Pain

The efficacy of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) was established in 2 randomized, 12-week, double-blind, placebo-controlled, fixed-dose studies in adult patients having diabetic peripheral neuropathy for at least 6 months. Study 1 and 2 enrolled a total of 791 patients of whom 592 (75%) completed the studies. Patients enrolled had Type I or II diabetes mellitus with a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for at least 6 months. The patients had a baseline pain score of ≥4 on an 11-point scale ranging from 0 (no pain) to 10 (worst possible pain). Patients were permitted up to 4 g of acetaminophen per day as needed for pain, in addition to Cymbalta. Patients recorded their pain daily in a diary.

Both studies compared Cymbalta 60 mg once daily or 60 mg twice daily with placebo. Study 1 additionally compared Cymbalta 20 mg with placebo. A total of 457 patients (342 Cymbalta, 115 placebo) were enrolled in Study 1 and a total of 334 patients (226 Cymbalta, 108 placebo) were enrolled in Study 2. Treatment with Cymbalta 60 mg one or two times a day statistically significantly improved the endpoint mean pain scores from baseline and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various degrees of improvement in pain from baseline to study endpoint, Figures 1 and 2 show the fraction of patients achieving that degree of improvement. The figures are cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

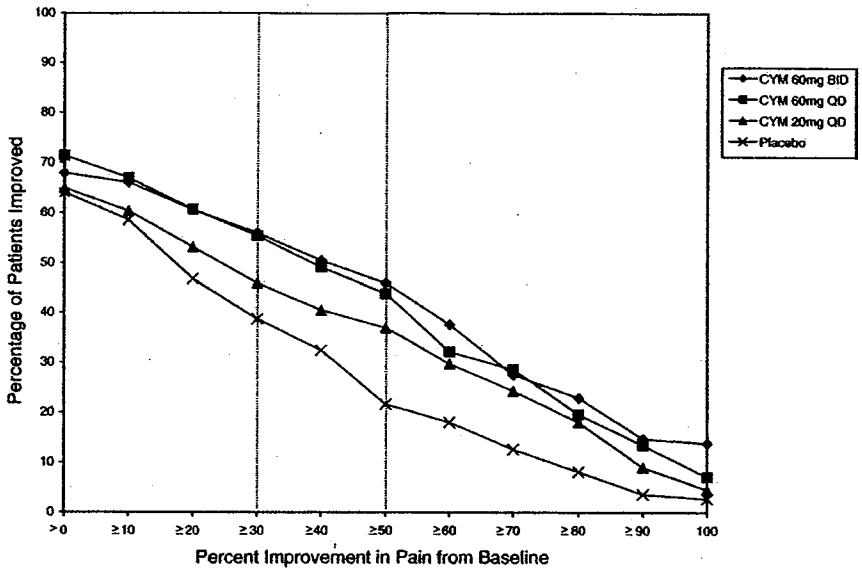


Figure 1: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 1

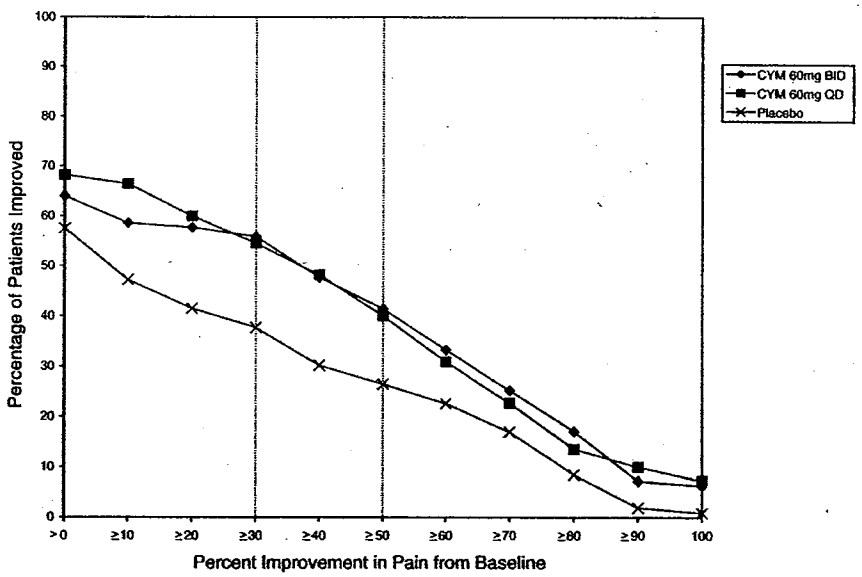


Figure 2: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 2

Generalized Anxiety Disorder

The efficacy of Cymbalta in the treatment of generalized anxiety disorder (GAD) was established in 1 fixed-dose randomized, double-blind, placebo-controlled trial and 2 flexible-dose randomized, double-blind, placebo-controlled trials in adult outpatients between 18 and 83 years of age meeting the DSM-IV criteria for GAD.

In 1 flexible-dose study and in the fixed-dose study, the starting dose was 60 mg once daily where down titration to 30 mg once daily was allowed for tolerability reasons before increasing it to 60 mg once daily. Fifteen percent of patients were down titrated. One flexible-dose study had a starting dose of 30 mg once daily for 1 week before increasing it to 60 mg once daily.

The 2 flexible-dose studies involved dose titration with Cymbalta doses ranging from 60 mg once daily to 120 mg once daily (N=168 and N=162) compared to placebo (N=159 and N=161) over a 10-week treatment period. The mean dose for completers at endpoint in the flexible-dose studies was 104.75 mg/day. The fixed-dose study evaluated Cymbalta doses of 60 mg once daily (N=168) and 120 mg once daily (N=170) compared to placebo (N=175) over a 9-week treatment period. While a 120 mg/day dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer additional benefit.

In all 3 studies, Cymbalta demonstrated superiority over placebo as measured by greater improvement in the Hamilton Anxiety Scale (HAM-A) total score and by the Sheehan Disability Scale (SDS) global functional impairment score. The SDS is a widely used and well-validated scale that measures the extent emotional symptoms disrupt patient functioning in 3 life domains: work/school, social life/leisure activities and family life/home responsibilities.

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

INDICATIONS AND USAGE

Major Depressive Disorder

Cymbalta is indicated for the treatment of major depressive disorder (MDD).

The efficacy of Cymbalta has been established in 8- and 9-week placebo-controlled trials of outpatients who met DSM-IV diagnostic criteria for major depressive disorder (*see* CLINICAL STUDIES).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

The effectiveness of Cymbalta in hospitalized patients with major depressive disorder has not been studied.

The effectiveness of Cymbalta in long-term use for major depressive disorder, that is, for more than 9 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Cymbalta for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

Diabetic Peripheral Neuropathic Pain

Cymbalta is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy (*see* CLINICAL STUDIES).

Generalized Anxiety Disorder

Cymbalta is indicated for the treatment of generalized anxiety disorder (GAD).

The efficacy of Cymbalta has been established in three 9- or 10-week placebo-controlled trials of outpatients who met DSM-IV diagnostic criteria for generalized anxiety disorder (*see* CLINICAL STUDIES).

Generalized anxiety disorder is defined by the DSM-IV as excessive anxiety and worry, present more days than not, for at least 6 months. The excessive anxiety and worry must be difficult to control and must cause significant distress or impairment in normal functioning. It must be associated with at least 3 of the following 6 symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and/or sleep disturbance.

The effectiveness of Cymbalta in long-term use for GAD, that is, for more than 10 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Cymbalta for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Hypersensitivity

Cymbalta is contraindicated in patients with a known hypersensitivity to duloxetine or any of the inactive ingredients.

Monoamine Oxidase Inhibitors

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

Uncontrolled Narrow-Angle Glaucoma

In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma.

WARNINGS

Clinical Worsening and Suicide Risk — Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose

changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (*see* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION, Discontinuing Cymbalta, for a description of the risks of discontinuation of Cymbalta).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Cymbalta should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder — A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Cymbalta is not approved for use in treating bipolar depression.

Monoamine Oxidase Inhibitors (MAOI) — In patients receiving a serotonin reuptake inhibitor in combination with a monoamine oxidase inhibitor, 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 serotonin reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. The effects of combined use of Cymbalta and MAOIs have not been evaluated in humans or animals. Therefore, because Cymbalta is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that Cymbalta not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of Cymbalta, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI.

Serotonin Syndrome — The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Cymbalta treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of Cymbalta with MAOIs intended to treat depression is contraindicated (*see* CONTRAINDICATIONS and WARNINGS, Potential for Interaction with Monoamine Oxidase Inhibitors).

If concomitant treatment of Cymbalta with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (*see* PRECAUTIONS, Drug Interactions).

The concomitant use of Cymbalta with serotonin precursors (such as tryptophan) is not recommended (*see* PRECAUTIONS, Drug Interactions).

PRECAUTIONS

General

Hepatotoxicity — Cymbalta increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.4% (31/8454) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In controlled trials in MDD, elevations of alanine transaminase (ALT) to >3 times the upper limit of normal occurred in 0.9% (8/930) of Cymbalta-treated patients and in 0.3% (2/652) of placebo-treated patients. In controlled trials in DPN, elevations of ALT to >3 times the upper limit of normal occurred in 1.68% (8/477) of Cymbalta-treated patients and in 0% (0/187) of placebo-treated patients. In the full cohort of placebo-controlled trials in any indication, elevation of ALT >3 times the upper limit of normal occurred in 1% (39/3732) of Cymbalta-treated patients compared to 0.2% (6/2568) of placebo-treated patients. In placebo-controlled studies using a fixed-dose design, there was evidence of a dose-response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively. Postmarketing reports have described cases of hepatitis with abdominal pain, hepatomegaly and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported.

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognized as an important predictor of severe liver injury. In clinical trials, three Cymbalta patients had elevations of transaminases and bilirubin, but also had elevation of alkaline phosphatase, suggesting an obstructive process; in these patients, there was evidence of heavy alcohol use and this may have contributed to the abnormalities seen. Two placebo-treated patients also had transaminase elevations with elevated bilirubin. Postmarketing reports indicate that elevated transaminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis. Postmarketing reports indicate that elevated transaminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis. Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Orthostatic Hypotension and Syncope — Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors (*see* CLINICAL PHARMACOLOGY, Drug-Drug Interactions, *and* PRECAUTIONS, Drug Interactions) and in patients taking duloxetine at doses above 60 mg daily. Consideration should be given to discontinuing duloxetine in patients who experience symptomatic orthostatic hypotension and/or syncope during duloxetine therapy.

Effect on Blood Pressure — In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. In a clinical pharmacology study designed to evaluate the effects of duloxetine on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg BID. At the highest 200 mg BID dose, the increase in mean pulse rate was 5.0-6.8 bpm and increases in mean blood pressure were 4.7-6.8 mm Hg (systolic) and 4.5-7 mm Hg (diastolic) up to 12 hours after dosing.

Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment (*see* ADVERSE REACTIONS, Vital Sign Changes).

Activation of Mania/Hypomania —In placebo-controlled trials in patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (2/2327) of duloxetine-treated patients and 0.1% (1/1460) of placebo-treated patients. No activation of mania or hypomania was reported in DPNP or GAD placebo-controlled trials. Activation of mania/hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other agents, Cymbalta should be used cautiously in patients with a history of mania.

Seizures — Duloxetine has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials, seizures/convulsions occurred in 0.04% (3/8504) of patients treated with duloxetine and 0.02% (1/6123) of patients treated with placebo. Cymbalta should be prescribed with care in patients with a history of a seizure disorder.

Hyponatremia — Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported and appeared to be reversible when Cymbalta was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Controlled Narrow-Angle Glaucoma — In clinical trials, Cymbalta was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma (*see* CONTRAINDICATIONS, Uncontrolled Narrow-Angle Glaucoma).

Discontinuation of Treatment with Cymbalta — Discontinuation symptoms have been systematically evaluated in patients taking Cymbalta. Following abrupt discontinuation in placebo-controlled clinical trials of up to 10-weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in either the MDD or GAD Cymbalta-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (*see* DOSAGE AND ADMINISTRATION).

Use in Patients with Concomitant Illness — Clinical experience with Cymbalta in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of Cymbalta's enteric coating. As duloxetine is rapidly hydrolyzed in acidic media to naphthol, caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics).

Cymbalta has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In three clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A_{1c} (HbA_{1c}) was 7.8%. In the 12-week acute treatment phase of these studies, Cymbalta was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 12 mg/dL in the Cymbalta group and decreased by 11.5mg/dL in the routine care group. HbA_{1c} increased by 0.5% in the Cymbalta and by 0.2% in the routine care groups.

Increased plasma concentrations of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis). For this reason, Cymbalta is not recommended for patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min) (*see* CLINICAL PHARMACOLOGY *and* DOSAGE AND ADMINISTRATION).

Markedly increased exposure to duloxetine occurs in patients with hepatic insufficiency and Cymbalta should not be administered to these patients (*see* CLINICAL PHARMACOLOGY *and* DOSAGE AND ADMINISTRATION).

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Cymbalta and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Cymbalta. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Cymbalta.

Clinical Worsening and Suicide Risk — Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Cymbalta should be swallowed whole and should not be chewed or crushed, nor should the contents be sprinkled on food or mixed with liquids. All of these might affect the enteric coating.

Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies Cymbalta has not been shown to impair psychomotor performance, cognitive function, or memory, it may be associated with sedation and dizziness. Therefore, patients should be cautioned about operating hazardous machinery including automobiles, until they are reasonably certain that Cymbalta therapy does not affect their ability to engage in such activities.

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

Although Cymbalta does not increase the impairment of mental and motor skills caused by alcohol, use of Cymbalta concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, Cymbalta should ordinarily not be prescribed for patients with substantial alcohol use.

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of Cymbalta and triptans, tramadol or other serotonergic agents.

Orthostatic Hypotension and Syncope — Patients should be advised of the risk of orthostatic hypotension and syncope, especially during the period of initial use and subsequent dose escalation, and in association with the use of concomitant drugs that might potentiate the orthostatic effect of duloxetine.

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

Patients should be advised to notify their physician if they are breast-feeding.

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

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions (also see CLINICAL PHARMACOLOGY, Drug-Drug Interactions)

Potential for Other Drugs to Affect Cymbalta

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2 — Concomitant use of duloxetine with fluvoxamine, an inhibitor of CYP1A2, results in approximately a 6-fold increase in AUC and about a 2.5-fold increase in C_{max} of duloxetine. Some quinolone antibiotics would be expected to have similar effects and these combinations should be avoided.

Inhibitors of CYP2D6 — Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 may result in higher concentrations of duloxetine. Paroxetine (20 mg QD) increased the concentration of duloxetine (40 mg QD) by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine, quinidine).

Potential for Duloxetine to Affect Other Drugs

Drugs Metabolized by CYP1A2 — *In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity, and it is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates (*see* CLINICAL PHARMACOLOGY, Drug Interactions).

Drugs Metabolized by CYP2D6 — Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg BID) in conjunction with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. Therefore, co-administration of Cymbalta with other drugs that are extensively metabolized by this isozyme and which have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with Cymbalta. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, Cymbalta and thioridazine should not be co-administered.

Drugs Metabolized by CYP3A — Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity (*see* CLINICAL PHARMACOLOGY, Drug Interactions).

Cymbalta May Have a Clinically Important Interaction with the Following Other Drugs:

Alcohol — When Cymbalta and ethanol were administered several hours apart so that peak concentrations of each would coincide, Cymbalta did not increase the impairment of mental and motor skills caused by alcohol.

In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen (*see* PRECAUTIONS, Hepatotoxicity).

CNS Acting Drugs — Given the primary CNS effects of Cymbalta, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action.

Serotonergic Drugs — Based on the mechanism of action of SNRIs and SSRIs, including Cymbalta and the potential for serotonin syndrome, caution is advised when Cymbalta is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (*see* WARNINGS, Serotonin Syndrome). The concomitant use of Cymbalta with other SSRIs, SNRIs or tryptophan is not recommended (*see* PRECAUTIONS, Drug Interactions).

Triptans — There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Cymbalta with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (*see* WARNINGS, Serotonin Syndrome).

Potential for Interaction with Drugs that Affect Gastric Acidity — Cymbalta has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Cymbalta with aluminum- and magnesium-containing antacids (51 mEq) or Cymbalta with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40-mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption.

Monoamine Oxidase Inhibitors — *See* CONTRAINDICATIONS *and* WARNINGS.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Duloxetine was administered in the diet to mice and rats for 2 years.

In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m^2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m^2 basis).

In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m^2 basis) did not increase the incidence of tumors.

Mutagenesis — Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*.

Impairment of Fertility — Duloxetine administered orally to either male or female rats prior to and throughout mating at doses up to 45 mg/kg/day (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m^2 basis) did not alter mating or fertility.

Pregnancy

Pregnancy Category C — In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development.

When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of 120 mg/day on a mg/m^2 basis, in rat; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m^2 basis in rabbit). However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (2 times the MRHD and ≈1 times the human dose of 120 mg/day on a mg/m^2 basis in rat; 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis in rabbits).

When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (5 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis); the no-effect dose was 10 mg/kg/day. Furthermore, behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

There are no adequate and well-controlled studies in pregnant women; therefore, duloxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects — Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (*see* WARNINGS, Monoamine Oxidase Inhibitors). When treating a pregnant woman with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (*see* DOSAGE AND ADMINISTRATION).

Labor and Delivery

The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established (*see* BOX WARNING *and* WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the use of Cymbalta in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use

Of the 2418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1074 patients in the DPN premarketing studies, 33% (357) were 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of subjects age 65 or over to determine whether they respond differently from younger subjects. In the MDD and DPN studies, no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other antidepressants, Cymbalta has been associated with cases of clinically significant hyponatremia (*see* Hyponatremia, under PRECAUTIONS).

ADVERSE REACTIONS

Cymbalta has been evaluated for safety in 2418 patients diagnosed with major depressive disorder who participated in multiple-dose premarketing trials, representing 1099 patient-years of exposure. Among these 2418 Cymbalta-treated patients, 1139 patients participated in eight 8- or 9-week, placebo-controlled trials at doses ranging from 40 to 120 mg/day, while the remaining 1279 patients were followed for up to 1 year in an open-label safety study using flexible doses from 80 to 120 mg/day. Two placebo-controlled studies with doses of 80 and 120 mg/day had 6-month maintenance extensions. Of these 2418 patients, 993 Cymbalta-treated patients were exposed for at least 180 days and 445 Cymbalta-treated patients were exposed for at least 1 year.

Cymbalta has also been evaluated for safety in 1074 patients with diabetic peripheral neuropathy representing 472 patient-years of exposure. Among these 1074 Cymbalta-treated patients, 568 patients participated in two 12- to 13-week, placebo-controlled trials at doses ranging from 20 to 120 mg/day. An additional 449 patients were enrolled in an open-label safety study using 120 mg/day for a duration of 6 months. Another 57 patients, originally treated with placebo, were exposed to Cymbalta for up to 12 months at 60 mg twice daily in an extension phase. Among these 1074 patients, 484 had 6 months of exposure to Cymbalta, and 220 had 12 months of exposure.

Cymbalta has also been evaluated for safety in 668 patients with generalized anxiety disorder representing 95 patient-years of exposure. These 668 patients participated in 9- or 10-week placebo-controlled trials at doses ranging from 60 mg once daily to 120 mg once daily. Of these 668 patients, 449 were exposed for at least 2 months to Cymbalta.

In the full cohort of placebo-controlled clinical trials for any indication, safety has been evaluated in 8504 patients treated with duloxetine and 6123 patients treated with placebo. In clinical trials, a total of 23,983 patients have been exposed to duloxetine. In duloxetine clinical trials, adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Clinical investigators recorded adverse events using descriptive terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing adverse events, grouping similar types of events into a smaller number of standardized event categories is necessary. In the tables and tabulations that follow, MedDRA terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Events reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

The cited figures provide the prescriber with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied. The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that 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.

Adverse Events Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials

Major Depressive Disorder

Approximately 10% of the 1139 patients who received Cymbalta in the MDD placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% of the 777 patients receiving placebo. Nausea (Cymbalta 1.4%, placebo 0.1%) was the only common adverse event reported as reason for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo).

Diabetic Peripheral Neuropathic Pain

Approximately 14% of the 568 patients who received Cymbalta in the DPN placebo-controlled trials discontinued treatment due to an adverse event, compared with 7% of the 223 patients receiving placebo. Nausea (Cymbalta 3.5%, placebo 0.4%), dizziness (Cymbalta 1.6%, placebo 0.4%), somnolence (Cymbalta 1.6%, placebo 0%) and fatigue (Cymbalta 1.1%, placebo 0%) were the common adverse events reported as reasons for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo).

Generalized Anxiety Disorder

Approximately 16% of the 668 patients who received Cymbalta in the GAD placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% of the 495 patients receiving placebo. Nausea (Cymbalta 3.7%, placebo 0.2%), vomiting (Cymbalta 1.4%, placebo 0%) and dizziness (Cymbalta 1.2%, placebo 0.2%) were the common

adverse events reported as reasons for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo).

Adverse Events Occurring at an Incidence of 2% or More Among Cymbalta-Treated Patients in Placebo-Controlled Trials

Major Depressive Disorder

Table 1 gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of MDD placebo-controlled trials and with an incidence greater than placebo. The most commonly observed adverse events in Cymbalta-treated MDD patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea; dry mouth; constipation; decreased appetite; fatigue; somnolence; and increased sweating (*see* Table 1).

Table 1: Treatment-Emergent Adverse Events Incidence in MDD Placebo-Controlled Trials[1]

System Organ Class / Adverse Event	Percentage of Patients Reporting Event	
	Cymbalta (N=1139)	Placebo (N=777)
Gastrointestinal Disorders		
Nausea	20	7
Dry mouth	15	6
Constipation	11	4
Diarrhea	8	6
Vomiting	5	3
Metabolism and Nutrition Disorders		
Appetite decreased[2]	8	2
Investigations		
Weight decreased	2	1
General Disorders and Administration Site Conditions		
Fatigue	8	4
Nervous System Disorders		
Dizziness	9	5
Somnolence	7	3
Tremor	3	1
Skin and Subcutaneous Tissue Disorders		
Sweating increased	6	2
Vascular Disorders		
Hot flushes	2	1
Eye Disorders		
Vision blurred	4	1
Psychiatric Disorders		

Insomnia[3]	11	6
Anxiety	3	2
Libido decreased	3	1
Orgasm abnormal[4]	3	1
Reproductive System and Breast Disorders		
Erectile dysfunction[5]	4	1
Ejaculation delayed[5]	3	1
Ejaculatory dysfunction[5, 6]	3	1

[1] Events reported by at least 2% of patients treated with Cymbalta and more often with placebo. The following events were reported by at least 2% of patients treated with Cymbalta for MDD and had an incidence equal to or less than placebo: upper abdominal pain, palpitations, dyspepsia, back pain, arthralgia, headache, pharyngitis, cough, nasopharyngitis, and upper respiratory tract infection.
[2] Term includes anorexia.
[3] Term includes middle insomnia.
[4] Term includes anorgasmia.
[5] Male patients only.
[6] Term includes ejaculation disorder and ejaculation failure.

Diabetic Peripheral Neuropathic Pain

Table 2 gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of DPN placebo-controlled trials (doses of 20 to 120 mg/day) and with an incidence greater than placebo. The most commonly observed adverse events in Cymbalta-treated DPN patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea; somnolence; dizziness; constipation; dry mouth; hyperhidrosis; decreased appetite; and asthenia (*see* Table 2).

Table 2: Treatment-Emergent Adverse Events Incidence in DPN Placebo-Controlled Trials[1]

System Organ Class / Adverse Event	Percentage of Patients Reporting Event			
	Cymbalta 60 mg BID (N=225)	Cymbalta 60 mg QD (N=228)	Cymbalta 20 mg QD (N=115)	Placebo (N=223)
Gastrointestinal Disorders				
Nausea	30	22	14	9
Constipation	15	11	5	3
Diarrhea	7	11	13	6
Dry mouth	12	7	5	4
Vomiting	5	5	6	4
Dyspepsia	4	4	4	3
Loose stools	2	3	2	1

General Disorders and Administration Site Conditions				
Fatigue	12	10	2	5
Asthenia	8	4	2	1
Pyrexia	3	1	2	1
Infections and Infestations				
Nasopharyngitis	9	7	9	5
Metabolism and Nutrition Disorders				
Decreased appetite	11	4	3	<1
Anorexia	5	3	3	<1
Musculoskeletal and Connective Tissue Disorders				
Muscle cramp	4	4	5	3
Myalgia	4	1	3	<1
Nervous System Disorders				
Somnolence	21	15	7	5
Headache	15	13	13	10
Dizziness	17	14	6	6
Tremor	5	1	0	0
Psychiatric Disorders				
Insomnia	13	8	9	7
Renal and Urinary Disorders				
Pollakiuria	5	1	3	2
Reproductive System and Breast Disorders				
Erectile dysfunction[2]	4	1	0	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	5	3	6	4
Pharyngolaryngeal pain	6	1	3	1
Skin and Subcutaneous Tissue Disorders				
Hyperhidrosis	8	6	6	2

[1] Events reported by at least 2% of patients treated with Cymbalta and more often than placebo. The following events were reported by at least 2% of patients treated with Cymbalta for DPN and had an incidence equal to or less than placebo: edema peripheral, influenza, upper respiratory tract infection, back pain, arthralgia, pain in extremity, and pruritus.

[2] Male patients only.

Generalized Anxiety Disorder

Table 3 gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of GAD placebo-controlled trials (doses of 60 to 120 mg once daily) and with an incidence greater than placebo. The most commonly observed adverse events in Cymbalta-treated GAD patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea; fatigue; dry mouth; somnolence; constipation; insomnia; appetite decreased; hyperhidrosis; libido decreased; vomiting; ejaculation delayed; and erectile dysfunction (*see* Table 3).

Table 3: Treatment-Emergent Adverse Events Incidence in GAD Placebo-Controlled Trials[1]

System Organ Class / Adverse Event	Percentage of Patients Reporting Event	
	Cymbalta (N=668)	Placebo (N=495)
Eye Disorders		
Vision blurred	4	2
Gastrointestinal Disorders		
Nausea	38	10
Dry mouth	12	4
Constipation	10	3
Diarrhea	8	6
Vomiting	5	2
Abdominal pain[2]	4	3
Dyspepsia[3]	4	3
General Disorders and Administration Site Conditions		
Fatigue[4]	13	5
Metabolism and Nutrition Disorders		
Appetite decreased[5]	8	3
Nervous System Disorders		
Dizziness	15	8
Somnolence[6]	12	3
Tremor	4	1
Paraesthesia[7]	2	1
Psychiatric Disorders		
Insomnia[8]	9	4
Libido decreased[9]	7	2
Agitation[10]	4	2
Orgasm abnormal[11]	3	0
Reproductive System and Breast Disorders		
Ejaculation delayed[12]	5	1
Erectile dysfunction[12]	5	1

Respiratory, Thoracic and Mediastinal Disorders Yawning	3	0
Skin and Subcutaneous Tissue Disorders Hyperhidrosis	7	2
Vascular Disorders Hot flushes	3	1

[1] Events reported by at least 2% of patients treated with Cymbalta and more often with placebo. The following events were reported by at least 2% of patients treated with Cymbalta for GAD and had an incidence equal to or less than placebo: nasopharyngitis, upper respiratory tract infection, headache, pollakiuria, and musculoskeletal pain (includes myalgia, neck pain).
[2] Term includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain.
[3] Term includes stomach discomfort.
[4] Term includes asthenia.
[5] Term includes anorexia.
[6] Term includes hypersomnia and sedation.
[7] Term includes hypoaesthesia.
[8] Term includes initial insomnia, middle insomnia, and early morning awakening.
[9] Term includes loss of libido.
[10] Term includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation.
[11] Term includes anorgasmia.
[12] Male patients only.

Adverse events seen in men and women were generally similar except for effects on sexual function (described below). Clinical studies of Cymbalta did not suggest a difference in adverse event rates in people over or under 65 years of age. There were too few non-Caucasian patients studied to determine if these patients responded differently from Caucasian patients.

Effects on Male and Female Sexual Function

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Table 4 displays the incidence of sexual side effects spontaneously reported by at least 2% of either male or female patients taking Cymbalta in MDD placebo-controlled trials.

Table 4: Treatment-Emergent Sexual Dysfunction-Related Adverse Events Incidence in MDD Placebo-Controlled Trials[1]

	Percentage of Patients Reporting Event	
	% Male Patients	% Female Patients

Adverse Event	Cymbalta (N=378)	Placebo (N=247)	Cymbalta (N=761)	Placebo (N=530)
Orgasm abnormal[2]	4	1	2	0
Ejaculatory dysfunction[3]	3	1	NA	NA
Libido decreased	6	2	1	0
Erectile dysfunction	4	1	NA	NA
Ejaculation delayed	3	1	NA	NA

[1] Events reported by at least 2% of patients treated with Cymbalta and more often than with placebo.
[2] Term includes anorgasmia.
[3] Term includes ejaculation disorder and ejaculation failure.
NA=Not applicable.

Because adverse sexual events are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, as shown in Table 5 below, patients treated with Cymbalta experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with Cymbalta experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on Cymbalta than on placebo as measured by ASEX total score. These studies did not, however, include an active control drug with known effects on female sexual dysfunction, so that there is no evidence that its effects differ from other antidepressants. Negative numbers signify an improvement from a baseline level of dysfunction, which is commonly seen in depressed patients. Physicians should routinely inquire about possible sexual side effects.

Table 5: Mean Change in ASEX Scores by Gender in MDD Placebo-Controlled Trials

	Male Patients		Female Patients	
	Cymbalta (n=175)	Placebo (n=83)	Cymbalta (n=241)	Placebo (n=126)
ASEX Total (Items 1-5)	0.56*	-1.07	-1.15	-1.07
Item 1 — Sex drive	-0.07	-0.12	-0.32	-0.24
Item 2 — Arousal	0.01	-0.26	-0.21	-0.18
Item 3 — Ability to achieve erection (men); Lubrication (women)	0.03	-0.25	-0.17	-0.18
Item 4 — Ease of reaching orgasm	0.40**	-0.24	-0.09	-0.13
Item 5 — Orgasm satisfaction	0.09	-0.13	-0.11	-0.17

n=Number of patients with non-missing change score for ASEX total.
*p=0.013 versus placebo.
**p<0.001 versus placebo.

Urinary Hesitation

Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related.

Laboratory Changes

Cymbalta treatment, for up to 9 weeks in MDD, 9-10 weeks in GAD or 13-weeks in DPN placebo-controlled clinical trials, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in Cymbalta-treated patients when compared with placebo-treated patients (*see* PRECAUTIONS).

Vital Sign Changes

In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure, averaging up to 2 mm Hg. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure (*see* PRECAUTIONS).

Duloxetine treatment, for up to 13-weeks in placebo-controlled trials typically caused a small increase in heart rate compared to placebo of up to 3 beats per minute.

Weight Changes

In placebo-controlled clinical trials, MDD and GAD patients treated with Cymbalta for up to 9 weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In DPN placebo-controlled clinical trials, patients treated with Cymbalta for up to 13-weeks experienced a mean weight loss of approximately 1.1 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients.

Electrocardiogram Changes

Electrocardiograms were obtained from duloxetine-treated patients and placebo-treated patients in clinical trials lasting up to 13-weeks. No clinically significant differences were observed for QTc, QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients. There were no differences in clinically meaningful QTcF elevations between duloxetine and placebo. In a positive-controlled study in healthy volunteers using duloxetine up to 200 mg BID, no prolongation of the corrected QT interval was observed.

Other Adverse Events Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of Duloxetine

Following is a list of MedDRA terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with duloxetine at multiple doses throughout the dose range studied during any phase of a clinical trial within the premarketing and postmarketing database (23,983 patients, 10,649.5 patient-years of exposure). The events included are those not already listed in Tables 1 through 3 and not considered in the WARNINGS and PRECAUTIONS sections. The events

were reported by more than one patient, are not common as background events and/or were considered possibly drug related (e.g., because of the drug's pharmacology) or potentially important.

It is important to emphasize that, although the events reported occurred during treatment with Cymbalta, 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 in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Blood and Lymphatic System Disorders — *Infrequent:* anemia and lymphadenopathy; *Rare:* leukopenia and thrombocytopenia.

Cardiac Disorders — *Frequent:* palpitations; *Infrequent:* atrial fibrillation, coronary artery disease, myocardial infarction, and tachycardia; *Rare:* bundle branch block right, cardiac failure, and cardiac failure congestive.

Ear and Labyrinth Disorders — *Frequent:* vertigo; *Infrequent:* ear pain.

Eye Disorders — *Frequent:* vision blurred; *Infrequent:* conjunctivitis, diplopia, and visual disturbance; *Rare:* glaucoma, macular degeneration, maculopathy, photopsia, and retinal detachment.

Gastrointestinal Disorders — *Frequent:* abdominal pain and gastritis flatulence; *Infrequent:* dysphagia, eructation, gastritis, halitosis, irritable bowel syndrome, and stomatitis; *Rare:* aphthous stomatitis, colitis, esophageal stenosis, gastric ulcer, gingivitis, hematochezia, impaired gastric emptying, and melena.

General Disorders and Administration Site Conditions — *Frequent:* chills/rigors; *Infrequent:* edema, edema peripheral, feeling abnormal, feeling hot and/or cold, influenza-like illness, malaise, and thirst; *Rare:* face edema and sluggishness.

Hepato-biliary Disorders —*Rare:* hepatic steatosis.

Infections and Infestations — *Infrequent:* gastroenteritis and laryngitis; *Rare:* diverticulitis.

Investigations — *Frequent:* weight decreased and weight increased; *Infrequent:* blood cholesterol increased; *Rare:* blood creatinine increased, urine output decreased, and white blood cell count increased.

Metabolism and Nutrition Disorders —*Infrequent:* dehydration, hypercholesterolemia, hyperlipidemia, hypoglycemia, and increased appetite; *Rare:* dyslipidemia and hypertriglyceridemia.

Musculoskeletal and Connective Tissue Disorders — *Frequent:* musculoskeletal pain; *Infrequent:* muscle tightness and muscle twitching; *Rare:* muscular weakness.

Nervous System Disorders — *Frequent:* dysgeusia, lethargy, and parasthesia/hypoesthesia; *Infrequent:* coordination abnormal, disturbance in attention, dyskinesia, hypersomnia, and myoclonus; *Rare:* dysarthria.

Psychiatric Disorders — *Frequent:* agitation, anxiety, libido decreased, nervousness, nightmare/abnormal dreams, and sleep disorder; *Infrequent:* apathy, bruxism, disorientation/confusional state, irritability, mood swings, restlessness, suicide attempt, and tension; *Rare:* completed suicide, mania, and pressure of speech.

Renal and Urinary Disorders —*Infrequent:* dysuria, micturition urgency, nocturia, urinary hesitation, urinary incontinence, urinary retention, urine flow decreased, and urine odor abnormal; *Rare:* nephropathy.

Reproductive System and Breast Disorders — *Frequent:* anorgasmia/orgasm abnormal, ejaculation delayed, and ejaculation disorder; *Infrequent:* menopausal symptoms.

Respiratory, Thoracic and Mediastinal Disorders — *Frequent:* yawning; *Infrequent:* throat tightness; *Rare:* pharyngeal edema.

Skin and Subcutaneous Tissue Disorders — *Frequent:* pruritus and rash; *Infrequent:* acne, alopecia, cold sweat, eczema, erythema, increased tendency to bruise, night sweats, photosensitivity reaction, and skin ulcer; *Rare:* dermatitis exfoliative, ecchymosis, and hyperkeratosis.

Vascular Disorders — *Frequent:* hot flush; *Infrequent:* flushing, orthostatic hypotension, and peripheral coldness; *Rare:* hypertensive crisis and phlebitis.

Postmarketing Spontaneous Reports

Adverse events reported since market introduction that were temporally related to duloxetine therapy and not mentioned elsewhere in labeling include: hallucinations, rash, anaphylactic reaction, angioneurotic edema, extrapyramidal disorder, glaucoma, hypersensitivity, hypertensive crisis, Stevens-Johnson Syndrome, erythema multiforme, supraventricular arrhythmia, trismus and urticaria.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Duloxetine is not a controlled substance.

Physical and Psychological Dependence

In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential. In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

While Cymbalta has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Cymbalta (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

There is limited clinical experience with Cymbalta overdose in humans. In premarketing clinical trials, cases of acute ingestions up to 1400 mg, alone or in combination with other drugs, were reported with none being fatal. Postmarketing experience includes reports of overdoses, alone or in combination with other drugs, with duloxetine doses of almost 2000 mg. Fatalities have been very rarely reported, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (mostly with mixed drugs) included serotonin syndrome, somnolence, vomiting, and seizures.

Management of Overdose

There is no specific antidote to Cymbalta, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug.

An adequate airway, oxygenation, and ventilation should be assured, and cardiac rhythm and vital signs should be monitored. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.

Activated charcoal may be useful in limiting absorption of duloxetine from the gastrointestinal tract. Administration of activated charcoal has been shown to decrease AUC and C_{max} by an average of one-third, although some subjects had a limited effect of activated charcoal. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be beneficial.

In managing overdose, the possibility of multiple drug involvement should be considered. A specific caution involves patients who are taking or have recently taken Cymbalta and might ingest excessive quantities of a TCA. In such a case, decreased clearance of the parent tricyclic and/or its active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (*see* PRECAUTIONS, Drug Interactions). 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

Initial Treatment

Major Depressive Disorder

Cymbalta should be administered at a total dose of 40 mg/day (given as 20 mg BID) to 60 mg/day (given either once a day or as 30 mg BID) without regard to meals.

There is no evidence that doses greater than 60 mg/day confer any additional benefits.

Diabetic Peripheral Neuropathic Pain

Cymbalta should be administered at a total dose of 60 mg/day given once a day, without regard to meals.

While a 120 mg/day dose was shown to be safe and effective, there is no evidence that doses higher than 60 mg confer additional significant benefit, and the higher dose is clearly less well tolerated. For patients for whom tolerability is a concern, a lower starting dose may be considered. Since diabetes is frequently complicated by renal disease, a lower starting dose and gradual increase in dose should be considered for patients with renal impairment (*see* CLINICAL PHARMACOLOGY, Special Populations *and* below).

Generalized Anxiety Disorder

For most patients, the recommended starting dose for Cymbalta is 60 mg administered once daily without regard to meals. For some patients, it may be desirable to start at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. While a 120 mg once daily dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer additional benefit. Nevertheless, if a decision is made to increase the dose beyond 60 mg once daily, dose increases should be in increments of 30 mg once daily. The safety of doses above 120 mg once daily has not been adequately evaluated.

Maintenance/Continuation/Extended Treatment

Major Depressive Disorder

It is generally agreed that acute episodes of major depression require several months or longer of sustained pharmacologic therapy. There is insufficient evidence available to answer the

question of how long a patient should continue to be treated with Cymbalta. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Diabetic Peripheral Neuropathic Pain

As the progression of diabetic peripheral neuropathy is highly variable and management of pain is empirical, the effectiveness of Cymbalta must be assessed individually. Efficacy beyond 12 weeks has not been systematically studied in placebo-controlled trials, but a one-year open-label safety study was conducted.

Generalized Anxiety Disorder

Generalized anxiety disorder is generally recognized as a chronic condition. The effectiveness of Cymbalta in long-term use for GAD, that is, for more than 10 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Cymbalta for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

Special Populations

Dosage for Renally Impaired Patients — Cymbalta is not recommended for patients with end-stage renal disease (requiring dialysis) or in severe renal impairment (estimated creatinine clearance <30 mL/min) (*see* CLINICAL PHARMACOLOGY).

Dosage for Hepatically Impaired Patients — It is recommended that Cymbalta not be administered to patients with any hepatic insufficiency (*see* CLINICAL PHARMACOLOGY *and* PRECAUTIONS).

Dosage for Elderly Patients — No dose adjustment is recommended for elderly patients on the basis of age. As with any drug, caution should be exercised in treating the elderly. When individualizing the dosage in elderly patients, extra care should be taken when increasing the dose.

Treatment of Pregnant Women During the Third Trimester — Neonates exposed to SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (*see* PRECAUTIONS). When treating pregnant women with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Cymbalta in the third trimester.

Dosage for Nursing Mothers — Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended. (*see* CLINICAL PHARMACOLOGY).

Discontinuing Cymbalta

Symptoms associated with discontinuation of Cymbalta and other SSRIs and SNRIs have been reported (*see* PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

Switching Patients to or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI (*see* CONTRAINDICATIONS *and* WARNINGS).

HOW SUPPLIED

Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules are available in 20, 30, and 60 mg strengths.

The 20 mg* capsule has an opaque green body and cap, and is imprinted with "20 mg" on the body and "LILLY 3235" on the cap:

NDC 0002-3235-60 (PU3235) — Bottles of 60
NDC 0002-3235-33 (PU3235) — (ID†100) Blisters

The 30 mg* capsule has an opaque white body and opaque blue cap, and is imprinted with "30 mg" on the body and "LILLY 3240" on the cap:

NDC 0002-3240-30 (PU3240) — Bottles of 30
NDC 0002-3240-90 (PU3240) — Bottles of 90
NDC 0002-3240-04 (PU3240) — Bottles of 1000
NDC 0002-3240-33 (PU3240) — (ID†100) Blisters

The 60 mg* capsule has an opaque green body and opaque blue cap, and is imprinted with "60 mg" on the body and "LILLY 3237" on the cap:

NDC 0002-3237-30 (PU3237) — Bottles of 30
NDC 0002-3237-90 (PU3237) — Bottles of 90
NDC 0002-3237-04 (PU3237) — Bottles of 1000
NDC 0002-3237-33 (PU3237) — (ID†100) Blisters

* equivalent to duloxetine base.
† Identi-Dose® (unit dose medication, Lilly).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Literature revised Month dd, yyyy

Eli Lilly and Company
Indianapolis, IN 46285, USA

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Medication Guide

About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant

4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal.*

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies,*** but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your health care provider before your child takes an antidepressant.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child.

After starting an antidepressant, your child should generally see his or her health care provider

- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your health care provider's advice about how often to come back
- More often if problems or questions arise (see Section 3)

You should call your child's health care provider between visits if needed.

3. You Should Watch for Certain Signs If Your Child is Taking an Antidepressant

Contact your child's health care provider ***right away*** if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying

- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her health care provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your health care provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®) has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®), sertraline (Zoloft®), fluvoxamine, and clomipramine (Anafranil®).

Your health care provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your health care provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your health care provider or pharmacist where to find more information.

Prozac® is a registered trademark of Eli Lilly and Company.

Zoloft® is a registered trademark of Pfizer Pharmaceuticals.

Anafranil® is a registered trademark of Mallinckrodt Inc.

This Medication Guide has been approved by the US Food and Drug Administration for all antidepressants.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-427 / S-011

SUMMARY REVIEW

MEMORANDUM

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

DATE: January 30, 2007

FROM: Ni A. Khin, M.D.
Team Leader
Division of Psychiatry Products, HFD-130

TO: File NDA 21-427/SE1-011 (This overview should be filed with the 4-27-2006 submission.)

SUBJECT: Recommendation of Approval Action for Cymbalta (duloxetine) for the Treatment of Generalized Anxiety Disorder (GAD)

1. BACKGROUND

Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI). It is approved in the U.S. since August 3, 2004, for use in the treatment of major depressive disorder (MDD) at doses up to 60 mg per day. It is also approved for the treatment of diabetic peripheral neuropathic pain at doses up to 120 mg/day (HFD-170). Duloxetine is available in 20, 30, 40 and 60 mg strengths. Currently, Lexapro (escitalopram), Paxil (paroxetine) and Effexor XR (venlafaxine) are labeled for the indication of GAD.

The studies supporting this efficacy supplement for generalized anxiety disorder (GAD) claim were conducted under IND 38,838 (originally submitted on 2/6/92 for Compound LY248686 HCl by Lilly). The content and format of this NDA efficacy supplement was discussed in a pre-sNDA meeting which was held on 8/17/05.

The sponsor submitted the above referenced supplemental NDA on April 27, 2006. The application included the efficacy results from three clinical studies: F1J-MC-HMBR, F1J-MC-HMDT, and F1J-MC-HMDU.

This supplemental NDA has been reviewed by Roberta Glass, M.D., Medical Officer, DPP (review dated 1/9/2007), George Kordzakhia Ph.D., from the Office of Biostatistics (review dated 1/9/2007), and Ron Kavanagh, Ph.D. the Office of Clinical Pharmacology (OCP) reviewer (review dated 12/6/2006).

2.0 CHEMISTRY

No new CMC information submitted in this sNDA.

3.0 PHARMACOLOGY/TOXICOLOGY

No pharmacology/toxicology issues submitted in this sNDA.

4.0 CLINICAL PHARMACOLOGY

The clinical pharmacology review covered the results from 7 clinical pharmacology studies (HMEE, HMCE, HMDS, SBCR, SBCS, HMDZ, HMEB) on excertion of duloxetine in human breast milk, PK information on the effect of ethnicity, gender, smoking, CYP1A2 inhibition, and receptor binding, and bioequivalence data for a different capsule shell. I refer to the review by Dr. Kavanagh for detail.

The OCP review provided a few labeling comments to changes in the labeling proposed by the sponsor in this submission. There was no issues identified that would preclude an approval action for this NDA.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of one double-blind, placebo-controlled, fixed dose study (study F1J-MC-HMBR) and two placebo-controlled flexible dose studies (F1J-MC-HMDT and F1J-MC-HMDU) to evaluate the efficacy and safety of duloxetine in the treatment of GAD. The study HMDU included venlafaxine as the active-control arm.

The sponsor indicated that results of these clinical studies demonstrated that duloxetine was superior to placebo on the primary efficacy variable. I would briefly describe the results of each of these studies pertinent to efficacy claim in the following subsection.

5.1.2 Summary of Studies Pertinent to Efficacy Claim

Study F1J-MC-HMBR

This was a multicenter, randomized, double-blind, placebo-controlled study comparing two fixed doses of duloxetine (60 mg, 120 mg) vs. placebo. This study enrolled adult patients with a DSM-IV diagnosis of GAD. After the screening (study period I), eligible subjects entered one week of single-blind placebo lead-in (study period II). The subjects were then randomized to receive duloxetine (60 or 120 mg given as oral capsules once daily in the morning without regard to food) or placebo for 9 weeks of acute treatment (study period III). All subjects in the duloxetine group received 30 mg of duloxetine for study week 1 during this period. Duloxetine dose was then tapered for 2 weeks (study period IV).

The study was conducted at 41 centers in the U.S and outside the U.S. (Finland, France, Germany, South Africa, Spain and Sweden). The number of subjects randomized (total N=513) in this study for duloxetine 60mg, 120 mg, and placebo were 168, 170 and 175, respectively. The ITT sample (N=507) consisted of 173 subjects in placebo group, 165 subjects in duloxetine 60 mg group, and 169 subjects in duloxetine 120 mg group. A total of 130 subjects (74.3%) in placebo group, 135 subjects (80.4%) in duloxetine 60 mg group, and 124 subjects (72.9%) in duloxetine 120 mg group completed the study. 124 subjects discontinued. The reasons for discontinuation from the study

included adverse events (more numbers in duloxetine treatment groups), lack of efficacy (more dropouts due to this reason in placebo group) and subject decision.

The subjects enrolled were mostly Caucasian (98%), mean age was approximately 44 yrs, and had approximately 2/3 female subjects. There seemed to be no significant differences in demographic characteristics among the treatment groups.

The primary efficacy variable was the Hamilton Anxiety Rating Scale (HAMA) which was assessed at baseline and at each weekly study visit during the 9 week acute therapy phase. Sheehan Disability Scale (SDS) was the key secondary variables identified in the protocol. The primary end point was the change from baseline of the HAMA total score at the last post-randomization treatment week for the LOCF dataset. The ANCOVA was the statistical model employed, with terms for treatment, investigator site, and baseline scores as the covariates. For multiple comparisons for 3 doses of duloxetine vs. placebo, the statistical testing was carried out with least-squares means (LS) adjustment. Dr. Kordzakhia confirmed the efficacy results. Sensitivity analysis (MMRM) was also done.

Efficacy Results on HAMA Total Scores in Study HMBR (LOCF):

Treatment Group (number of subjects)	Mean Baseline HAMA Total Scores (SD)	Mean total HAMA scores at Endpoint (SD)	Placebo-adjusted LS mean change (SE)	P-values (vs. placebo)
Duloxetine 60 mg (N=165)	25.05 (7.18)	12.32 (8.79)	-12.8(0.68)	<0.001
Duloxetine 120 mg (N=169)	25.13 (7.24)	12.74 (9.55)	-12.5(0.67)	<0.001
Placebo (N=173)	25.82 (7.66)	17.19 (9.96)	-8.38(0.67)	-

Comment: Both Drs. Glass and Kordzakhia considered this a positive study for duloxetine, and I agree with them.

Study F1J-MC-HMDT

This was a multicenter, randomized, double-blind, placebo-controlled, flexible dose (60-120 mg) study. This study enrolled adult patients with a DSM-IV diagnosis of GAD. Following the screening phase (study period I), eligible subjects entered one week of single-blind placebo lead-in (study period II). Then, the subjects were randomized to receive duloxetine (60 to 120 mg given as oral capsules once daily in the morning without regard to food) or placebo for 10 weeks of acute treatment (study period III). Patients randomized to the duloxetine treatment group were required to tolerate a minimum of duloxetine 60 mg qd (achieved by week 5) and titrated to a maximum of 120 mg duloxetine if needed for efficacy and if tolerated. The study was concluded with a two week drug tapering phase.

The study was conducted in 28 centers in the U.S. The number of subjects (total N=327) randomized in this study for duloxetine 60-120 mg group, and placebo were 168, and 159, respectively. The ITT sample (N=319) consisted of 158 placebo treated subjects and 161 duloxetine treated subjects. A total of 202 subjects completed the study: 109 subjects (68.6%) in placebo group; 93 subjects (55.4%) in duloxetine 60-120 mg group. Out of 125 subjects discontinued, 75 subjects (44.6%) were in the duloxetine group and 50 subjects (31.4%) were in the placebo group. The reasons for discontinuation from the study included adverse events [statistically

significant between in duloxetine treatment and placebo groups; 34 (20.2%) vs. 13 (8.2%)], lack of efficacy, subject decision, lost to follow up, protocol violations and physician decision.

The subjects enrolled were mostly Caucasians (approximately 79%), mean age of 41 yrs age, and had approximately 62% female subjects. There seemed to be no significant differences in demographic characteristics among the treatment groups.

The primary efficacy variable was the Hamilton Anxiety Rating Scale (HAMA). Sheehan Disability Scale (SDS) was the key secondary variable identified in the protocol. The primary end point was the change from baseline of the HAMA total score to the end of the acute therapy phase for the LOCF dataset. The ANCOVA was the statistical model employed, with terms for treatment, investigator site, and baseline scores as the covariates. The statistical testing was carried out with least-squares means (LS) adjustment. Dr. Kordzakhia confirmed the efficacy results. Sensitivity analysis (MMRM) was also done.

Efficacy Results on HAMA Total Scores in Study HMDT (LOCF):

Treatment Group (number of subjects)	Mean Baseline HAMA Total Scores (SD)	Mean Total HAMA score at Endpoint (SD)	LS mean change	P-values (vs. placebo)
Duloxetine 60-120 mg (N=161)	22.54 (7.44)	14.27 (9.58)	-8.12(0.7)	0.023
Placebo (N=158)	23.49 (7.91)	17 (10.24)	-5.89(0.7)	-

Comment: Both Drs. Glass and Kordzakhia considered this a positive study for duloxetine, and I agree with them.

Study F1J-MC-HMDU

This was a multicenter, randomized, double-blind, placebo-and active-controlled, flexible dose (duloxetine 60-120 mg) study. Venlafaxine 75-225 mg was used as the active comparator. This study enrolled adult patients with a DSM-IV diagnosis of GAD. Following the screening phase, eligible subjects entered one week of single-blind placebo lead-in. Then, the subjects were randomized to receive duloxetine (starting dose at 30 mg qd for 1 week; titrated to flexible doses of 60 to 120 mg given as oral capsules once daily in the morning without regard to food), venlafaxine (starting dose at 37.5 mg qd for 1 week; titrated to 75 to 225 mg) or placebo for 10 weeks of acute treatment. The study was concluded with a two week drug tapering phase.

The study was conducted in 30 centers in the U.S. The number of subjects (total N=487) randomized for duloxetine 60-120 mg group, venlafaxine 75-22 mg, and placebo were 162, 164 and 161, respectively. The ITT sample was 466 subjects in which 149 subjects in duloxetine 60-120 mg group, 159 subjects in venlafaxine 75-225 mg, and 158 subjects in placebo group. A total of 290 subjects completed the study: 100 subjects (62.1%) in placebo group; 88 subjects (54.3%) in duloxetine 60-120 mg group; and 102 subjects (62.2%). Out of 197 subjects discontinued, 74 subjects were in the duloxetine group; 61 subjects were in the placebo group and 62 subjects were in the venlafaxine group. The reasons for discontinuation from the study included adverse events (more numbers in duloxetine treatment and venlafaxine groups); lost to follow up, and subject decision.

The subjects enrolled were mostly Caucasians (approximately 70%), mean age of 40 yrs, and had approximately 62% female subjects. There seemed to be no significant differences in demographic characteristics among the treatment groups.

The primary efficacy variable was the Hamilton Anxiety Rating Scale (HAMA). Sheehan Disability Scale (SDS) was the key secondary variable identified in the protocol. The primary end point was the change from baseline of the HAMA total score to the end of the acute therapy phase for the LOCF dataset. The ANCOVA was the statistical model employed, with terms for treatment, investigator site, and baseline scores as the covariates. The statistical testing was carried out with least-squares means (LS) adjustment. Dr. Kordzakhia confirmed the efficacy results. Sensitivity analysis (MMRM) was also done.

Efficacy Results on HAMA Total Scores in Study HMDU (LOCF):

Treatment Group (number of subjects)	Mean Baseline HAMA Total Scores (SD)	Mean Total HAMA score at Endpoint (SD)	LS mean change	P-values (vs. placebo)
Duloxetine 60-120 mg (N=149)	25.77 (5.66)	13.95 (8.55)	-11.8 (0.69)	0.007
Placebo (N=158)	24.98 (5.82)	16.06 (9.29)	-9.19 (0.67)	-
Venlafaxine 75-225 mg (N=159)	24.92 (5.48)	12.90 (8.95)	-12.4 (0.67)	<0.001

Comment: Both Drs. Glass and Kordzakhia considered this a positive study for duloxetine, and I agree with them.

5.1.3 Comments on Other Important Clinical Issues

Secondary Efficacy Variable

Sheehan Disability Scale (SDS) Global Functional Impairment score was the key secondary variable identified in the above referenced protocols. The key secondary objective was to evaluate the efficacy of duloxetine (120 mg/day for study HMBR; flexible dose 60 to 120 mg for studies HMDT and HMDU) compared with placebo on the SDS score. The sponsor used the sequential testing procedure with pre-specified sequence of testing. Based on the ANCOVA model, all duloxetine treatment arms showed results statistically superior to placebo on this secondary measure in all three studies. For the fixed dose study HMBR, the 120 mg duloxetine group did not show any different effect compared to the 60 mg duloxetine group (LS mean change of SDS scores -7.76 in duloxetine 60 mg vs -7.04 in duloxetine 120 mg, compared to -3.83 in the placebo). Dr. Kordzakhia confirmed the sponsor's analysis results.

Dose Response Relationship

The sponsor intends to have a claim that ".. [redacted] " Both Drs. Glass and Kordzakhia commented this claim is unacceptable because available data indicated there was no additional benefit to the dose of duloxetine 120 mg over duloxetine 60 mg in the GAD placebo-controlled studies. I agree with them.

b(4)

Subgroup Analyses

The sponsor performed exploratory subgroup analyses in order to detect subgroup interactions on the basis of gender (M,F), age (<55 yrs, ≥55 yrs) and race (Caucasian, non-Caucasian). Dr. Kordzakhia confirmed the sponsor's analysis. Analysis by race was not performed for study HMBR since there were only two non-Caucasian patients in the placebo group and one non-Caucasion in the duloxetine 120 mg group. The treatment effect appeared to be numerically in favor of duloxetine when compared to placebo among all subgroups.

In a clinical setting, the disorder diagnosed somewhat more frequently in woman than in man. The sex ratio is approximately two-thirds female in the epidemiological studies. As noted by Dr. Kordzakhia in his review, the study subject population for HMDU consisted of approximately two-thirds female, but there did not seem to show numerical difference between the duloxetine and the placebo groups in change from baseline to endpoint in the HAMA total scores.

In addition, exploratory subgroup analyses were conducted on the basis of anxiety severity at baseline and prior use of benzodiazepines. Subjects with total HAMA scores less than 22 at baseline showed numerically a smaller treatment response, as measured by mean change in HAMA total score from baseline to endpoint visit, compared to subjects with total HAMA score equal or greater than 22 at baseline. No difference in treatment effect was seen when data was analyzed in groups with or without prior benzodiazepine use.

Dr. Kordzakhia also performed an exploratory analysis on treatment comparisons at each visit to see whether treatment effects were consistent across the visits. Without adjustment for multiplicity, the nominal p-values indicated that the treatment effect of duloxetine might be seen by Visit 5 (week 2) based on data from study HMBR and HMDT; and by Visit 3 (week 1) based on study HMDU.

Duration of Treatment

The studies were conducted for short-term use of Cymbalta in the treatment of GAD. There is no data pertinent to the long-term efficacy of Cymbalta in GAD in this submission. Since the course of this disorder is chronic, it would be good to have data from a longer term study. Based on the safety data provided in this submission, there is an ongoing relapse prevention study for GAD (study HMDV). In this case, we may not need to ask the sponsor to conduct a long-term study as part of the phase 4 commitment.

5.1.4 Conclusions Regarding Efficacy Data

In summary, the efficacy analyses of all 3 studies supported the efficacy claim of duloxetine in the treatment of GAD in both dose groups tested.

5.2 Safety Data

5.2.1 Satety Database

As stated by Dr. Glass in her review, the safety review of this sNDA is limited to the sponsor's combined database consisting of 3 GAD trials with the data cut-off date of 12/19/2005 for the original GAD submission and 04/26/2006 for the safety update, respectively. The sponsor also

provided safety updates including SAE data from an ongoing relapse prevention study for GAD (study HMDV) as well as study reports of other open label extension studies (F1J-XM-HMED; F1J-US-HMDR).

A total of 668 subjects were treated with duloxetine and 495 subjects received placebo. Based on the sponsor's calculation, there is an exposure of 95.05 patient years in this safety database. 509 patients had an exposure ≥30 days and 449 subjects had an exposure of ≥60 days.

Out of the 668 subjects treated with duloxetine, 104 subjects (11%) discontinued at post-baseline due to adverse events, compared to 21 subjects (4%) from the placebo group.

There was one death reported. A 50 yr old female with past medical history of intermittent headaches (treated with aspirin) and herniated disks (treated with ibuprofen) died from a cerebral haemorrhage after 102 days of open label treatment of duloxetine 60-120 mg qd in ongoing relapse prevention study HMDV.

Serious adverse events were available from these double-blind GAD trials. 7 subjects who experienced SAE were the duloxetine treated patients. 4 SAEs reports in the safety update included 2 subjects who received duloxetine in study HMDV while the blind has not been broken on 2 subjects in study HDMW. I refer to Table 7.1.2 in Dr. Glass's clinical review for detail events.

5.2.2 Safety Findings and Issues of Particular Interest

5.2.2.1 Common and Drug-Related Adverse Events

The approach that we have used to identify the adverse event profile is by identifying the adverse events for the drug as common (used 5% as the cut-off) and considered as drug related (a risk for drug that is twice or more the placebo risk). These AEs included nausea, fatigue, dry mouth, somnolence, constipation, insomnia, decreased appetite, hyperhidrosis, decreased libido, vomiting, delayed ejeculation and erectile dysfunction.

These observed AEs seem consistent with the previously observed safety profile described in the current duloxetine labeling.

5.2.2.2 Vital Signs and ECG Data

A statistically significant mean increase from baseline in heart rate was observed between duloxetine (N=447) and placebo (N=343) (+2.51 vs. -1.27; $p<0.001$). Similarly, mean changes from baseline to final on-therapy assessment were statistically significantly different between duloxetine and placebo for systolic and diastolic BP, and a dose-dependent orthostatic BP change. These findings appear to be consistent with the current labeling.

Based on the ECG data obtained in GAD studies, there is a modest increase in QTcB between duloxetine and placebo (+4.54 vs. -1.67; $p<0.001$). We may consider including a sentence about the QTc data in GAD population in the labeling.

While I acknowledge Dr. Glass' recommendation that this QTc finding in the GAD population be reviewed by the Agency QTc committee to determine if any future studies are needed to clarify these findings, I do not feel it is necessary to consult with the QT team because of the following reasons.

- QTc prolongation was not observed in the thorough QT study F1J-LC-HMCG(d) (ref: DFS reviews under the duloxetine IND [redacted] b(4)
  - It was noted in the clinical review (dated 1/28/05) of Dr. George Benson, DRUP-MO, that the study report was reviewed by the Division of Reproductive and Urologic Products and also by the OCP. It was noted in Dr. Benson's review that the Clinical Pharmacology reviewer believes that "the thorough QT study demonstrates that duloxetine does not prolong the QT interval." Briefly, the study HMGC (N=117) was a placebo-and moxifloxacin-controlled study of effects of supratherapeutic doses of duloxetine (maximum dose of 200 mg bid) on the QT interval. The primary endpoint was the change from baseline in QTc interval for duloxetine 200 mg compared to placebo at 2, 6, 10 and 12 hours post-dosing using the Fredericia correction method. Moxifloxacin significantly prolonged the QTC interval at all time points, particularly, change from baseline of QTcF for moxifloxacin vs. placebo was 9 msec vs. 2.3 msec at 2 hours, and 4.3 msec vs. 1.6 msec at 6 hours. At all time points measured, the LS mean change in QTcF decreased from baseline with duloxetine 200 mg bid relative to placebo. At 6 hours (tmax), LS mean QTcF decreased by 4.2 ms for duloxetine versus an increase of 2.1 msec for placebo ($p<0.0001$).
- No significant QT finding was observed in the clinical trial database for other indications (MDD, DNP).
- For the ECG data collected in the GAD population, there was no reference to the timing of the ECG in relation to dosing or food intake. Unlike the QT study, the exclusionary criteria in the GAD studies did not mention QTcB>450 ms or ECG reading considered outside the normal limit by the investigator as one of the exclusionary criteria.

5.2.2.3 Laboratory Tests

There were statistically significant difference in mean changes from baseline to endpoint in abnormal laboratory parameters including alkaline phosphatase, AST, cholesterol and uric acid between duloxetine and placebo. In regards to a CPK value of above 5000 U/L, there were three patients in duloxetine treatment group compared to one patient in the placebo group. Two patients who had withdrawal due to elevated CPK at week 4 and 8. Based on the narratives provided, it seems to me Dr. Glass is unable to reach conclusion on the clinical significance of elevated CPK results in these GAD subjects. Given the fact that rhabdomyolysis has been included as one of the issues of continued sponsor vigilance, this finding of elevated CPK is not unexpected at this time.

Dr. Marc Stone, a MO from DPP safety group, is currently reviewing post-marketing safety reports on hepatic cases and data mining report from the sponsor on epidemiologic studies of duloxetine and hepatic injury. We will follow up if any labeling change on this topic is warranted.

5.2.2.4 Tapering Emergent Adverse Events

During the tapering phase, the AE occurring with a higher frequency in the duloxetine group compared to placbo group that was statistically significant include dizziness, headaches, and insomnia.

5.2.2.5 Post-Marketing Safety Reports on Hallucinations and Serious skin reactions

The Office of Surveillance and Epidemiology (OSE) has reviewed the post marketing reports on hallucinations and serious skin reactions such as EM, SJS and TEN and recommended labeling changes. I note Dr. Glass agreement with the OSE's recommendation that serious skin reaction be added to the Precautions section of the labeling. The sponsor has submitted a CBE labeling supplement in which hallucinations was included as the post-marketing AE.

5.2.3 Conclusion Regarding Safety Data

Overall, this submission revealed safety findings of duloxetine in GAD population consistent with the previously observed safety profile of duloxetine as described in current labeling. No specific safety concerns raised by the clinical reviewer except for a modest increase in QTc in the GAD clinical trial ECG data. We should further discuss any post-marketing safety issues with this drug need follow-up as duloxetine is the first drug in DPP which will be used in the pilot study to assess the post marketing safety evaluation of new molecular entities.

6.0 WORLD LITERATURE

The sponsor provided a brief literature review. Based on Dr. Glass' review, the submitted materials did not provide additional safety information to the sponsor's database.

7.0 FOREIGN REGULATORY ACTION

Based on the sponsor's submission list, as of February 2006, this drug has been approved in 35 countries for MDD, 2 countries for diabetes neuropathic pain, and in 14 countries for stress urinary incontinence.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 3 study sites. DSI recommended that data from these inspected sites appear acceptable in support of this NDA. Inspectional findings did not seem to raise any major concern on integrity of study data.

10.0 LABELING AND ACTION LETTER

10.1 Final Draft of Labeling Attached to the Action Package

The sponsor's proposed language in this GAD submission has been modified. All these labeling changes will be negotiated with the sponsor.

We plan to incorporate part of the changes proposed in three labeling supplements (SLR 006, 009 and 013). Both Dr. Kavanagh and Glass reviews included labeling comments on these 3 CBEs. Dr. Glass also reviewed the OSE evaluation of PM reports on hallucinations and serious skin reactions and made labeling recommendations. Based on Dr. Lourdes Villalba's review on orthostasis, syncope, BP, hyponatremia/SIADH, and glucose data, labeling changes would also be made. We already have an agreed upon language with the sponsor on syncope, orthostasis, effect on BP and hyponatremia/SIADH.

A copy of final labeling should be included in the action letter.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to support that duloxetine is effective and reasonably safe in the treatment of GAD. I concur with Dr. Glass' recommendation that we consider approval of this NDA supplement provided that we reach an agreement with the sponsor regarding the language in the labeling.

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/s/

Ni Aye Khin
1/30/2007 07:33:34 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-427 / S-011

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 21-427
Submission Number	S 011
Submission Code	SE-1
Letter Date	4/27/06
Stamp Date	4/27/06
PDUFA Goal Date	2/27/07
Reviewer Name	Roberta Glass, M.D.
Review Completion Date	1/9/07
Established Name	Duloxetine
(Proposed) Trade Name	Cymbalta
Therapeutic Class	Serotonin and norepinephrine re-uptake inhibitor
Applicant	Eli Lilly & Co.
Priority Designation	S
Formulation	Capsule
Dosing Regimen	20 mg, 30 mg, 40 mg & 60 mg qd (or bid)
Indication	Generalized Anxiety Disorder
Intended Population	Adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended that duloxetine be approved for the indication of GAD with a maximum dose set at duloxetine 60 mg qd. The labeling could state that duloxetine 120 mg daily did not offer additional beneficial treatment effects over 60 mg daily.

It is also recommended that the issue of QTc prolongation seen in the GAD population be reviewed by the FDA QTc committee to determine if any further studies are needed to clarify these findings.

Please see the labeling section for further recommendations.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Duloxetine is the first drug to be assessed in the pilot study assessing the post marketing evaluation of new molecular entities. This will provide an opportunity to assess the safety profile since the marketing of duloxetine in 2004; there have been multiple post-marketing reports of concern including: liver injury, hyponatremia and SAIDH, allergic reactions (including anaphylactic shock) and life-threatening skin reactions [such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)]. It may also be important to assess if the liver injury risk listed as a "Precaution" rather than a "Warning" is sufficient, as there have been many liver injury cases seen post market in patients who drink alcohol while taking duloxetine.

1.2.2 Required Phase 4 Commitments

Given that GAD is generally a chronic condition, the sponsor needs to explore the effects of duloxetine with long term use.

1.2.3 Other Phase 4 Requests

The geriatric population was underrepresented in the GAD safety and efficacy data base; it is recommended that the sponsor further study this group with a design powered to assess efficacy and appropriately monitor safety for this population. If it appears that duloxetine is used in children with GAD, it would be prudent for the sponsor to formally study efficacy and safety in this population.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Duloxetine is a selective serotonin and norepinephrine uptake inhibitor (SSRNI), and has been marketed since 2004. It is currently indicated for the treatment of patients with major depressive disorder and diabetic peripheral neuropathy.

This application for duloxetine proposes to support labeling changes to include the indication of generalized anxiety disorder (GAD). There were three studies reviewed to determine the safety and efficacy of duloxetine to treat GAD: **HMBR**, **HMDT**, and **HMDU**.

- HMBR-a placebo controlled, 9 week, adult, fixed dose (60, 120 mg or pbo) study.
- HMDT- a flexible dose (60-120 mg, or pbo), placebo controlled, 10 week study.
- HMDU- a flexible dose placebo- and active-controlled, 10 week study (duloxetine: 60 to 120 mg , venlafaxine ER: 75-225 mg or pbo).

There were 668 patients diagnosed with GAD exposed to duloxetine in the primary placebo controlled integrated safety database. The sponsor calculated that in this safety data base there was an exposure of 95.09 patient years. 509 (76%) patients had an exposure of $\geq$ 30 days, and 449 (67%) patients had an exposure of $\geq$ 60 days.

The majority of the patients in these studies were Caucasian females in their early to mid forties (range of 18 to 83). There were few non-Caucasians represented in this patient population.

1.3.2 Efficacy

For the primary efficacy variable, the Hamilton Anxiety Rating Scale (HAMA), the sponsor demonstrates a statistically significant difference in change from baseline when comparing duloxetine treatment with placebo using the ANCOVA model for all three placebo-controlled studies. It is noted that both duloxetine 60 mg qd and duloxetine 120 mg qd were equally effective compared to placebo.

For the key secondary variable, the Sheehan Disability Scale Global Functional Impairment score (**SDS**), the sponsor demonstrates a statistically significant difference in change from baseline to endpoint for the duloxetine treatment group compared to placebo for all three controlled studies for GAD.

In special subgroup analyses, it appeared that duloxetine may be less effective in patients with less severe symptoms of anxiety (according to scores in the primary efficacy variable) compared to patients with greater severity of symptoms.

Also of note is there were very few non-Caucasians enrolled in any of the controlled studies.

1.3.3 Safety

The safety data base for this review was limited to the placebo-controlled studies for the indication of generalized anxiety disorder (GAD). Overall, the safety profile in this supplement was consistent with current labeling. Many of the safety concerns that arose with this NDA data base have been discussed in the marketed labeling for duloxetine.

It was surprising to observe a QTc prolongation in this GAD population. When the sponsor "corrected" for baseline discrepancies, there no longer appeared to be a QTc prolongation comparing duloxetine with placebo. Also of consideration is that the sponsor conducted a clinical pharmacology study specifically addressing the issue of QTc prolongation (with the positive control moxifloxicin); the results of this study did not support a QTc prolongation with duloxetine use compared to placebo.

Another safety observation in this data base included several cases of elevated creatine phosphokinase (CPK). The sponsor offered the explanation of rhabdomyolysis, citing the following other associated symptoms observed with greater frequency in the duloxetine groups compared to placebo groups: asthenia, muscle tightness, and increased alanine transaminase (ALT). It would be helpful to get more information such as body temperature, need for hospitalization after discharge and the time it took for the CPK to normalize to determine the safety concern regarding this observation.

Other findings included elevated heart rate, diastolic and systolic blood pressure. Also noted in this safety data base were statistically significant changes from baseline comparing duloxetine with placebo for the following laboratory values: alkaline phosphatase, AST, bicarbonate, chloride, cholesterol, phosphorus, urea nitrogen, uric acid, band, lymphocytes, and UA-specific.

1.3.4 Dosing Regimen and Administration

Duloxetine (Cymbalta ™) is currently labeled for the indications of major depressive disorder and diabetic peripheral neuropathic pain.

For **major depressive disorder**, the recommended dose is 40 mg/day (given as 20 mg bid) to 60 mg/day (given as 60 mg qd or 30 mg bid) without regard to meals. It has also been noted that doses > 60 mg/day have not shown any additional benefit.

For **diabetic peripheral neuropathic pain**, the recommended dose is 60 mg/day, without regard to meals. Again, there was no evidence that doses > 60 mg/day have shown any additional benefit.

For **special populations**, the labeling states that duloxetine is not recommended for patients with end-stage renal disease, severe renal impairment, or hepatic insufficiency.

In the proposed labeling, the sponsor adds the indication of **generalized anxiety disorder**. This proposed labeling states that the recommended starting dose for duloxetine is 60 mg without regard to meals. They go on to specify that some patients may need to be titrated to this dose by starting at 30 mg daily for 1 week, and some patients may benefit by raising the dose up to duloxetine 120 mg daily (titrating by increments of 30 mg once daily).

1.3.5 Drug-Drug Interactions

As stated in the marketed labeling, duloxetine has the potential to inhibit CYP1A2, thus increasing the concentration of drugs such as fluvoxamine and quinolone antibiotics. Because of duloxetine's inhibition of CYP2D6, concomitant use may result in higher concentration of drugs such as paroxetine, fluoxetine, quinidine, tricyclic antidepressnats (e.g.nortriptyline, amitryptline, and imiprmaine), phenothiazines and Type 1C antiarrhythmics (e.g. propafenone, flecainide).

1.3.6 Special Populations

The marketed labeling states that duloxetine is not recommended for patients with end-stage renal disease, severe renal impairment, or hepatic insufficiency. Dosages do not need to be adjusted for elderly patient; however, care should be taken when increasing the dose. Class labeling for SSRIs or SNRIs includes that neonates exposed in the late third trimester have developed complications requiring hospitalization, respiratory support, and tube feeding. In the current labeling, administration to nursing mothers is not recommended as no data is available (please see proposed labeling, below, for updated information). It is noted that duloxetine has a pregnancy category C due to adverse effects seen on embryo/fetal and postnatal development in laboratory animals.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Duloxetine is a selective serotonin and norepinephrine uptake inhibitor (SSRNI), and has been marketed in the United States since 2004. It is currently indicated for the treatment of patients with major depressive disorder and diabetic peripheral neuropathy. [redacted] b(4)

This submission includes three placebo controlled studies to support labeling claims for the use of duloxetine to treat generalized anxiety disorder. The current labeling recommends doses up to duloxetine 120 mg; however, the data does not support evidence of an increased benefit of doses > duloxetine 60 mg daily. The finding of no additional benefit of doses above duloxetine 60 mg daily is consistent with the findings for both major depressive disorder and diabetic peripheral neuropathy.

2.2 Currently Available Treatment for Indications

The medications considered most effective to treat anxiety disorders are benzodiazepines, mainly because of their rapid onset of 30 to 90 minutes [e.g. alprazolam (Xanax ™), chlordiazepoxide (Librium™), clonazepam (Klonipin™), diazepam (Valium™), and lorzepam (Ativan™)]. There are many potential complications with treatment using benzodiazepines including addiction potential, drowsiness, reduced muscle coordination and balance; memory difficulties have also been a serious adverse effect. A non-benzodiazepine anxiolytic is buspirone (BuSpar ™) which is not thought to be as effective due to a longer onset of action than benzodiazepines; however, it does not share the potential abuse/addictive risk commonly associated with benzodiazepine use.

There are two drugs originally categorized as "anti-depressants" which are currently labeled for the indication of generalized anxiety disorder [Lexapro™ (escitalopram) and Paxil™ (paroxetine)]. Many other "anti-depressants" are prescribed off-label for patients suffering with generalized anxiety disorders.

2.3 Availability of Proposed Active Ingredient in the United States

Duloxetine (Cymbalta™) has been marketed in the United States since 2004.

2.4 Important Issues With Pharmacologically Related Products

Duloxetine shares class label warnings with the SSRIs, SNRIs, and general warnings of anti-depressants. (please refer to the current labeling for more details).

2.5 Presubmission Regulatory Activity

Duloxetine was first marketed for the indication of major depressive disorder in 2004, and has since been labeled for the use in patients with diabetic peripheral neuropathic pain.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No new information was submitted in this NDA.

3.2 Animal Pharmacology/Toxicology

No animal studies were submitted with this NDA.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of data in this review are the clinical trials submitted by the sponsor (4/27/06; 6/7/06; Safety Update: 8/22/06). Sponsor labeling supplements are also considered to update duloxetine labeling (10/4/06; 9/14/06; 8/22/06; 7/17/06; 7/6/06;5/5/06; 1/23/06; 8/9/05).

Also considered were the following FDA reviews and documents:

Statistical Review and Evaluation by Yeh-Fong Chen, Ph.D. and George Kordzakhia, Ph.D. (draft).

OSE Post-Marketing Safety Review: Duloxetine Serious Skin and Allergic Reactions by Oluchi Elekwachi, PharmD, MPH (11/13/06).

Clinical Investigations Summary: Duloxetine by Sherbet Samuels, R.N., M.P.H. (11/9/06).

Pharmacology Review of labeling Supplement for excretion of duloxetine into breast milk by Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D. (1/23/06).

OND Safety Review: duloxetine-orthostatic hypotension and syncope by Lordes Villalba, M.D. (8/28/06).

OND Safety Review: duloxetine-hyponatremia and SIADH by Lordes Villalba, M.D. (8/28/06).

DDRE Postmarketing Safety Review: Hallucinations with duloxetine use by Sonny Saini, Pharm.D. (8/2/06).

AERS spontaneous reports of hepatotoxdicity with duloxetine submitted by sponsor in Feb. 2006 by Marc Stone, M.D. (6/7/06).

4.2 Tables of Clinical Studies

The three placebo controlled studies used to support the claim of GAD are HMBR, HMDT, and HMDU. Please refer to the sponsor's table (Table 4.2) below for a summary of these studies.

Table 4.2 Sponsor's table of the placebo-controlled studies for Generalized Anxiety Disorder in adults

Study and Title	Design	Number of Randomized Patients	Diagnosis	Duration of Treatment (active treatment)	Test Product / Dosage / Regimen / Route of Administration
F1J-MC-HMBR Duloxetine Hydrochloride Once Daily Compared with Placebo in the Treatment of Generalized Anxiety Disorder	Multi-center, double-blind, placebo-controlled Phase 3 study with a single-blind placebo lead-in.	N=513 M=165; F=348	GAD	9 weeks	Duloxetine 60 mg PO QD 120 mg PO QD Placebo
F1J-MC-HMDT Duloxetine Hydrochloride Once Daily Compared with Placebo in the Treatment of Generalized Anxiety Disorder.	Multi-center, randomly assigned, double-blind, placebo-controlled, Phase 3 study with a single-blind placebo lead-in.	N=327 M=125; F=202	GAD	10 weeks	Duloxetine 60 to 120mg PO QD Placebo
F1J-MC-HMDU A Comparison of Duloxetine Hydrochloride, Venlafaxine Extended Release, and Placebo in the Treatment of Generalized Anxiety Disorder	Multi-center, randomized, double-blind, placebo- and active-controlled Phase 3 study	N=487 M=182; F=305	GAD	10 weeks	Duloxetine 60 to 120 mg PO QD Venlafaxine 75 to 225 mg PO QD Placebo

Abbreviations: F = female, GAD = generalized anxiety disorder, M = male, N = number, PO = orally, QD = once daily.

4.3 Review Strategy

For the purpose of evaluating the data to support the sponsor's claim of efficacy of duloxetine for the treatment of generalized anxiety disorder, there were three placebo controlled studies reviewed (please refer to section 4.2. above).

4.4 Data Quality and Integrity

A DSI report (Samuels: 11/9/06) stated that the three clinical investigators/sites inspected were acceptable to be considered for efficacy. There were instances of inadequate record keeping noted (Dr. Robert Horne, M.D./113), but ultimately the data from this site was considered acceptable. [Please refer to Clinical Investigations Summary: Duloxetine by Sherbet Samuels, R.N., M.P.H. (11/9/06)].

4.5 Compliance with Good Clinical Practices

The DSI report investigating three study sites did not find violations that would compromise the efficacy findings of the pivotal studies.

4.6 Financial Disclosures

The sponsor submitted separate certifications of Financial Interests and Arrangements of Clinical Investigators (all signed: 3/16/2006) for studies HMBR, HMDT, and HMDU. The Medical Director at Eli Lilly and Company signed the Form 3454 testifying that, to his knowledge, there were no financial arrangements made with investigators that could affect the outcome of the studies as defined in 21 CFR 54.2 (a), and that no listed investigator (attached to the form) was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f) for the listing of investigators attached to each 3454.

However, there were four separate forms of 3454 itemizing the following investigators that had received significant payments from the sponsor. The sponsor states that in an analysis of combining the following investigators, there was no potential effect on the outcome of the study HMDT; the —— investigators (———————————) enrolled a total of —— patients (—— % of the total n= ——). The investigators who received substantial monetary payments (i.e. accrued equity above suggested limits) from the sponsor are listed as follows: b(6)

1. ——————————— of Site ——(Study ———) received Lily payments of **$ 35,250.00** from April 2004 to December 2005. The sponsor calculates that this site enrolled —— patients (———————). The sponsor states that the statistical analysis completed concludes that ——————— data would have no potential impact on the study outcome. b(6)

2. ——————————— of Site ——(Study ———) received Lily payments of **$88,550.00** from April 2004 to December 2005. The sponsor calculates that this site enrolled —— patients (———————). The sponsor states that the statistical analysis completed concludes that ——— data would have no potential impact on the study outcome. b(6)

3. ——————————— of Sites ——(Study ———and ————) received Lily payments of **$230,000.00** prior to April 2004 and **$110,400.00** from April 2004 to December 2005. The sponsor calculates that this site enrolled patients (————————). For Study —— the sponsor calculated that this site enrolled patients (————————). The sponsor states that the statistical analysis completed concluded that this site's data would have no potential impact on the results of either study. b(6)

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Duloxetine has an elimination half-life of 12 hours (range 8-17 hrs.). Pharmacokinetics are dose proportional over the therapeutic range. Steady state concentrations are achieved after 3 days of dosing. Elimination of duloxetine is mainly hepatic involving two P450 isozymes, CYP2D6 and CYP1A2. Cmax is achieved at 6 hours post dose. Food does not affect the Cmax, but does delay the time to reach peak concentration from 6 to 10 hours. Evening doses appear to have a 3 hour delay in absorption and a one-third increase in clearance of duloxetine compared to morning dosing. Duloxetine is excreted primarily through urine as metabolites (70%), and excreted in feces (20%).

5.2 Pharmacodynamics

Animal studies have shown that duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to add to the pharmacologic activity of duloxetine.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication for this NDA is **Generalized Anxiety Disorder (GAD)** in the adult population. As correctly stated in the sponsor's labeling, generalized anxiety disorder is defined by the DSM-IV as excessive anxiety and worry, present more days than not, for at least 6 months. The excessive anxiety and worry must be difficult to control and must cause significant distress or impairment in normal functioning. It must be associated with at least 3 of the following 6 symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and/or sleep disturbance.

6.1.1 Methods

For the purposes of determining the efficacy of duloxetine for the treatment of GAD, the following three studies were reviewed (HMBR, HMDT, and HMDU):

1. HMBR-a placebo controlled, 9 week, adult, fixed dose (60, 120 mg or pbo) study:
   Entered: n=513;
   Completed: n=389: pbo: n=130 (74.3%);
   duloxetine 60 mg: n=135 (80.4%);
   duloxetine 120: n=124 (72.9%),

2. HMDT- a flexible dose (60-120 mg, or pbo), placebo-controlled, 10 week study:
   Entered: n=327
   Completed: n=202 pbo: n=109 (68.6%)
   duloxetine 60-120 mg: n=93 (55.4%) , and

3. HMDU- a flexible dose, placebo- and active-controlled, 10 week study (duloxetine: 60 to 120 mg , venlafaxine ER: 75-225 mg or pbo):
   Entered: n=487
   Completed: n=290 pbo: n=100 (62.1%);
   duloxetine 60-120: n=88 (54.3%)
   venlafaxine: n=102 (62.2%)

General Discussion of Endpoints

For all the placebo controlled studies, the primary efficacy variable was the **Hamilton Anxiety Rating Scale (HAMA)**. This is a clinician-administered rating scale used to assess the severity of anxiety, its improvement during the course of treatment, and the timing of such improvement. The HAMA consists of 14 items, attempting to provide an overall measure of general anxiety (including psychic anxiety and somatic anxiety). Each item is rated on a 5-point scale of 0 (not present) to 4 (very severe). The HAMA total score is the sum of the 14 items and ranges from 0 to 56. Higher scores indicate a greater degree of symptom severity. [See Appendix 10.2.1 for a copy of the HAMA Scale].

The sponsor has designated the **Sheehan Disability Scale** as the key secondary variable for all the placebo controlled studies. The sponsor used this scale to assess the patient's degree of disability. The SDS is a patient-rated scale consisting of three items evaluating impairment in work/school, social life/leisure activities, and family life/home responsibilities. Each item is scored from 0 (not at all) to 10 (very severely). The three items are summarized to evaluate global functional impairment so that global SDS score ranges from 0 (unimpaired) to 30 (highly impaired). Higher scores are associated with greater functional impairment. [See Appendix 10.2.2 for a copy of the Sheehan Disability Scale].

Study Design

There were three pivotal studies reviewed for this indication of GAD: HMBR, HMDT, and HMDU (summarized in this section, below). The sponsor did not pool any of the efficacy data, and each study was reviewed separately. For all of the three studies, psychotropic medications were not permitted during the study. Zaleplon (up to 10 mg/day), zolpidem (up to 10 mg/day), zopiclone (up to 7.5 mg/day), or chloral hydrae (up to 1000 mg/day) were allowed to be used intermittently at bedtime, for a maximum of 3 times per week, and not more than 9 total doses were allowed. Patients were encouraged to keep their caffeine or nicotine use consistent during the course of the study.

Study **HMBR** is a multi-center, 9 week, randomized, double blind, placebo-controlled study preceded by a placebo lead-in, and concluding with a re-randomized two week drug tapering phase. After the placebo lead-in, patients were randomized to one of three groups: 1) duloxetine 60 mg qd, 2) duloxetine 120 mg qd, or 3) placebo. Please refer to Appendix 10.1.1 for a more detailed review of Study HMBR.

Study **HMDT** is a multi-center, 10 week, randomized, double blind, placebo-controlled study preceded by a placebo lead-in, and concluding with a re-randomized two week drug-tapering phase. After the placebo lead-in, patients were randomized to one of two groups: 1) duloxetine (flexible dose 60-120 mg qd), or 2) placebo. Patients randomized to the duloxetine treatment group were required to tolerate a minimum of duloxetine 60 mg qd (achieved by week 5) and could be titrated to a maximum of 120 mg duloxetine if needed for efficacy and if tolerated. Please refer to Appendix 10.1.2 for a more detailed review of Study HMDT.

Study **HMDU** is a multi-center, 10 week, randomized, double blind, placebo- and comparator-controlled study preceded by a placebo lead-in, and concluding with a two week drug tapering phase. After the placebo lead-in, patients were randomized to one of three groups: 1) duloxetine 60-120 mg qd (starting dose at 30 mg x 1 week), 2) venlafaxine 75-225 mg qd (starting dose at 37.5 mg x 1 week), or 3) placebo. Please refer to Appendix 10.1.3 for a more detailed review of Study HMDU.

Efficacy Findings

[For more details, please refer to the Statistical Review and Evaluation by Yeh-Fong Chen, Ph.D. and George Kordzakhia, Ph.D.]

6.1.4.1 Demographics and Baseline Characteristics

As can be seen from Tables 6.1.4.1a through 6.1.4.1c below, for all three pivotal studies the majority of patients studied were Caucasian females, in their early to mid 40s. It appears that the baseline characteristics were fairly well balanced for all study groups for the three pivotal studies.

Table 6.1.4.1a HMBR: Summary demographic and baseline characteristic for **ITT** population (extracted from the Statistical Review and Evaluation by Drs. Chen and Kordzkhia)

Patient Status	Placebo	Duloxetine 60mg	Duloxetine 120mg
No Patients	173	165	169
Age (years)			
Mean (S.D.)	44.27 (13.37)	42.99 (12.90)	44.03 (12.65)
Gender, N (%)			
Female	115 (66.47%)	105 (63.63%)	122 (72.18%)
Male	58 (33.52%)	60 (36.36%)	47 (27.81%)
Race			
Caucasian	172 (99.42%)	160 (98.15%)	168 (98.24%)
Other	1 (0.57%)	3 (1.84%)	3 (1.75%)
Baseline HAMA Total Score			
Mean (SD)	25.82 (7.66)	25.05 (7.18)	25.13 (7.24)

Table 6.1.4.1b HMDT: Summary demographic and baseline characteristic for **ITT** population (extracted from the Statistical Review and Evaluation by Drs. Chen and Kordzkhia)

Patient Status	Placebo	Duloxetine 60-120mg
No Patients	158	161
Age (years)		
Mean (S.D.)	41.07 (14.18)	42.18 (13.72)
Gender, N (%)		
Female	99 (62.65%)	99 (61.49%)
Male	59 (37.34%)	62 (38.50%)
Race		
Caucasian	123 (77.84%)	128 (79.50%)
Other	35 (22.15%)	33 (20.49%)
Baseline HAMA Total Score		
Mean (SD)	23.49 (7.91)	22.54 (7.44)

Table 6.1.4.1c HMDU: Summary demographic and baseline characteristic for **ITT** population (extracted from the Statistical Review and Evaluation by Drs. Chen and Kordzkhia)

Patient Status	Placebo	Duloxetine 60-120 mg	Venlafaxine
No Patients	158	149	159
Age (years)			
Mean	42.12 (14.17)	40.48 (13.64)	40.25 (13.23)
Gender, N (%)			
Female	98 (62.02%)	96 (64.42%)	99 (62.26%)
Male	60 (37.97%)	53 (35.57%)	60 (37.73%)
Race			
Caucasian	110 (69.62%)	99 (66.44%)	115 (72.32%)
Other	48 (30.37%)	49 (32.88%)	44 (27.67%)
HAMA Total Score			
Mean (SD)	24.98 (5.82)	25.77 (5.66)	24.92 (5.48)

6.1.4.2 Inclusion/Exclusion criteria

Patients chosen for these studies were physically healthy adults and diagnosed with generalized anxiety disorder according the DSM-IV criteria. Required for participation was a CGI-Severity score ≥ 4, a Covi Anxiety Scale (CAS) ≥ 9 score, no item in the Raskin Depression Scale (RDS) was > 3, and the CAS score > the RDS score. Co-morbid Social Phobia or Specific Phobia that are considered to be secondary to the condition under study (GAD) were allowed.

Excluded from the study were patients with a co-morbid DSM-IV Axis I diagnosis, alcohol/drug/caffeine abuse, or uncontrolled narrow angle glaucoma. Also excluded were patients with a lack of response to two or more adequate trials of antidepressants and/or benzodiazepines. Sexually active females were required to use medically accepted forms of birth control. Psychotherapy or other non-drug therapies were not allowed to be started within 6 weeks prior to enrollment.

6.1.4.3 Efficacy Findings

For the primary efficacy variable, the HAMA, the sponsor demonstrated a statistically significant difference in change from baseline when comparing duloxetine treatment with placebo using the ANCOVA model for all three placebo-controlled studies. Please refer to Table 6.1.4.3a (below) which summarizes the statistical significance of duloxetine treatment compared to placebo. It is noted that both duloxetine 60 mg qd and duloxetine 120 mg qd were equally effective compared to placebo.

In their statistical review, Drs. Chen and Kordzkhia offer a secondary analysis for the primary

endpoint of the HAMA total score using a repeated measures analysis, and confirm that the data demonstrated a statistically significant difference in comparing duloxetine change from baseline HAMA score to placebo (please refer to the statistical review for details).

For the key secondary variable, the Sheehan Disability Scale Global Functional Impairment score (**SDS**), the sponsor demonstrates a statistically significant difference in change from baseline to endpoint for the duloxetine treatment group compared to placebo for all three controlled studies for GAD (please see Table 6.1.4.3b, below).

Table 6.1.4.3a Primary Efficacy Variable Results: HAMA total scores, mean change from baseline to Endpoint for all placebo controlled studies in GAD.
(extracted from the Statistical Review and Evaluation by Drs. Chen and Kordzkhia)

Study Treatment	Number of patients	Baseline Mean (SD) (raw data)	Endpoint Mean (SD) (raw data)	LS Change Mean (SE)	**p-value** Dulox. Vs. Placebo
Study **HMBR**					
Placebo	173	25.82 (7.66)	17.19 (9.96)	-8.38 (0.67)	
DLX 60mg	165	25.05 (7.18)	12.32 (8.79)	-12.8 (0.68)	**< 0.001**
DLX 120mg	169	25.13 (7.24)	12.74 (9.55)	-12.5 (0.67)	**< 0.001**
Study **HMDT**					
Placebo	158	23.49 (7.91)	17.00 (10.24)	-5.89 (0.70)	
DLX60-120mg	161	22.54 (7.44)	14.27 (9.58)	-8.12 (0.70)	**0.023**
Study **HMDU**					
Placebo	158	24.98 (5.82)	16.06 (9.29)	-9.19 (0.67)	
DLX60-120mg	149	25.77 (5.66)	13.95 (8.55)	-11.8 (0.69)	**0.007**
VEN 75-225mg	159	24.92 (5.48)	12.90 (8.95)	-12.4 (0.67)	**<0.001**

Table 6.1.4.3b Key Secondary Efficacy Variable Results: **Sheehan Disability Scale** mean change from baseline to Endpoint for all placebo controlled studies in GAD.
(extracted from the Statistical Review and Evaluation by Drs. Chen and Kordzkhia)

Study Treatment	Number of patients	Baseline Mean (SD) (raw data)	Endpoint Mean (SD) (raw data)	LS Change Mean (SE)	p-value vs. Placebo
Study HMBR					
Placebo	163	15.05 (7.29)	11.39 (8.12)	-3.83 (0.56)	
DLX 60 mg	156	15.26 (7.40)	7.38 (6.79)	-7.76 (0.58)	< 0.001
DLX 120 mg	160	14.97 (7.51)	8.08 (8.27)	-7.04 (0.57)	< 0.001
Study HMDT					
Placebo	141	14.64 (7.78)	11.42 (8.71)	-3.11 (0.66)	
DLX60-120mg	144	14.26 (7.24)	8.42 (7.96)	-5.78 (0.66)	0.004

Study HMDU					
Placebo	125	17.52 (5.82)	12.08 (7.53)	-5.42 (0.68)	
DLX60-120mg	122	17.41 (6.44)	9.49 (7.92)	-8.03 (0.69)	0.007
VEN 75-225mg	139	17.55 (5.43)	9.57 (8.06)	-7.97 (0.64)	0.006

6.1.4.4 Subgroup Analysis

Table 6.1.4.4a (below) below (extracted from the Statistical Review and Evaluation by Drs. Chen and Kordzkhia) summarizes subgroup analyses conducted by Drs. Chen and Kordzkhia, FDA statisticians. From Table 6.1.4.4a, it appears that duloxetine is less effective in patients ≥ 55 y.o.; however, this study was not powered sufficiently to consider this a significant finding.

Of significant note in these special subgroup analyses is that duloxetine did not show statistical significance in patients with a baseline HAMA score of < 22; suggesting that duloxetine was not effective for patients with less severe GAD symptoms (according to their HAMA total score). (Please refer to Table 6.1.4.4b below).

Table 6.1.4.4a Summary table of Subgroup analysis of age for controlled studies for GAD; [adapted from the Statistical Review and Evaluation by Drs. Chen and Kordzkhia]

Age, mean (SE)					
HMBR					
	Placebo N=173	DLX 60mg N=165	p-value vs. placebo	DLX 120mg N=169	p-value vs. placebo
<55 years N=399	-8.760 (0.788) N=132	-13.131 (0.776) N=136	<0.0001	-13.120 (0.790) N=131	0.0001
>=55 years N=108	-7.033 (1.249) N=41	-11.879 (1.486) N=29	0.0142	-10.345 (1.298) N=38	0.0690
HMDT					
	Placebo N=158	DLX 60-120mg N=161	p-value vs. placebo		
<55 years N=260	-6.262 (0.791) N=129	-8.000 (0.785) N=131	0.1203		
>=55 N=59	-6.333 (1.527) N=29	-10.610 (1.500) N=30	0.0545		
HMDU					

	Placebo N=158	DLX 60-120mg N=149	p-value vs. placebo	VEN 75-225mg N=159	p-value vs. placebo
<55 years N=391	-9.207 (0.767) N=129	-11.813 (0.783) N=124	0.0181	-12.409 (0.742) N=138	0.0029
>=55 N=75	-8.278 (1.425) N=29	-10.116 (1.536) N=25	0.3851	-10.190 (1.670) N=21	0.3866

Table 6.1.4.4b Summary table of Subgroup analysis of HAMA total score mean change from baseline to endpoint for controlled studies for GAD;
[adapted from the Statistical Review and Evaluation by Drs. Chen and Kordzkhia]

HMBR

	Placebo	DLX 60mg	p-value vs. placebo	DLX 120mg	p-value vs. placebo
Anxiety severity, mean (SE)					
score <22 N=162	-5.850 (0.997) N=56	-7.129 (1.045) N=51	0.3776	-6.941 (1.006) N=55	0.4425
score >=22 N=345	-9.548 (0.866) N=117	-15.552 (0.876) N=114	<0.001	-15.121 (0.874) N=114	<0.0001

HMDT

	Placebo N=158	DLX 60-120mg N=161	p-value vs. placebo
Anxiety severity, mean (SE)			
score <22 N=133	-4.133 (0.899) N=64	-6.079 (0.866) N=69	0.1221
score >= 22 N=186	-7.786 (1.013) N=94	-10.240 (1.024) N=92	0.0907

HMDU

	Placebo N=158	DLX 60-120mg N=149	p-value vs. placebo	VEN 75-225mg N=159	p-value vs. placebo
Anxiety severity, mean (SE)					
score <22 N=134	-6.338 (1.037) N=48	-5.864 (1.138) N=40	0.7593	-8.808 (1.058) N=46	0.0980
score >=22 N=332	-10.129 (0.858) N=110	-13.759 (0.863) N=109	0.0031	-13.398 (0.847) N=113	0.0071

Efficacy Conclusions

All three controlled studies submitted in the GAD population provide evidence that duloxetine is effective in the treatment of generalized anxiety disorder (GAD).

The doses in these studies range from duloxetine 60 mg qd to duloxetine 120 mg qd; it is noted that in study HMBR, the only fixed dose study, the duloxetine 120 mg qd dose does not demonstrate any advantage over the duloxetine 60 mg group.

In special subgroup analyses, it appears that duloxetine may be less effective in patients with a less severe symptoms of anxiety (according to scores in the primary efficacy variable) compared to patients with greater severity of symptoms.

Also of note is there are very few non-Caucasians enrolled in any of the controlled studies.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This safety review is limited to the sponsor's data base of patients diagnosed with generalized anxiety disorder (GAD). The cut-off for the safety data base for original GAD submission is 12/19/05. The cut-off for the safety data base reported in the safety update is 4/26/06.

Deaths

There is one death reported in the safety update (cut-off 4/26/06) occurring during an ongoing relapse prevention study for GAD (Study HMDV); a 50 year old Caucasian female died from a cerebral hemorrhage after 102 days of duloxetine treatment in an open label study for generalized anxiety disorder. The only relevant past medical history is intermittent headaches (treated with aspirin) and herniated disks (treated with ibuprofen). The sponsor's narrative contains very little information regarding the episode; the narrative states that the patient's husband refused to release her medical records. See below for summary table.

Table 7.1.1 Death in the GAD safety data base (from safety update)

PATIENT #	AGE/ GENDER	DOSE/ DURATION	EVENT
HMDV-107-1731	50/F	60-120 mg qd /102 days	Death due to cerebral hemorrhage

Other Serious Adverse Events

The table below (Table 7.1.2) summarizes serious adverse events in the GAD population: the information for this table is extracted from the an appendix in the safety summary in which the sponsor listed all indications. The sponsor did not provide a section or organize the data for the indication of GAD only.

Table 7.1.2 Table of serious adverse events occurring in patients with the indication of GAD in the duloxetine treatment group.

PATIENT #	AGE/ GENDER	DOSE/ DURATION	EVENT
HMDT 104-1409	41/F	60-120 mg qd /95 days	Day 61: c/o severe migraine with numbness and pain on left side of face. Event required hospitalization x 2 days; treated with IV hydromorphone, sumatriptan and IV ketorolac, and oxocodon. MRI/CT: negative; labs: WNL d/c diagnosis: acute migraine. No hospital records in CFR
HMDT-118-2817	65/M	60 mg qd /10 days	Discontinued due to severe anxiety. 6 or 27 days after discontinuation (inconsistent in the narrative), patient died due to asphyxiation after choking on a piece of meat.
HMDT-120-3019	61 /F	120 mg qd /47 days	Coded as "Discontinued due to exacerbation of back pain." Symptoms also included neck pain with radiation down left arm. On day 47, patient was hospitalized for severe abdominal pain. Patient also c/o neck pain with radiation down left arm. CT showed cervical spondolyosis and canal stenosis at multilevels; MRI: degenerative disc disease in thoracic vertebrae. Had high WBC count (21,000): tests normal. No infection or malignancy noted. No explanation for abdominal pain found; appears to have resolved by end of hospital stay. No hospital records in CRF.
HMDT-129-3910	30 /M	60-120 mg qd Day 1: 60 mg Day 13: 90 mg Day 31: 120 mg	Day 34: Hospitalized for chest pain and pressure, SOB, hypertension (bp not avail), fast heart rate (150 bpm) with new onset rapid atrial fibrillation accompanied with hypertension. Treated with adenosine, IV diltiazem, warfarin,

PATIENT #	AGE/ GENDER	DOSE/ DURATION	EVENT
		Duration is unclear: CFR and narrative are conflicting	flecainide. *ECG and hospital labs not available (???)* ECHO showed left atrial enlargement, mild left ventricular hypertrophy, aortic root dilitaion. Hospital discharge diagnosis was paroxysmal atrial fibrillation. CPK level Baseline: 243 U/L (NL=0-198) Day 13: 437 U/L Day 51: 322 U/L According to narrative, pt on the study drug for 30 more days and was d/ced due to "racing heart" which did not resolve until duloxetine was discontinued (~65 days).
HMDU-202-2232	24/F	90 mg q.d. /25 days	Day 23: Alcohol Abuse, self mutilation, lack of efficacy. Patient stopped medication on her own when she started to drink alcohol heavily after break up of relationship; she also experienced episodes of cutting herself which resolved 12 days after stopping duloxetine.
HMDU-207-2709	58/F	120 mg /65 days	Malignant kidney neoplasm (renal cell carcinoma); vomiting and stomach pain. Unclear when patient discontinued from the study.
HMDU-220-4003	23/F	120 mg qd /80 days	Intestinal ulcer. Patient completed the study.
From Safety Update			
HMDW 402-4207	19/M	blinded	Aggression
HDMW-800-8010	22/M	blinded	Hyperglycemia; incomplete laboratory information in the narrative. Glucose level normal at baseline and close to normal one week after discontinuation of study drug.
HMDV-851-8614	44/F	60 m/112 days; blinded/12 days	Manic episode
HMDV-117-2709	60/F	120 mg qd/ 301 days	Renal calculi (Day 65) and acute bronchitis (5 days after d/c)

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Adverse events associated with dropouts

In the combined data base of the three pivotal controlled GAD studies, more patients assigned to duloxetine treatment withdrew due to adverse events compared to patients taking placebo. There were 104 (or 11% of n=668) duloxetine patients who withdrew early from the study compared to 21 (or 4% of n=495) placebo patients. The most frequent reasons listed for withdrawal were nausea, dizziness, somnolence, anxiety, vomiting and headache; the duloxetine group experienced nausea, dizziness, somnolence and anxiety at a statistically significant level when compared to placebo (see Table 7.1.3.1, below). These adverse events are consistent with the current labeling profile for duloxetine treatment of MDD. Please refer to the sponsor's safety summary for a complete listing of frequency of adverse events associated with withdrawal.

Table 7.1.3.1 Withdrawals due to Adverse events observed to be more significant in the duloxetine groups compared to the placebo group.

EVENT	DULOXETINE	PLACEBO	P-VAULE
Nausea	104 (15.57%)	21 (4.24%)	<0.001
Dizziness	25 (3.74)	1 (0.2)	<0.001
Vomiting	8 (1.2)	1 (0.2)	0.066
Somnolence	9 (1.35)	0	0.012
Anxiety	4 (o.6)	0	0.066

7.1.4 Other Search Strategies

There were no other search strategies utilized in this review.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

It is unclear from the protocols if adverse events were specifically solicited or if adverse events were only recorded when a patient made specific complaints.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor grouped treatment-emergent adverse events by occurrence, using the Medical Dictionary for Regulatory Activities (MedDRA™) terminology to classify events.

7.1.5.3 Incidence of common adverse events

The sponsor reports that the following adverse events had both an incidence of ≥ 5% in the duloxetine treatment group and also had a statistically significant greater occurrence compared to the placebo group: nausea, dizziness dry mouth, fatigue, constipation, insomnia, somnolence, hyperhidrosis, and libido decrease. Table 7.1.5.3a below lists the adverse events that demonstrate both a higher incidence in duloxetine and a statistically significant difference comparing duloxetinewith the placebo groups. Table 7.1.5.3b below summarizes the frequency observed by organ systems comparing duloxetine and placebo groups in the GAD safety data base.

Table 7.1.5.3a Adverse events with great frequency in the duloxetine compared to placebo group with statistical significance. [adapted from sponsor table in safety summary.

Event	PLACEBO (N=495) n(%)	DULOXETINE (N=668) n(%)	DULOXETINE VS. PLACEBO p-Value CMH(a)	DULOXETINE VS. PLACEBO p-Value Exact(b)
Nausea	51(10.3%)	257(38.5%)	<.001	<.001
Dizziness	38(7.7%)	97(14.5%)	<.001	<.001
Dry mouth	19(3.8%)	79(11.8%)	<.001	<.001
Fatigue	18(3.6%)	77(11.5%)	<.001	<.001
Constipation	16(3.2%)	64(9.6%)	<.001	<.001
Insomnia	14(2.8%)	55(8.2%)	<.001	<.001
Somnolence	9(1.8%)	55(8.2%)	<.001	<.001
Hyperhidrosis	11(2.2%)	50(7.5%)	.001	<.001
Libido decreased	7(1.4%)	39(5.8%)	<.001	<.001
Vomiting	11(2.2%)	32(4.8%)	.017	.027
Decreased appetite	9(1.8%)	28(4.2%)	.007	.027
Vision blurred	9(1.8%)	24(3.6%)	.035	.076
Anorexia	4(0.8%)	27(4.0%)	.002	<.001
Tremor	3(0.6%)	26(3.9%)	<.001	<.001
Sedation	5(1.0%)	23(3.4%)	.012	.007
Hot flush	5(1.0%)	17(2.5%)	.036	.080
Yawning	0(0.0%)	20(3.0%)	<.001	<.001
Paraesthesia	3(0.6%)	13(1.9%)	.041	.073
Urinary hesitation	2(0.4%)	12(1.8%)	.008	.032
Erectile dysfunction	1(0.2%)	12(1.8%)	.006	.010
Stomach discomfort	2(0.4%)	11(1.6%)	.022	.051
Weight increased	11(2.2%)	2(0.3%)	.002	.003
Ejaculation delayed	1(0.2%)	11(1.6%)	.013	.017
Feeling jittery	2(0.4%)	10(1.5%)	.026	.082
Anorgasmia	1(0.2%)	10(1.5%)	.015	.029
Bruxism	1(0.2%)	9(1.3%)	.016	.051
Dysuria	0(0.0%)	10(1.5%)	.013	.007
Mydriasis	0(0.0%)	10(1.5%)	.007	.007
Accommodation disorder	0(0.0%)	8(1.2%)	.040	.024
Restless legs syndrome	0(0.0%)	8(1.2%)	.019	.024
Sleep disorder	0(0.0%)	5(0.7%)	.028	.076

Table 7.1.5.3b Common events by organ systems; comparative frequency of statistical significance

ORGAN SYSTEM	DULOXETINE % OF N=668	PLACEBO % OF N=495
Gastrointestinal disorders	55.7%;	28.7%
Nervous system disorders	42.5%	29.9%
Psychiatric disorders	24.6%	12.7%
General disorders and administration site conditions	19.2%	9.5%
Infections and infestations	11.7%	20.2%

7.1.5.4 Common adverse event tables

Table 7.1.5.4 (below) is a common adverse event table extracted from the sponsor's proposed labeling. Otherwise, a common adverse event table was not located in the submission.

In Table 7.1.5.4, as it is presented in the labeling, the sponsor summarizes the common adverse events occurring both in ≥ 2% or more of patients and also with a higher incidence in the duloxetine group compared to placebo treatment. In the text prior to the table, the sponsor lists the following adverse events as occurring ≥ 5% and twice the incidence in placebo patients as: nausea, fatigue, dry mouth, somnolence, constipation, insomnia, appetite decreased, hyperhidrosis, libido decrease, vomiting, ejaculation delayed, and erectile dysfunction.

Table 7.1.5.4 Treatment –Emergent Adverse Events Incidence in GAD Placebo-Controlled Trials occurring in ≥ 2% or more of patients and also with a higher incidence in the duloxetine group compared to placebo treatment (table is as presented in the sponsor's proposed labeling)

• **System Organ Class / Adverse Event**	• **Percentage of Patients Reporting Event**	
	• **Cymbalta** • **(N=668)**	• **Placebo** • **(N=495)**
• **Eye Disorders** • **Vision blurred**	• **4**	• **2**
• **Gastrointestinal Disorders** • **Nausea** • **Dry mouth**	• **38** • **12**	• **10** • **4**

• Constipation	• 10	• 3
• Diarrhea	• 8	• 6
• Vomiting	• 5	• 2
• Abdominal pain[2]	• 4	• 3
• Dyspepsia[3]	• 4	• 3
• General Disorders and Administration Site Conditions		
• Fatigue[4]	• 13	• 5
• Metabolism and Nutrition Disorders		
• Appetite decreased[5]	• 8	• 3
• Nervous System Disorders		
• Dizziness	• 15	• 8
• Somnolence[6]	• 12	• 3
• Tremor	• 4	• 1
• Paraesthesia[7]	• 2	• 1
• Psychiatric Disorders		
• Insomnia[8]	• 9	• 4
• Libido decreased[9]	• 7	• 2
• Agitation[10]	• 4	• 2
• Orgasm abnormal[11]	• 3	• 0
• Reproductive System and Breast Disorders		
• Ejaculation delayed[12]	• 5	• 1
• Erectile dysfunction[12]	• 5	• 1
• Respiratory, Thoracic and Mediastinal Disorders		
• Yawning	• 3	• 0
• Skin and Subcutaneous Tissue Disorders		
• Hyperhidrosis	• 7	• 2
• Vascular Disorders		
• Hot flushes	• 3	• 1

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory tests were conducted at screening and at discontinuation for the three placebo controlled studies in the GAD safety data base.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

This review will discuss the laboratory values for the 3 placebo-controlled studies for the indication of GAD (Studies HMBR, HMDT, and HMDU).

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Table 7.1.7.3.1 (below) lists the laboratory values that were determined by the sponsor to have a statistically significant difference in mean change from baseline when comparing the duloxetine treatment group with the placebo group.

Table 7.1.7.3.1 All laboratory values in the GAD safety data base that were determined to have a statistically significant difference in change from baseline comparing duloxetine and placebo treatment groups.[adapted from sponsor's safety summary appendix table 2.7.4.7.20].

Lab Test	Lab Unit	Therapy	N	--Baseline-- Mean	SD	Change to --Endpoint-- Mean	SD	Therapy* P-value
ALKALINE PHOSPHATASE	U/L	PLA	410	72.79	23.04	-0.54	8.98	.005
		DLX	551	70.15	21.74	1.26	10.36	
AST/SGOT	U/L	PLA	403	22.68	7.38	0.05	16.07	<.001
		DLX	537	22.48	7.36	0.70	7.85	
BICARBONATE, HCO3	mmol/L	PLA	410	23.65	2.74	0.16	2.98	.004
		DLX	546	23.53	2.48	0.81	2.69	
CHLORIDE	mmol/L	PLA	412	104.04	2.50	-0.05	2.63	<.001
		DLX	551	104.11	2.42	-0.61	2.52	
CHOLESTEROL	mmol/L	PLA	412	5.21	1.01	-0.07	0.69	.027
		DLX	551	5.31	1.06	0.04	0.75	
INORGANIC PHOSPHORUS	mmol/L	PLA	411	1.13	0.16	0.02	0.17	.003
		DLX	551	1.15	0.17	-0.02	0.18	
UREA NITROGEN	mmol/L	PLA	412	4.96	1.45	0.22	1.23	.012
		DLX	551	4.99	1.46	0.06	1.24	
URIC ACID	umol/L	PLA	412	314.53	88.78	-0.65	53.32	<.001
		DLX	551	309.86	88.70	-11.12	42.74	
BANDS	GI/L	PLA	195	0.0004	0.0057	-0.000	0.0057	.035
		DLX	184	0.0000	0.0000	0.002	0.0248	

LYMPHOCYTES	GI/L	PLA	345	2.0208	0.6061	-0.021	0.4433	.036
		DLX	484	2.0462	0.6002	-0.074	0.4570	
UA-SPECIFIC GRAVITY	NO UNITS		5333	1.02	0.01	0.00		0.01

7.1.7.3.2 Marked outliers and dropouts for laboratory abnormalities

Comparing incidents of endpoints laboratory abnormalities of the duloxetine and placebo groups, the sponsor found that statistical significance was seen in the following laboratory values:

- high cholesterol (duloxetine: 4.7% versus placebo: 1.9%);
- low phosphorus (duloxetine: 0 versus placebo: 1.1%)

There were two patients who had withdrawals due to elevated CPK, one at Week 4, and the other at Week 8. According to the sponsor's summary, there were three patients found to have a maximum CPK value of greater than 5000 U/L, with one being above 10,000 U/L. In the placebo group, only one patient had a maximum value of greater than 5000 U/L, and none had a value over 10,000 U/L. Individual duloxetine-treated patients with large increases of CPK are presented below in Table 7.1.7.3.2.

The sponsor did not provide a very adequate summary of the elevated creatine phosphokinase (CPK) levels found in patients. Table 7.1.7.3.2 (below) was constructed by reading all narratives related to elevated CPK in the GAD patients.

Table 7.1.7.3.2 Summary of GAD patients presenting with > 2 x upper limit of normal CPK levels (information found by reviewing all narratives)

PT # AGE/ GENDER	CPK LEVEL (MAXIMUM) NL= 0-198 U/L	OTHER LAB ABNL	OTHER SYMPTOMS/SIGNS MISC. INFO
HMBR 100-1020 48/M	3928	SGOT Glucose LDL	Discontinued due to "elevation of CK" Hot flushes, nausea, sedation 41 days of duloxetine 60 mg
HMDU 219-3921 33/M	1323	↓MCH ↓Leukocyte ↓count ↓Neutophils Total protein creatinine	d/ced due to "elevated CK" ,dysuria, headache 49 day of duloxetine 120 mg qd 28 days after discontinuing study drug CK =338 U/L.
HMBR 402-4209 32 /M	923 U/L	SGOT SGPT	Discontinued study due to "shocks through body, headache, and tremor." 65 days duloxetine 60 mg qd
HMDT 125-3504 33/M	599	SGOT	Discontinued due to "hot flashes" 8 days of duloxetine 60 mg qd (no temperature recorded in CFR)

PT # AGE/ GENDER	CPK LEVEL (MAXIMUM) NL= 0-198 U/L	OTHER LAB ABNL	OTHER SYMPTOMS/SIGNS MISC. INFO
HMDT 118-2814 26/M	715	Cholesterol Triglycerides LDL	Discontinued due to "Energy increased," Insomnia 70 of duloxetine 120 mg qd
HMBR 103-132 53/M	440	Glucose, fasting HDL	D/ced due to "nausea" 58 days of duloxetine 60 mg
HMBR 100-1014	447	Cholesterol TG, LDL ↓ Bilirubin	D/ced due to "nausea" 11 days od duloxetine 60 mg
HMDT 129-3910 31/M	437	SGGT UA	D/ced due to "new onset atrial fibrillation" 62 days of duloxetine120 mg qd
HMBR 404-4416	1303 (NL: 0-169)	SGOT, LDL, CK-MB	Discontinued due to "myocardial infarct" 62 day of duloxetine (dose unclear)

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs that were monitored weekly included sitting pulse and blood pressure. Height and weight were recorded at baseline, and weight was measured again at discontinuation.

As documented in the current labeling for MDD, duloxetine "was associated with mean increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg compared to placebo."

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The safety data base included the three placebo-controlled studies (HMBR, HMDT, and HMDU) in the population diagnosed with GAD.

7.1.8.3 Standard analyses and explorations of vital signs data

The data from the GAD safety data base suggests that there was a statistically significant mean increase (baseline to endpoint) in pulse, systolic and diastolic blood pressure when comparing duloxetine with placebo. There also appears to be a statistically significant decrease in weight for the duloxetine group (see Table 7.1.8.3.1, below). These findings appear to be consistent

with the current labeling. It is also noted that there were no withdrawal from the study due to vital sign changes.

Table 7.1.8.3 Mean change from baseline for vital signs of the integrated safety data base for GAD (adapted from sponsor table in safety summary)

			----Baseline----		--Change to Endpoint--		
Vital	Therapy	n	Mean	SD	Mean	SD	P-value
Pulse	Duloxetine	647	72.27	9.57	1.61	10.29	
	Placebo	489	72.31	9.36	-0.53	9.27	<.001
SI SYS	Duloxetine	647	121.52	15.30	1.06	12.01	
	Placebo	489	121.82	14.59	-1.00	11.73	.005
SI DIA	Duloxetine	647	76.51	10.23	1.25	8.99	
	Placebo	489	76.77	9.30	-0.60	8.18	.001
Weight(Kg)	Duloxetine	584	75.57	18.89	-0.48	2.48	
	Placebo	423	77.96	19.18	0.44	2.62	<.001

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

In the safety data base for this GAD supplement, ECGs were assessed at baseline and at discontinuation. There was no reference made to the timing of ECGs in relation to dosing or food intake.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The safety data base included the three controlled studies (HMBR, HMDT, and HMDU) in the population diagnosed with GAD. In the protocols for these studies, there is no mention of exclusion criteria related to ECG finding (i.e. no exclusion for QT prolongation).

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Please see Appendix Table 10.3.1 for the mean change of all ECG parameter found in the GAD safety data base.

For the GAD safety data base, a QTc prolongation is demonstrated in this pre-market population with GAD. Table 7.1.9.3.1a (below) demonstrates that this change occurs when using both the Bazet's and Fredericia's correction (although there is not a very significant heart increase observed with duloxetine, so it is not entirely clear if Fredericia's correction is the better correction).

Table 7.1.9.3.1a Mean Change from baseline for heart rate, QT, QTcB (Bazett's correction), and QTcF (Fredericia's correction) for the GAD safety data base
[adapted from sponsor's table in safety study report]

Indication	HR			QT			QTcB			QTcF		
	Base	Change	p-Value	Base	Change	p-Value	Base	Change	p-Value	Base	Change	p-Value
GAD												
DLX (N=447)	68.01	+2.51	<.001	387.76	-2.78	.001	409.71	+4.54	<.001	401.97	+2.03	.047
PBO (N=343)	68.47	-1.27		391.31	+2.24		414.88	-1.67		406.55	-0.30	

In an effort to explain this discrepancy, the sponsor makes their case that there "is about a 5-msec difference in baseline QTcB and QTcF values in the GAD studies as opposed to an approximate difference of 1-msec in all other groups" (as seen in Appendix table 10.3.2). The sponsor offers alternative analyses of all ECG parameters for the GAD safety data base "correcting" for this difference of the baseline QTc and QTcF (See Appendix table 10.3.3)

The sponsor also states that this finding of a QTc prolongation was not observed in the primary safety data base for other indications (See Appendix table 10.3.2) . Also, Study HMGC, a placebo-controlled study of electrophysiological effects of supratherapueutic doses of duloxetine (200 mg bid) on the QT interval (with the positive control moxifloxicin), was conducted; according to the sponsor's study report, findings from this study include the following:

- Compared with placebo, duloxetine 200 mg twice daily does not produce clinically relevant increases in the QT interval as determined using Fredericia's correction since the upper limit of the two-sided 90% confidence interval was less than 10 msec (and actually less than 5 msec) at each time point.

- The overall study population experienced a dose-dependent increase in orthostasis when exposed to duloxetine compared with placebo; subjects who had averaged orthostatic changes outside of outlier boundaries had few orthostatic-related adverse events.

7.1.9.3.2. Marked outliers and dropouts for ECG abnormalities

There were no withdrawals or serious adverse events reported which were attributed to ECG abnormalities from the GAD safety data base.

The relative frequency of QTc > 30 msec and >60 msec can be seen from Table 7.1.9.3.2 below. Compared to placebo, duloxetine shows a statistically higher percentage of patients with a QTc prolongation of 30-60 msec using Bazett's formula (Dulox: 7.8% versus Pbo: 2.9%), whereas using the Fredericha's formula, this statistical significance disappears [it is unclear if the heart rate increase due to duloxetine is significant enough to merit the use of Fredericia's equation.]

There were no QTc changes > 60 msec reported in the duloxetine group; whereas one patient (0.3%) in the placebo group was reported to have a QTc change of >60 msec. Also, there did not appear to be a significant difference in the emergent of a prolonged QTc when comparing the duloxetine and the placebo treatment groups.

The actual maximum values of QTc for either group for the GAD population was not located in this submission.

7.1.9.3.2a Sponsor table of QTc changes >30 and >60 msec for the safety data base for GAD

		PLACEBO			DULOXETINE				
ECG parameters	Abnormality	N	n	Percent	N	n	Percent	CMH P-value	Fisher's Exact P-value
QTcB	Inc <=30	350	339	96.9 %	462	426	92.2 %	.004	.006
QTcB	30< Inc<=60	350	10	2.9 %	462	36	7.8 %	.002	.003
QTcB	Inc >60	350	1	0.3 %	462	0	0.0 %	.311	.431
QTcF	Inc <=30	350	343	98.0 %	462	446	96.5 %	.194	.286
QTcF	30< Inc<=60	350	7	2.0 %	462	16	3.5 %	.194	.286
QTcF	Inc >60	350	0	0.0 %	462	0	0.0 %		

7.1.10 Immunogenicity

No immunogenicity studies were submitted in this application.

7.1.11 Human Carcinogenicity

No Carcinogenicity studies were submitted with this application

7.1.12 Special Safety Studies

In the last two week of all three placebo-controlled studies, the sponsor conducted a tapering phase in which patients underwent a two week, drug-tapering phase.

The tapering scheme for the fixed dose trial (HMBR) re-randomized the patient group taking duloxetine 120 mg qd to 1 of 2 treatment groups: duloxetine 60 mg QD for 1 week followed by

duloxetine 30 mg QD for 1 week; or placebo for 2 weeks. Patients randomized to duloxetine 60 mg QD were re-randomized to 1 of 2 treatment groups: duloxetine 30 mg QD for 1 week followed by placebo for 1 week; or placebo for 2 weeks. Patients randomized to placebo remained on placebo for the drug-tapering phase.

For the two weeks of the tapering phase in the flexible dose studies (HMDT and HMDU), patients taking duloxetine 120 mg QD or 90 mg QD received duloxetine 60 mg QD for 1 week followed by 30 mg QD for 1 week. Patients taking duloxetine 60 mg QD received duloxetine 30 mg QD for 1 week followed by placebo for 1 week. Patients taking placebo remained on placebo for the duration of the drug-tapering phase.

The sponsor reported that there were 75 (23.7%) duloxetine-treated and 35 (16.7%) placebo-treated patients who experienced at least one taper-emergent adverse event. As can be seen in **Table 7.1.12** (below), adverse events that were observed occurring with a statistically significant higher frequency in the duloxetine group compared to placebo group are: dizziness, headache, insomnia, and URIs.

It did not appear that tapering at a slower rate (in one week increments of 30 mg versus abrupt discontinuation) affected the incidence of adverse events compared to the placebo group.

Table 7.1.12 Tapering Phase: Adverse Events occurring with a higher frequency in the duloxetine group compared to placebo group that was statistically significant (extracted from Table 2.7.4.1.10 in the sponsor's safety summary)

Event	PLACEBO (N=210) n(%)	DULOXETINE (N=316) n(%)	DULOXETINE VS. PLACEBO p-Value CMH(a)	DULOXETINE VS. PLACEBO p-Value Exact(b)
Dizziness	4(1.9%)	24(7.6%)	.155	.005
Headache	2(1.0%)	13(4.1%)	.195	.034
Insomnia	0(0.0%)	8(2.5%)	.133	.024
Upper respiratory tract infection	6(2.9%)	1(0.3%)	.082	.018

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There are no studies on withdrawal phenomena and/or abuse potential submitted with this application.

7.1.14 Human Reproduction and Pregnancy Data

There are no studies assessing the effects of duloxetine on human reproduction and pregnancy in GAD patients. However, there was a labeling supplement submitted (1/23/06) which addresses breast milk excretion. This study was reviewed by the Division of Clinical Pharmacology (Kavanagh: 10/17/06). Dr. Kavanagh notes that the excretion of duloxetine metabolites into human breast milk was not examined, and summarizes the sponsor's findings as follows:

- Duloxetine is detected in breast milk; steady state duloxetine concentrations in breast milk are one fourth those in plasma.

- The estimated daily infant dose of duloxetine from breast milk is approximately 7 μg (range 4 to15 μg), or about 1/10,000 the total daily maternal dose (80 mg). The estimated daily infant dose based on body weight normalization is about 2 μg /kg/day, or approximately 0.14% of the maternal dose.

- Adverse events and vital sign changes in healthy, lactating, postpartum women were similar to those seen in other duloxetine studies of healthy subjects.

7.1.15 Assessment of Effect on Growth

There are no studies which specifically assess for growth changes in the GAD population. There appears to be a slight mean weight decrease when mean changes from baseline for duloxetine compared with placebo in the short term placebo-controlled GAD safety data base.

7.1.16 Overdose Experience

There are no reports on overdose in this GAD population.

7.1.17 Post-marketing Experience

Duloxetine was approved for marketing in the United States in August, 2004, and is currently marketed for major depressive disorder (MDD)and diabetic peripheral neuropathy (DPNP). According to the sponsor, as of February 2006, duloxetine has been marketed as Cymbalta®/Xeristor® in 35 countries for MDD and 2 countries for DPNP, and as Yentreve®/Ariclam® in 14 countries for SUI (stress urinary incontinence). [Please see sponsor's submission for complete listing].

In the United States, there have been many post-marketing reports regarding safety issues with duloxetine, and duloxetine is going to be the first drug used in the pilot study to assess the post marketing evaluation of new molecular entities.

Of concern in the Medwatch reports are: liver injury, hyponatremia and SAIDH, hallucinations, allergic reactions (including anaphylactic shock) and life-threatening skin reactions [such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and/or toxic epidermal necrolysis (TEN)].

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

There were three placebo-controlled studies used to assess the safety and efficacy of duloxetine in patients diagnosed with GAD. The following is a summary of these studies:

1. Study **HMBR** (n=513) is a multi-center, 9 week, randomized, fixed dose, double blind, placebo-controlled study with three treatment groups: placebo (n=175); duloxetine 60 mg (n=168); duloxetine 120 mg (n=170).

2. Study **HMDT** (n=327) is a multi-center, 10 week, randomized, double blind, flexible dose, placebo-controlled study with two groups: duloxetine 60-120 mg qd (n=93); or placebo (n=168).

3. Study **HMDU** (n=487) is a multi-center, 10 week, randomized, double blind, flexible dose, placebo- and comparator-controlled study with three treatment groups: duloxetine 60-120 mg qd (n=162), 2) venlafaxine 75-225 mg qd (n=164), or 3) placebo (n=161).

7.2.1.2 Demographics

The majority of patients in the GAD studies were Caucasian females in their early to mid-forties. The breakdown of subgroups for each of the placebo-controlled studies is the following:

In Study HMDR, there are 348 women (67.84) and 165 men (32.16) with a mean age of 43.78 years old (range 18 to 83 years). The population consists of 505 (98.44%) Caucasians, 3 (0.58%) African-Americans, 1 (.19%) Hispanics, and 4 (0.7%) Asian.

In Study HMDT, there are 305 women (62.63%) and 182 men (37.37) with a mean age of 39.49 years old (range 18 to 83 years). The population consists of 539 (69.75%) Caucasians, 78 (16.05 %) African-Americans, 56 (11.52%) Hispanics, 13 (2.47%) Asian, and 1 (0.21) Native American.

In Study HMDU, there are 305 women (62.63%) and 182 men (37.37) with a mean age of 39.49 years old (range 18 to 83 years). The population consists of 539 (69.75%) Caucasians, 78 (16.05 %) African-Americans, 56 (11.52%) Hispanics, 13 (2.47%) Asian, and 1 (0.21) Native American.

7.2.1.3 Extent of exposure (dose/duration)

There are 668 patient diagnosed with GAD exposed to duloxetine in the primary placebo controlled integrated safety database. The sponsor calculates that in this safety data base there is an exposure of 95.09 patient years. 509 (76%) patients had an exposure of ≥ 30 days, and 449 (67%) patients had an exposure of ≥ 60 days.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The only other secondary clinical data used to evaluate the safety of the GAD is Study HMGC, a placebo-controlled study of electrophysiological effects of supratherapueutic doses of duloxetine (200 mg bid) on the QT interval (with the positive control moxifloxacin). This study added information and perspective in light of the evidence that the QTc was prolonged for the GAD safety data base.

7.2.3 Literature

In an addendum submission (6/7/06), the sponsor included a brief literature review conducted by conducted by William G. Losin, Pharm.D from Global Medical Information Associate, Neurosciences Group, Lilly Research Labs. There were three abstracts and four poster titles submitted. A review of this material submitted did not provide additional safety information to the sponsor's data base.

7.2.3 Adequacy of Overall Clinical Experience

There were few non-Caucasians included in the data base for GAD.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There were no special animal and/or in vitro testing accompanying this submission.

7.2.5 Adequacy of Routine Clinical Testing

The data presented was limited to the adult population.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

There were no special studies conducted for the GAD indication.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

A major concern for this drug is its effects of the liver. Many of the MedWatch reports submitted have incomplete data to help assess causality. Many reports are also confounded by the fact that many patients using this medication may already have underlying complications. It would be helpful if the sponsor could conduct a longitudinal study to assess the effects of duloxetine on the liver. It is also recommended that the sponsor make a better effort to organize and collect more complete data on the post-marketing reports regarding liver injury.

7.2.8 Assessment of Quality and Completeness of Data

The narratives presented in this submission were unclear in many circumstances. There were several inconsistencies between the narratives, the summary tables, and the CFR.

Also, the presentation of the GAD safety data was very confusing. The sponsor embedded many GAD safety tables, narratives, and SAEs within tables and narratives of other indications. In some cases, the sponsor did not sort out the safety information for GAD, but fused it with other indications, not allowing for a complete review of patients in the GAD data base only.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Many of the safety concerns that arose with this NDA data base have been discussed in the marketed labeling for duloxetine.

Of note in the safety data base for the GAD pre-market population is that there appears to be a QTc prolongation at endpoint when comparing the duloxetine and placebo change from baseline. It is noted that these ECGs were taken without regard to timing of dosing or food intake. The sponsor felt that if the baseline QTc readings were "corrected," a QTc prolongation was no longer observed. It is also noted that a clinical pharmacology study specifically addressing the issue of QTc prolongation was conducted and results did not support a QTc prolongation with duloxetine use [Study HMGC, a placebo-controlled study of electrophysiological effects of supratherapueutic doses of duloxetine (200 mg bid) on the QT interval (with the positive control moxifloxacin)].

It is curious that there is a finding of QTc prolongation in the GAD population. Although Study HMGC provides reassurance that duloxetine does not cause a QTc prolongation in the general

population; it could be possible that the GAD population has some unique cardiac complications as has been seen with an association of mitral valve prolapse and anxiety disorders.

Another safety observation is the cases of elevated creatine phosphokinase (CPK). The sponsor offered the explanation of rhabdomyolysis, citing the following other associated symptoms observed with greater frequency in the duloxetine groups compared to placebo groups: asthenia, muscle tightness, and increased alanine transaminase (ALT). The sponsor offers a serotonin syndrome as another alternative explanation. In the above Section 7.1.7.3.2, there were three patients (HMBR-100-1020; HMDU-219-3921; HMBR-402-4209) who had elevations of CPK > 3 times the ULN. It would be helpful to get more information such as body temperature, need for hospitalization after discharge and the time it took for the CPK to normalize to determine the safety concern regarding this observation.

Other findings included elevated heart rate, diastolic and systolic blood pressure. Also noted in this safety data base were statistically significant changes from baseline comparing duloxetine with placebo for the following laboratory values: alkaline phosphatase, AST, bicarbonate, chloride, cholesterol, phosphorus, urea nitrogen, uric acid, band, lymphocytes, and UA-specific.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

In the proposed labeling, the sponsor recommends starting dose for duloxetine is 60 mg without regard to meals. They go on to specify that some patients may need to be titrated to this dose by starting at 30 mg daily for 1 week, and some patients may benefit by raising the dose up to duloxetine 120 mg daily (titrating by increments of 30 mg once daily).

However, as with the MDD and diabetic peripheral neuropathy population tested, there was no evidence that doses > 60 mg/day have shown any additional benefit.

8.2 Drug-Drug Interactions

There was no new information regarding drug-drug interactions in this supplement.
As stated in the marketed labeling, duloxetine has the potential to inhibit CYP1A2, thus increasing the concentration of drugs such as fluvoxamine and quinolone antibiotics. Because of duloxetine's inhibition of CYP2D6, it may result in higher concentration of drugs such as paroxetine, fluoxetine, quinidine, tricyclic antidepressnats (e.g.nortriptyline, amitryptline, and imiprmaine), phenothiazines and Type 1C antiarrhythmics (e.g. propafenone, flecainide).
Please

8.3 Special Populations

There was no new information submitted in this supplement.

For **special populations**, the labeling states that duloxetine is not recommended for patients with end-stage renal disease, severe renal impairment, or hepatic insufficiency.

8.4 Pediatrics

There was no pediatric exposure in the GAD data base.

8.5 Advisory Committee Meeting

There have been no advisory committee meetings held to discuss duloxetine.

8.6 Literature Review

In the brief literature review that the sponsor submitted, there was no mention of any unknown adverse events.

8.7 Postmarketing Risk Management Plan

There have been many postmarketing reports regarding safety issues with duloxetine. Duloxetine is going to be the first drug used in the pilot study to assess the post marketing evaluation of new molecular entities. This will provide an opportunity to assess the safety profile since the marketing of duloxetine in 2004; there have been multiple post-marketing reports of concern including: liver injury, hyponatremia and SAIDH, allergic reactions (including anaphylactic shock) and life-threatening skin reactions [such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)].

It may also be important to assess if the liver injury risk listed as a "Precaution" rather than a "Warning" is sufficient, as there have been many liver injury cases seen post market in patients who drink alcohol while taking duloxetine.

9 OVERALL ASSESSMENT

9.1 Conclusions

The three placebo controlled studies all support the use of duloxetine in the treatment of GAD in adults. There are many safety concerns regarding duloxetine which can be discussed in labeling, and will be revisited when the post-market pilot review is completed.

9.2 Recommendation on Regulatory Action

It is recommended that duloxetine be approved for the indication of GAD with a maximum dose set at duloxetine 60 mg qd. The labeling could state that duloxetine 120 mg daily did not offer any beneficial treatment effects over 60 mg daily.

It is also recommended that the issue of QTc prolongation seen in the GAD population be reviewed by the FDA QTc committee to determine if any further studies are needed to clarify these findings.

Because of the numerous post marketing liver injury cases occurring in patients who are concomitantly drinking alcohol, it would be helpful to highlight this concern by putting liver injury risks in the "Warnings" section rather than in the "Precaution."

Please see the labeling section for further recommendations.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Duloxetine is the first drug to be assessed in the pilot study assessing the post marketing evaluation of new molecular entities.

9.3.2 Required Phase 4 Commitments

Given that GAD is generally a chronic condition, the sponsor needs to explore the effects of duloxetine with long term use.

9.3.3 Other Phase 4 Requests

The geriatric population was underrepresented in the GAD safety an efficacy data base; it is recommended that the sponsor further study this group with a design powered to assess efficacy and appropriately monitor safety for this population. If it appears that duloxetine is used in children with GAD, it would be prudent for the sponsor to formally study it's efficacy and safety in this population.

9.4 Labeling Review

The following are recommended labeling changes with line #s based on the sponsor's annotated labeling:

Under **Special Population**

- **[Lines 110- 119]** Nursing Mothers
  [The recommendations below are excerpts from the review by Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D. (12/17/06) in response to the sponsor's labeling supplement (1/23/06)]:

  The following is a correction of the sponsor's proposed Lines 110-119:

Nursing Mothers —

b(4)

Under **CLINCAL STUDIES**
Generalized Anxiety Disorder

- **[Lines 217-250]** This section needs to include the statement that "..There was no evidence that doses greater than 60 mg/day confer any additional benefit." Also it would be of helpful information to add the statistical finding that "

b(4)

Under **Precautions**

General

- **[Lines 382-416]** Hepatotoxicity

  This portion of the labeling was already negotiated with the sponsor; please refer to NDA Supplement Approval Letter dated 6/6/06.

It may also be important to assess if the liver injury risk listed as a "Precaution" rather than a "Warning" is sufficient, as there have been many liver injury cases seen post market in patients who drink alcohol while taking duloxetine.

- **Orthostatic Hypotension and Syncope**

[The following text was negotiated with the sponsor to insert precautions regarding orthostatic hypotension and syncope (see OND Safety review by Lourdes Villalba, M.D.:8/28/06) and accepted in the sponsor's labeling supplement of 10/4/06)]:

" — Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors (*see* CLINICAL PHARMACOLOGY, Drug-Drug Interactions, *and* PRECAUTIONS, Drug Interactions) and in patients taking duloxetine at doses above 60 mg daily. Consideration should be given to discontinuing duloxetine in patients who experience symptomatic orthostatic hypotension and/or syncope during duloxetine therapy."

- **[Lines 417-426] Effect on Blood Pressure**

In their labeling supplement of 10/4/06, the sponsor reverted back to the currently marketed labeling for this section; however, the proposed labeling in the GAD efficacy supplement is modified. It is noted, though, that the sponsor included the following wording in the 10/4/06 labeling supplement and it is recommended that this excerpt be reviewed by the Division of Clinical Pharmacology :

In a clinical pharmacology study designed to evaluate the effects of duloxetine on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg BID. At the highest 200 mg BID dose, the increase in mean pulse rate was 5.0-6.8 bpm and increases in mean blood pressure were 4.7-6.8 mm Hg (systolic) and 4.5-7 mm Hg (diastolic) up to 12 hours after dosing.

As a comment to the proposed labeling for the GAD submission, it is recommended that sponsor retain the statement that ".... [Lines 419-421] —— b(4)

It is also recommended that the Line 423-424 be removed: "There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure."

- **[Lines 427-435]** Activation of Mania/Hypomania

  The sponsor is attempting to present this precaution by fusing all data from all the placebo-controlled trial with duloxetine. It is recommended that the sponsor keep these indications separate, as a patient diagnosed with MDD (already showing evidence of a mood disorder) may have a very different risk than a patient experiencing GAD.

- **[Lines 436-443]** Seizures

  As with activation of Mania/Hypomania, it is unclear if patients with different diagnoses will have different risks for the development of seizures. As the labeling stands now, seizures were not observed in the placebo-controlled studies of diabetic peripheral neuropathy; when weighing risks/benefits, this many be important information for the clinician.

- Hyponatremia The sponsor inserted this topic in their labeling supplement of 10/4/06 as recommended by OND Safety review by Lourdes Villalba, M.D (9/5/06) to include as follows:

  "Hyponatremia — Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported and appeared to be reversible when Cymbalta was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted."

- **[Lines 447-454] Discontinuation of Treatment with Cymbalta**

  Please refer to section 7.1.12 for discussion of the events occurring with a statistical significance for the GAD population. If the sponsor chooses to fuse all of the placebo controlled trial, it is recommended that they also add "insomnia" to

this list [Lines 451-2]. It is also recommended that the following sentence be removed:

[Lines 453-454] " [redacted] " b(4)

- Use in Patients with Concomitant Illness

[Line 480] There was a QTc prolongation observed in the GAD population. The sponsor was able to do a statistical "correction" to make this finding less pronounced, but it is not a true statement that patients with GAD in the ' [redacted] ." b(4)

- **Further information regarding glucose control in patients with diabetic neuropathic pain**

The sponsor proposed labeling in their labeling supplement of 1/23/06. The review by the Safety Team, DPP/DNP is pending at the time of this review

TOPIC Recommended to be included in Precautions:

- **Serious Skin/Hypersensitivity Reaction**

[Recommendations based on considerations of post-marketing reports as reviewed by Oluchi Elekwachi, PharmD, MPH, Safety Evaluator in the Division of Drug Risk Evaluation, Office of Surveillance and Epidemiology (11/13/06)]

Dr. Elekwachi recommended that "Serious Skin/Hypersensitivity Reaction" be added to precautions, to inform prescribing physicians that serious allergic reactions (including anaphylactic shock) and life-threatening skin reactions [such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and/or toxic epidermal necrolysis (TEN)] have been reported in the post-market data base of duloxetine.

"Alerting health care professionals would be prudent, given the increased usage of duloxetine since its approval in 2004." (Elekwachi, 11/13/06)

Under the section **Information for Patients**

- **[Lines 657-663] Nursing Mothers (excerpt from Kavanaugh: 12/17/06) should be corrected as follows:**

Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended.

b(4)

- **[Lines 668-676] Geriatric Use**

  As recommended by Dr. Villalba (review of 8/15/06), the following excerpt should be added to the proposed labeling:

  "As with other antidepressants, CYMBALTA has been associated with cases of clinically significant hyponatremia (see Hyponatremia under PRECAUTIONS)."

Under the section Adverse Events Occurring at an Incidence of 2% or More Among Cymbalta-Treated Patients in Placebo-Controlled Trials

- **Generalized Anxiety Disorder**

  [Lines 745-6] It is recommended that ***"somnolence"*** be added to the list common events reported as reasons for discontinuation.

- **[Lines 821-858] Effects on Male and Female Sexual Function**

  It is recommended that there be an addition to this section reflecting data for the GAD population.

- **[Line 870] Vital Sign Changes**

  Please refer to recommended changes (above) Under **Precautions**: Effect on Blood Pressure (Lines 417-424).

- **[Line 889-891] Weight Changes**

  It is questionable if the sponsor can make claims regarding weight based on uncontrolled data.

- **[Lines 895-904] Electrocardiogram Changes**

  This section needs to be reviewed by a clinical pharmacology reviewer. Also, please refer to discussion for Use in Patients with Concomitant Illness (above).

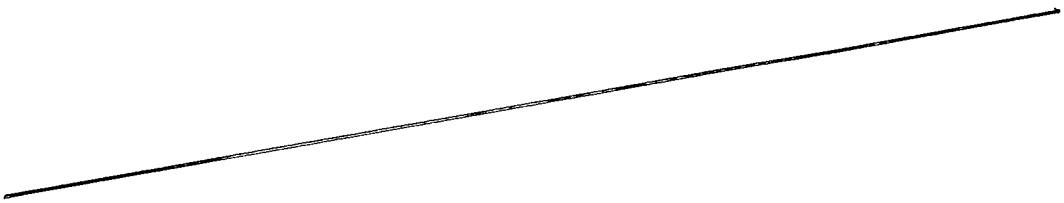
- **[Line 981] Post Marketing Spontaneous Reports**

  It is recommended that the sponsor delete the words '[redacted]' as most of these events have occurred more often than "rarely" in the post-marketing data base. b(4)

Under **DOSAGE AND ADMINISTRATION**

- **[Lines 1057-1059] Generalized Anxiety Disorder**

  Because these was no additional benefit to the dose of duloxetine 120 mg daily over duloxetine 60 mg in the GAD placebo-controlled studies, it is recommended that the following sentence be removed from the proposed labeling:



b(4)

  It is also recommended that the following sentence be added to this section:

  "There is no evidence that doses greater than 60 mg/day confer any additional benefits."

Under **Special Populations**

- **[Lines 1096-1100]** Dosage for Nursing Mothers
  (excerpt from Kavanaugh: 12/17/06):

  As recommended by in Dr. Kavanaugh's review (12/17/06), the following wording should be added to the proposed labeling:

Dosage for Nursing Mothers — Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended.

b(4)

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Summary Review of Study HMBR

Study HMBR

Investigators/Location

This is a multicenter study including 41 principal investigators in seven countries including Finland, France, Germany, South Africa, Spain, Sweden and the United States. Please refer to the sponsor's study report of HMBR Appendix 16.1.4 for a full listing of all principal and subinvestigators.

Study Plan

Objective(s)/Rationale

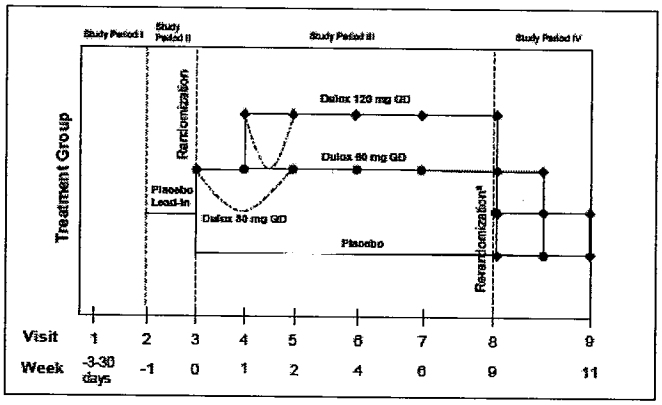
The primary objective of this study was to determine the safety and efficacy of duloxetine in treating adult patients diagnosed with generalized anxiety disorder.

Population

Patients chosen for this study were physically healthy adults diagnosed with generalized anxiety disorder according the DSM-IV criteria. Required for participation was a CGI-Severity score $\geq$ 4, a Covi Anxiety Scale (CAS) $\geq$ 9 score, no item in the Raskin Depression Scale (RDS) was > 3, and the CAS score > the RDS score. Excluded from the study were patients with a co-morbid DSM-IV Axis I diagnosis, alcohol/drug/caffeine abuse, or uncontrolled narrow angle glaucoma. Also excluded were patients with a lack of response to two or more adequate trials of antidepressants and/or benzodiazepines. Sexually active females were required to use medically accepted forms of birth control. Psychotherapy or other non-drug therapies were not allowed to be started within 6 weeks prior to enrollment.

Design

It is a 9 week, randomized, double blind, placebo- controlled study preceded by a placebo lead in, and concludes with a re-randomized two week drug taping phase (see sponsor's schematic of the entire study plan below). After the placebo lead in, patients were randomized to one of three groups: 1) duloxetine 60 mg qd, 2) duloxetine 120 mg qd, or 3) placebo. The following is the sponsor's schematic of the study design:



Patients were instructed to take medications in the morning without regard to food intake. Psychotropic medications were not permitted during the study. Zaleplon (up to 10 mg/da), zolpidem (up to 10 mg/day), zopiclone (up to 7.5 mg/day), or chloral hydrae (up to 1000 mg/day) were allowed to be used intermittently at bedtime, for a maximum of 3 times per week, and not more than 9 total does were allowed. Patients were encouraged to keep their caffeine or nicotine use consistent during the course of the study.

Screening included a history and physical, ECG, routine labs, pregnancy test (for sexually active females), urinalysis, and CYP2D6 and DRD4*7 genotyping. Vital signs (sitting) were monitored weekly; ECGs, weight, and laboratory analyses were obtained at the discontinuation of the study. The sponsor specifically added in the correspondence of 12/1/06 that a psychiatric evaluation was conducted at screening. The protocol states that the Mini-International Neuropsychiatric Interview (MINI) was used to establish the diagnosis and exclude other psychiatric illnesses at Visit 1. (The MINI is a standardized diagnostic interview based on DSM-IV criteria.). Patients with co-morbid social phobia or specific phobia may be allowed to participate in the study provided that GAD is the primary diagnosis.

Analysis Plan

The primary efficacy analysis was the mean change from baseline to endpoint in the HAMA total score for the double blind acute therapy phase of the study comparing the duloxetine 120 mg qd group with placebo. The treatment group differences were to be evaluated using the ANCOVA.

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 639 patients entered, 513 patients were screened and randomized into double-blind treatment. Reasons given for ineligibility included lost to follow-up (n=5), personal conflict (n=15), entry criteria not met (n=28), and physician decision (n=4).

Of the 168 patients randomized to the duloxetine 60 mg group, 33 (19.6%) patients discontinued during the acute phase. Of the 170 patients randomly assigned to the duloxetine 120 mg group, 46 (27.1%) patients discontinued; meanwhile of the 175 patients randomized to placebo, 45 (25.7%) discontinued. Thus, the completion rates were as follows: 1) duloxetine 60 mg: 80.4% (or n=135), 2) duloxetine 120 mg: 72.9% (n=124), and 3) placebo: 74.3% (n=130). Reasons for early withdrawal included the following: adverse events, lack of efficacy, subject decision, lost to follow up, protocol violation, physician decision, and entry criteria exclusion.

Table 10.1.1a Reasons for withdrawal during Study HMBR

Reasons for Withdrawal	Duloxetine 60 mg N=168	Duloxetine 120 mg N=170	Placebo N=175
Adverse events	19 (11.3%)	26 (15.3%)	45 (25.6%)
Lack of efficacy	3 (1.9)	6 (3.5)	23 (13.1)
Subject decision	4 (2.4)	7 (4.1)	9 (5.1)
Lost to follow up	4 (2.4)	3 (1.9)	4 (2.3)
Protocol violation	2 (1.2)	1 (0.6)	3 (1.7)
Physician decision	1 (0.6)	2 (1.2)	2 (1.1)
Entry criteria excusion	0	1 (0.6)	0
Total withdrawal Total completed	33 (19.6) 135 (80.4)	46 (27.1) 124 (72.9)	45 (25.7) 130 (74.3)

Demographics /Group Comparability

The majority of the patients in this study were Caucasian females comprised of 348 women (67.84) and 165 men (32.16) with a mean age of 43.78 years old (range 18 to 83 years). The population consisted of 505 (98.44%) Caucasians, 3 (0.58%) African-Americans, 1 (.19%) Hispanics, and 4 (0.7%) Asian. The sponsor did not find a statistically significant difference in baseline demographics between the placebo and duloxetine groups.

Concomitant Medications

Concomitant medications used most frequently included ibuprofen (67 patients or 13.1%) tylenol (59 patients or 11.5%), aspirin (27 or 5.3%), levothyroxine (23 patients or 4.5%), estradiol (15 patients or 2.9%), and ethinylestradiol/levonorgestrel (11 patients or 2.1%). There were no notable differences in the treatment group. Table 10.1.1b below is a breakdown of select

concomitant medications according to treatment group.

Table 10.1.1b Concomitant medications used by ≥ 2% of patients Study HMBR (adapted from sponsor's table HMBR.11.7 from study report HMBR)

Concomitant Therapy	PLACEBO (N=130) n	(%)	DLX60QD (N=135) n	(%)	DLX120QD (N=124) n	(%)
PATIENTS WITH >= 1 DRUG	84	(64.6)	67	(49.6)	67	(54.0)
PATIENTS WITH NO DRUGS	46	(35.4)	68	(50.4)	57	(46.0)
IBUPROFEN	10	(7.7)	11	(8.1)	14	(11.3)
PARACETAMOL	13	(10.0)	11	(8.1)	9	(7.3)
LEVOTHYROXINE SODIUM	6	(4.6)	4	(3.0)	6	(4.8)
ACETYLSALICYLIC ACID	4	(3.1)	6	(4.4)	2	(1.6)
ESTRADIOL	4	(3.1)	3	(2.2)	5	(4.0)
ETHINYLESTRADIOL/LEVONORGESTREL	3	(2.3)	2	(1.5)	4	(3.2)

Efficacy Results

For the primary efficacy variable, the sponsor reported a statistically significant difference at p= < 0.001 for LS means comparing both duloxetine treatment groups with placebo in the change from baseline of the HAMA Total Score. When comparing the duloxetine 60 mg with the 120 mg treatment group, there was no statistical difference observed (p=0.757).

The following sponsor table presents a summary of these findings.

Table 10.1.1c Study HMBR: HAMA Total Score Mean Change from Baseline to Endpoint (adapted from sponsor's table from HMBR Study Report Table HMBR.11.10)

HAMA Total Score

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1)PLACEBO	173	25.82	7.66	26.0	7.0	44.0	17.19	9.96	17.0	0.0	53.0	-8.62	9.17	-7.0	-38.0	12.0
2)DLX60QD	165	25.05	7.18	25.0	2.0	40.0	12.32	8.79	10.0	0.0	49.0	-12.73	9.79	-13.0	-32.0	18.0
3)DLX120QD	169	25.13	7.24	26.0	6.0	44.0	12.74	9.55	11.0	0.0	44.0	-12.39	10.10	-13.0	-33.0	24.0

Main Effects (Type III SS) — Raw Data

Therapy	F=13.82	df=2,475	p=<.001
Investigator	F=2.06	df=28,475	p=0.001

Least Squares Means for Change from Baseline

1)PLACEBO	-8.38	(SE= 0.67)
2)DLX60QD	-12.8	(SE= 0.68)
3)DLX120QD	-12.5	(SE= 0.67)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-4.38	Two-sided 95% CI :	(-6.23 , -2.54)	t=-4.68	p=<.001
DLX120QD - PLACEBO	diff=-4.09	Two-sided 95% CI :	(-5.92 , -2.26)	t=-4.39	p=<.001
DLX120QD - DLX60QD	diff= 0.29	Two-sided 95% CI :	(-1.56 , 2.14)	t= 0.31	p=0.757

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.
Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

Conclusions

The results from study support the claim that duloxetine is effective in the treatment of GAD in adults. There was no statistically significant difference observed when comparing the duloxetine 60 mg qd and the duloxetine 120 mg qd groups. It is also noted that the population studied had very few non-Caucasians enrolled.

10.1.2 Summary Review of HMDT

Study HMDT

Investigators/Location

This is a multicenter study including 28 principal investigators in the United States. Please refer to the sponsor's study report of HMDT Appendix 16.1.4 for a full listing of all principal and subinvestigators.

Study Plan

Objective(s)/Rationale

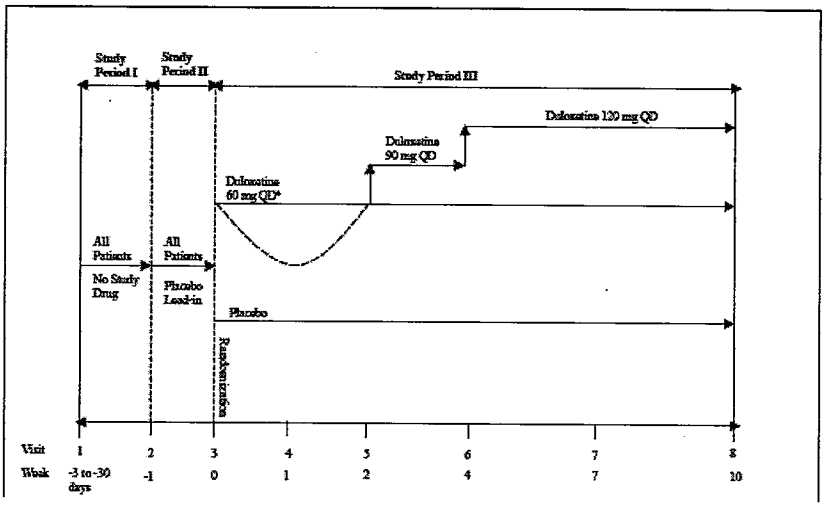
The primary objective of this study was to determine the safety and efficacy of duloxetine in treating adult patients old diagnosed with generalized anxiety disorder.

Population

Patients chosen for this study were physically healthy adults and diagnosed with generalized anxiety disorder according the DSM-IV criteria. Required for participation was a CGI-Severity score ≥ 4, a Covi Anxiety Scale (CAS) ≥ 9 score, no item in the Raskin Depression Scale (RDS) was > 3, and the CAS score > the RDS score. Excluded from the study were patients with a co-morbid DSM-IV Axis I diagnosis, alcohol/drug/caffeine abuse, or uncontrolled narrow angle glaucoma. Also excluded were patients with a lack of response to two or more adequate trials of antidepressants and/or benzodiazepines. Sexually active females were required to use medically accepted forms of birth control. Psychotherapy or other non-drug therapies were not allowed to be started with in 6 weeks prior to enrollment. Also excluded from the study were patients with a history of transcranial magnetic stimulation, seizures or psychosurgery or ECT with the past 12 months.

Design

This study was a 10 week, randomized, double blind, controlled study preceded by a placebo lead in., and concluded with a re-randomized two week drug taping phase After the placebo lead in, patients were randomized to one of two groups: 1) duloxetine (flexible dose 60-120 mg qd, or 2) placebo. Patients randomized to the duloxetine treatment group were required to tolerate a minimum of duloxetine 60 mg qd (achieved by week 5) and could be titrated to a maximum of 120 mg duloxetine if needed for efficacy and if tolerated. The following is the sponsor's design schematic:



Patients were instructed to take medications in the morning without regard to food intake. Psychotropic medications were not permitted during the study. Zaleplon (up to 10 mg/day), zolpidem (up to 10 mg/day), zopiclone (up to 7.5 mg/day), or chloral hydrate (up to 1000 mg/day) were allowed to be used intermittently at bedtime, for a maximum of 3 times per week, and not more than 9 total does were allowed. Patients were encouraged to keep their caffeine or nicotine use consistent during the course of the study.

Screening included a history and physical, vitals, ECG, routine labs, pregnancy test (for sexually active females), urinalysis, snd urine drug screen. Vital signs (sitting) were monitored weekly; ECGs, laboratory analyses, and weight were obtained at the discontinuation of the study.

Analysis Plan

The primary efficacy analysis was the mean change from baseline to endpoint in the HAMA total score for the double blind acute therapy phase of the study comparing the duloxetine 60-120 mg qd group with placebo. The treatment group differences were to be evaluated using the ANCOVA model.

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 515 patients entered, 327 patients were screened and randomized into double-blind treatment. Reasons given for ineligibility were not located in the study report.

Of the 168 patients randomized to the duloxetine 60-120 mg group, 75 (44.6%) patients discontinued during the acute phase; meanwhile of the 159 patients randomized to placebo, 50 (31.4%) discontinued. Thus, the completion rates were as follows: 1) duloxetine 60-120 mg: 55.4% (or n=93) and 2) placebo: 68.6% (n=109). Reasons for early withdrawal included the following: adverse events, lack of efficacy, subject decision, lost to follow up, protocol violation, and physician decision. As can be seen in Table 10.1.2a below, there is a higher rate of patients who discontinued to a adverse event in the duloxetine compared to placebo; this difference was shown to have a statistical significance (p=0.002).

Table 10.1.2a Reasons for withdrawal during Study HMBR

Reasons for Withdrawal	Duloxetine 60-120 mg N=168	Placebo N=159
Adverse events	34 (20.2%)	13 (8.2%)
Lack of efficacy	3 (1.8)	7 (4.4)
Subject decision	17 (10.1)	12 (7.5)
Lost to follow up	13 (7.7)	13 (8.2)
Protocol violation	3 (1.8)	1 (0.6)
Physician decision	5 (3)	4 (2.5)
Total withdrawal Total completed	75 (44.6) 93 (55.4)	50 (31.4) 109 (68.6)

Demographics /Group Comparability

The majority of the patients in this study were Caucasian females comprised of 202 women (61.77) and 125 men (38.23) with a mean age of 41.62 years old (range 19 to 77 years). The population consisted of 258 (78.9%) Caucasians, 41 (12.54%) African-Americans, 19 (5.81%) Hispanics, and 9 (9.75%) Asian. The sponsor did not find a statistically significant difference in baseline demographics between the placebo and duloxetine groups.

Concomitant Medications

Concomitant medications used most frequently included ibuprofen (67 patients or 20.5%), Tylenol (57 patients or 17.4%), aspirin (32 patients or 9.8%), and multivitamin

(ergocalciferol/ascorbic acid/folic acid/thiamine) n=67 patients or 20.5%. There were no notable differences in the treatment group. Table 10.1.2b below is a breakdown of select concomitant medications according to treatment group.

Table 10.1.2b Concomitant medications used by ≥ 5 % of patients Study HMDT (adapted from sponsor's table HMDT.11.6 from study report HMDT)

Concomitant Therapy	PLACEBO (N=159) n (%)	DLX60120 (N=168) n (%)	TOTAL (N=327) n (%)
PATIENTS WITH >= 1 DRUG	125 (78.6)	136 (81.0)	261 (79.8)
PATIENTS WITH NO DRUGS	34 (21.4)	32 (19.0)	66 (20.2)
IBUPROFEN	31 (19.5)	36 (21.4)	67 (20.5)
ERGOCALCIFEROL/ASCORBIC ACID/FOLIC ACID/THIAM	27 (17.0)	36 (21.4)	63 (19.3)
PARACETAMOL	26 (16.4)	31 (18.5)	57 (17.4)
ACETYLSALICYLIC ACID	14 (8.8)	18 (10.7)	32 (9.8)
ASCORBIC ACID	9 (5.7)	15 (8.9)	24 (7.3)

Efficacy Results

For the primary efficacy variable, the sponsor reported a statistically significant difference at p= 0.023 for LS means comparing both duloxetine treatment groups with placebo in the change from baseline of the HAMA Total Score.

The following sponsor table presents a summary of these findings.

Table 10.1.2c Study HMDT: HAMA Total Score Mean Change from Baseline to Endpoint (adapted from sponsor's table from HMDT Study Report Table HMDT.11.10)

HAMA Total Score

	Baseline					Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1)PLACEBO	158	23.49	7.91	23.0	3.0	46.0	17.00	10.24	17.0	0.0	46.0	-6.49	9.13	-5.0	-30.0	13.0
2)DLX60120	161	22.54	7.44	22.0	7.0	43.0	14.27	9.58	12.0	0.0	38.0	-8.27	9.56	-7.0	-32.0	17.0

Main Effects (Type III SS) Raw Data
Therapy F=5.19 df=1,295 p=0.023
Investigator F=1.51 df=21,295 p=0.073

Least Squares Means for Change from Baseline
1)PLACEBO -5.89 (SE= 0.70)
2)DLX60120 -8.12 (SE= 0.70)

Pairwise Comparison of LS Means
DLX60120 - PLACEBO diff=-2.23 Two-sided 95% CI : (-4.15 , -0.30) t=-2.28 p=0.023

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.
Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

Conclusions

The results from this study spport the claim that duloxetine is effective in the treatment of GAD in adults. It is also noted that the population studied included a low number of non-Caucasians.

10.1.3 Review Summary of Study HMDU

Study HMDU

Investigators/Location

This was a multicenter study including 40 principal investigators in the United States. Please refer to the sponsor's study report of HMBR Appendix 16.1.4 for a full listing of all principal and subinvestigators.

Study Plan

Objective(s)/Rationale

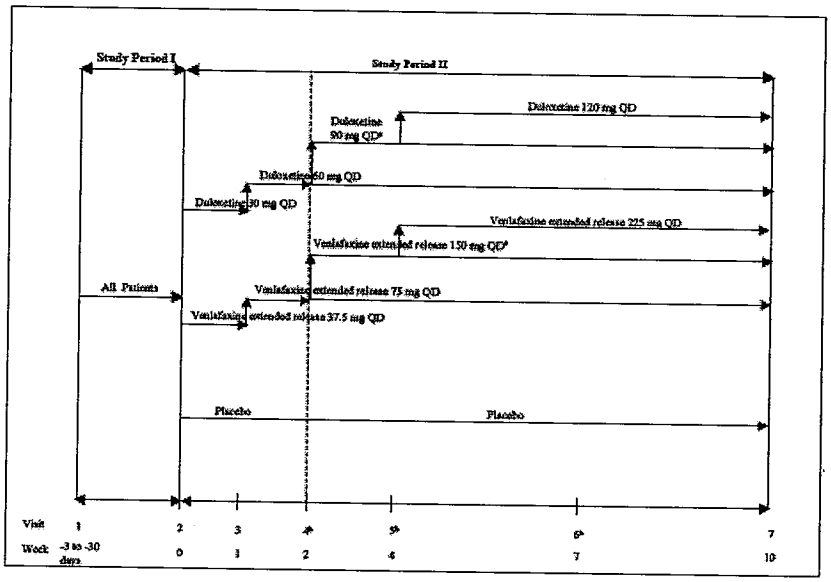
The primary objective of this study was to determine the safety and efficacy of duloxetine in treating adult patients diagnosed with generalized anxiety disorder.

Population

Patients chosen for this study were physically healthy adults and diagnosed with generalized anxiety disorder according the DSM-IV criteria. The sponsor specifically added in the correspondence of 12/1/06 that a psychiatric evaluation was conducted at screening. The protocol states that the Mini-International Neuropsychiatric Interview (MINI) was used to establish the diagnosis and exclude other psychiatric illnesses at Visit 1. (The MINI is a standardized diagnostic interview based on DSM-IV criteria.) Patients with co-morbid social phobia or specific phobia may be allowed to participate in the study provided that GAD is the primary diagnosis. Required for participation was a CGI-Severity score $\geq$ 4, a Covi Anxiety Scale (CAS) $\geq$ 9 score, no item in the Raskin Depression Scale (RDS) was > 3, the CAS score > the RDS score, and the Hospital Anxiety and Depression Scale (HADS) anxiety subscale score $\geq$10 at intake. Excluded from the study were patients with a co-morbid DSM-IV Axis I diagnosis, alcohol/drug/caffeine abuse, or uncontrolled narrow angle glaucoma. Also excluded were patients with a lack of response to two or more adequate trials of antidepressants and/or benzodiazepines. Sexually active females were required to use medically accepted forms of birth control. Psychotherapy or other non-drug therapies were not allowed to be started with in 6 weeks prior to enrollment.

Design

This study is a 10 week, randomized, double blind, placebo- and comparator-controlled study preceded by a placebo lead in, and concluded with a two week drug taping phase After the placebo lead in, patients were randomized to one of three groups: 1) duloxetine 60-120 mg qd (starting dose at 30 mg x 1 week), 2) venlafaxine 75-225 mg qd (starting dose at 37.5 mg x 1 week), or 3) placebo. The following is the sponsor's schematic of the study design:



Patients were instructed to take medications in the morning without regard to food intake. Psychotropic medications medications were not permitted during the study. Zaleplon (up to 10 mg/day), zolpidem (up to 10 mg/day), zopiclone (up to 7.5 mg/day), or chloral hydrae (up to 1000 mg/day) were allowed to be used intermittently at bedtime, for a maximum of 3 times per week, and not more than 9 total does were allowed. Patients were encouraged to keep their caffeine or nicotine use consistent during the course of the study.

Screening included a history and physical, ECG, routine labs, pregnancy test (for sexually active females), urinalysis, and urine drug screen. Vital signs (sitting) were monitored weekly; ECGs, weight and laboratory analyses were obtained at the discontinuation of the study.

Analysis Plan

The primary efficacy analysis is the mean change from baseline to endpoint in the HAMA total score for the double blind acute therapy phase of the study comparing the duloxetine 60-120 mg qd group with placebo. The treatment group differences were to be evaluated using the ANCOVA model.

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 707 patients entered, 487 patients were screened and randomized into double-blind treatment. Reasons given for ineligibility were not located in this submission.

Of the 487 patients randomized to the duloxetine 60-120 mg group, 74 (45.7%) patients discontinued during the acute phase. Of the 161 patients randomly assigned to the placebo group, 61 (37.9%) patients discontinued; meanwhile of the 164 patients randomized to the venlafaxine group, 62 (37.8%) discontinued. Thus, the completion rates were as follows: 1) duloxetine 60-120 mg: 54.3% (or n=88), 2) venlafaxine: 62.2% (n=100) and 3) placebo: 62.1% (n=99). Reasons for early withdrawal included the following: adverse events, lack of efficacy, subject decision, lost to follow up, protocol violation, physician decision, and sponsor decision.

Table 10.1.3a Reasons for withdrawal during Study HMDU

Reasons for Withdrawal	Duloxetine N=168	Venlafaxine N=164	Placebo N=161
Adverse events	23 (14.2%)	18 (11%)	3 (1.9%)
Lack of efficacy	2 (1.2)	2 (1.2)	6 (3.7)
Subject decision	18 (11.1)	20 (12.2)	20 (12.4)
Lost to follow up	25 (15.4)	17 (10.4)	26 (16.1)
Protocol violation	5 (3.1)	2 (1.2)	5 (3.1)
Physician decision	1 (0.6)	2 (1.2)	1 (0.6)
Sponsor decision	0	1 (0.6)	0
Total withdrawal Total completed	74 (45.7) 88 (54.3)	62 (37.8) 102 (62.2)	61 (37.9) 100 (62.1)

Demographics /Group Comparability

The majority of the patients in this study were Caucasian females comprised of 305 women (62.63%) and 182 men (37.37) with a mean age of 39.49 years old (range 18 to 83 years). The population consisted of 539 (69.75%) Caucasians, 78 (16.05 %) African-Americans, 56 (11.52%) Hispanics, 13 (2.47%) Asian, and 1 (0.21) Native American. The sponsor did not find a statistically significant difference in baseline demographics between the placebo and duloxetine groups.

Concomitant Medications

Concomitant medications used most frequently included ibuprofen (393 patients or 80.7%), Tylenol (96 patients or 19.7%), aspirin (50 or 10.5%), multivitamin (94 or 17.2%), Vit. C (28 patients or 5.7%), naproxen (28 patients or 5.7%), and calcium (26 patients or 5.3%). There were no notable differences in the treatment group. Table 10.1.3b below is a breakdown of select concomitant medications according to treatment group.

Table 10.1.3b Concomitant medications used by at least 5% of patients in Study HMDU (adapted from sponsor's table HMDU.11.6 from study report HMDU)

Concomitant Therapy	PLACEBO (N=161) n	(%)	DLX60120 (N=162) n	(%)	VEN75225 (N=164) n	(%)	Total (N=487) n	(%)	p-Value*
PATIENTS WITH >= 1 DRUG	131	(81.4)	128	(79.0)	134	(81.7)	393	(80.7)	.805
PATIENTS WITH NO DRUGS	30	(18.6)	34	(21.0)	30	(18.3)	94	(19.3)	.805
IBUPROFEN	48	(29.8)	43	(26.5)	42	(25.6)	133	(27.3)	.676
PARACETAMOL	36	(22.4)	30	(18.5)	30	(18.3)	96	(19.7)	.599
ERGOCALCIFEROL/ASCORBIC ACID/FOLIC ACID/THIAM	35	(21.7)	23	(14.2)	26	(15.9)	84	(17.2)	.177
ACETYLSALICYLIC ACID	16	(9.9)	16	(9.9)	19	(11.6)	51	(10.5)	.882
ASCORBIC ACID	13	(8.1)	12	(7.4)	3	(1.8)	28	(5.7)	.018
NAPROXEN SODIUM	10	(6.2)	10	(6.2)	8	(4.9)	28	(5.7)	.858
CALCIUM	12	(7.5)	6	(3.7)	8	(4.9)	26	(5.3)	.322

Efficacy Results

For the primary efficacy variable, the sponsor reported a statistically significant difference at p= 0.007 for LS means comparing both duloxetine treatment groups with placebo in the change from baseline of the HAMA Total Score. When comparing placebo and venlafaxine using the primary efficacy variable, a p-value of <0.001 was found. When comparing the duloxetine 60 mg with the 120 mg treatment group, there was no statistical difference observed (p=0.757).

The following sponsor table presents a summary of these findings.

Table 10.1.3c Study HMDU: HAMA Total Score Mean Change from Baseline to Endpoint (adapted from sponsor's Study Report HMDU Table HMDU.11.11

HAMA Total Score

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1)PLACEBO	158	24.98	5.82	24.0	8.0	41.0	16.06	9.29	16.0	0.0	42.0	-8.92	8.66	-9.0	-37.0	16.0
2)DLX60120	149	25.77	5.66	25.0	14.0	39.0	13.95	8.55	12.0	0.0	40.0	-11.82	8.95	-11.0	-35.0	19.0
3)VEN75225	159	24.92	5.48	24.0	8.0	40.0	12.90	8.95	10.0	0.0	40.0	-12.02	9.39	-12.0	-32.0	15.0

Main Effects (Type III SS) Raw Data

Therapy	F=6.54	df=2,434	p=0.002
Investigator	F=1.85	df=28,434	p=0.006

Least Squares Means for Change from Baseline

1)PLACEBO	-9.19	(SE= 0.67)
2)DLX60120	-11.8	(SE= 0.69)
3)VEN75225	-12.4	(SE= 0.67)

Pairwise Comparison of LS Means

DLX60120 - PLACEBO	diff=-2.59	Two-sided 95% CI : (-4.47 , -0.71)	t=-2.71	p=0.007
VEN75225 - PLACEBO	diff=-3.21	Two-sided 95% CI : (-5.05 , -1.37)	t=-3.42	p=<.001

Type III Sums of Squares from ANOVA: Model-Treatment,PINVID and Baseline.
Note: N-Number of patients with a baseline and at least one non-missing post-baseline data.

Conclusions

The results from this study support the claim that duloxetine is effective in the treatment of GAD in adults. The results also showed that the comparator control, venlafaxine, was also effective in treating this population when compared to placebo.

10.2 Efficacy Scales

Appendix 10.2.1 Primary efficacy variable for pivotal studies: HMBR, HMDU, and HMDT: Hamilton Anxiety Rating Scale (HAMA)

HAMILTON ANXIETY SCALE

INFORMATION NOT OBTAINED ☐ 93

Rate the patient using the complete description of the scores provided in the worksheet. Check only one box for each item.

1. **ANXIOUS MOOD:** Worries, anticipation of the worst, fearful anticipation, irritability

☐ 0
☐ 1
☐ 2
☐ 3
☐ 4

2. **TENSION**: Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feeling of restlessness, inability to relax

☐ 0
☐ 1
☐ 2
☐ 3
☐ 4

3. **FEARS**: Of dark, of strangers, of being alone, of animals, of traffic, of crowds

☐ 0
☐ 1
☐ 2
☐ 3
☐ 4

4. **INSOMNIA:** Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors

☐ 0
☐ 1
☐ 2
☐ 3
☐ 4

5. **INTELLECTUAL (COGNITIVE)**: Difficulty in concentration, poor memory

☐ 0
☐ 1
☐ 2
☐ 3
☐ 4

6. **DEPRESSED MOOD**: Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing

☐ 0
☐ 1
☐ 2
☐ 3
☐ 4

7. **SOMATIC (MUSCULAR)**: Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone

☐ 0
☐ 1
☐ 2
☐ 3
☐ 4

8. **SOMATIC (SENSORY)**: Tinnitus, blurring of vision, hot and cold flushes, feeling of weakness, pricking sensation

☐ 0
☐ 1
☐ 2
☐ 3
☐ 4

HAMILTON ANXIETY SCALE

9. **CARDIOVASCULAR SYMPTOMS:** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

☐ 0
☐ 1
☐ 2
☐ 3
☐ 4

10. **RESPIRATORY SYMPTOMS:** Pressure or constriction in chest, choking feelings, sighing, dyspnea

☐ 0
☐ 1
☐ 2
☐ 3
☐ 4

11. **GASTROINTESTINAL SYMPTOMS:** Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation

☐ 0
☐ 1
☐ 2
☐ 3
☐ 4

12. **GENITOURINARY SYMPTOMS:** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

☐ 0
☐ 1
☐ 2
☐ 3
☐ 4

13. **AUTONOMIC SYMPTOMS:** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair

☐ 0
☐ 1
☐ 2
☐ 3
☐ 4

14. **BEHAVIOR AT INTERVIEW:** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos

☐ 0
☐ 1
☐ 2
☐ 3
☐ 4

Evaluator's Initials _____
First Middle Last

(DNDE)

Total Score of Questions 1-14 _____

Appendix 10.2.2 Sheehan Disability Scale: Key secondary variable

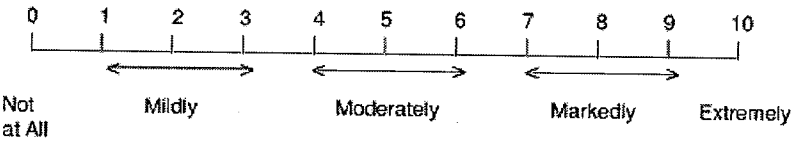
SHEEHAN DISABILITY SCALE

INFORMATION NOT OBTAINED ☐ 93

On each scale below, circle one number that best describes your situation now.

WORK* / SCHOOL

The symptoms have disrupted your work / school work:

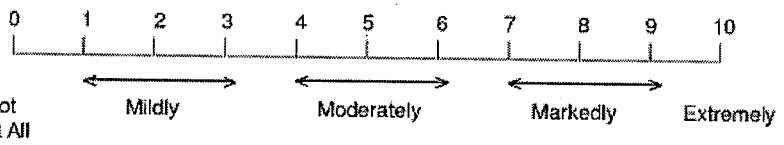


☐ 1 I have not worked / studied at all during the past week for reasons unrelated to the disorder.

*Work includes paid, unpaid volunteer work or training

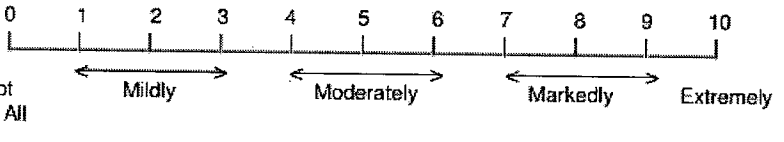
SOCIAL LIFE

The symptoms have disrupted your social life / leisure activities:



FAMILY LIFE / HOME RESPONSIBILITIES

The symptoms have disrupted your family life / home responsibilities:



10.3 Safety Tables

Table 10.3.1 ECG parameters; mean change from baseline for heart rate and other ECG intervals for the GAD safety data base. [compilation of multiple sponsor tables in the safety report]

Heart Rate

RUN

	Baseline					Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Duloxetine	447	68.0	10.9	67.0	45.0	107.0	70.52	11.07	69.0	43.0	106.0	2.51	10.18	3.0	-34.0	44.0
Placebo	343	68.5	10.8	67.0	39.0	105.0	67.20	10.99	66.0	42.0	112.0	-1.27	10.05	-1.0	-52.0	43.0

PR Interval

	Baseline					Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Duloxetine	447	155.3	21.0	153.0	106.0	268.0	152.14	21.22	150.0	104.0	288.0	-3.16	11.97	-3.0	-62.0	41.0
Placebo	343	157.1	22.6	155.0	106.0	246.0	156.09	24.37	154.0	0.0	257.0	-0.97	16.82	-1.0	-213.0	34.0

RR Interval

	Baseline					Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Duloxetine	447	904.7	144.2	895.5	560.7	1333.3	871.80	136.71	869.6	566.0	1395.3	-32.93	128.62	-30.0	-540.7	393.3
Placebo	343	898.8	146.7	895.5	571.4	1538.5	916.26	146.94	909.1	535.7	1428.6	17.42	125.92	13.6	-439.6	560.6

QRS Interval

	Baseline					Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Duloxetine	447	97.8	9.6	97.0	69.0	144.0	97.65	10.28	97.0	73.0	152.0	-0.11	7.96	0.0	-29.0	27.0
Placebo	343	98.9	11.5	98.0	75.0	156.0	99.55	11.63	98.0	73.0	155.0	0.69	8.65	1.0	-33.0	25.0

QT Interval

	Baseline					Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Duloxetine	447	387.8	27.9	387.0	317.0	484.0	384.98	27.87	384.0	311.0	470.0	-2.78	23.25	-2.0	-89.0	84.0
Placebo	343	391.3	29.8	390.0	307.0	509.0	393.55	29.92	391.0	329.0	498.0	2.24	24.51	2.0	-93.0	85.0

QTc Bazetts Interval

	Baseline					Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Duloxetine	447	409.7	20.5	409.0	343.0	476.0	414.25	20.68	414.0	357.0	474.0	4.54	18.20	5.0	-50.0	59.0
Placebo	343	414.9	22.8	413.0	351.0	520.0	413.21	22.07	414.0	360.0	483.0	-1.67	18.35	-2.0	-83.0	63.0

QTc Fredericias Interval

	Baseline					Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Duloxetine	447	402.0	17.9	401.6	350.2	452.4	404.00	18.38	403.3	351.0	471.6	2.03	14.76	2.2	-50.9	42.5
Placebo	343	406.5	20.4	404.6	348.8	492.7	406.25	19.75	405.6	353.8	473.3	-0.30	15.96	0.1	-60.5	42.8

QTc Regression Interval

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Duloxetine	447	405.6	18.3	404.1	346.8	461.7	408.84	18.78	408.2	353.7	473.4	3.24	15.70	3.9	-45.9	50.5
Placebo	343	410.4	20.9	409.0	352.3	505.1	409.52	20.14	409.0	356.9	478.1	-0.93	16.49	-0.4	-57.7	48.8

Table 10.3.2 Sponsor's table of QT values for all indication (unclear which studies are being assessed for each indication; for GAD this includes the three placebo controlled studies).

Table 2.7.4.1.13. Mean Baseline and Change in Electrocardiograms By Indication

Indication	HR			QT			QTcB			QTcF		
	Base	Change	p-Value	Base	Change	p-Value	Base	Change	p-Value	Base	Change	p-Value
GAD												
DLX (N=447)	68.01	+2.51	<.001	387.76	-2.78	.001	409.71	+4.54	<.001	401.97	+2.03	.047
PBO (N=343)	68.47	-1.27		387.76	+2.24		414.88	-1.67		406.55	-0.30	
MDD												
DLX (N=506)	68.93	+2.66	<.001	392.31	-6.52	.002	416.46	+0.71	.486	408.16	-1.79	.231
PBO (N=260)	69.01	+0.32		393.65	+0.23		417.76	+0.36		409.43	-0.12	
DPNP												
DLX (N=737)	72.59	+3.18	<.001	393.56	-7.24	<.001	428.39	+1.09	.657	416.42	-1.85	.010
PBO (N=316)	73.64	-0.61		390.39	+2.11		428.44	+0.81		415.37	+1.28	
Fibro												
DLX (N=93)	66.31	+6.33	<.001	400.73	-15.31	<.001	418.46	+2.24	.138	412.58	-3.95	.223
PBO (N=92)	67.08	+0.40		398.87	-2.30		418.33	-0.86		411.76	-1.29	
SUI												
DLX (N=801)	68.14	+3.46	<.001	399.59	-8.20	<.001	422.08	+2.07	.108	414.50	-1.48	<.001
PBO (N=828)	67.95	+0.68		400.40	+2.76		422.60	+0.69		415.11	+1.42	
Other UI												
DLX (N=140)	69.61	+3.87	<.001	396.60	-7.43	.001	423.93	+3.08	.072	414.68	-0.65	.643
PBO (N=140)	69.15	-0.68		397.91	+0.81		423.37	-0.89		414.73	-0.26	

Abbreviations: Base = baseline; DLX = duloxetine; DPNP = diabetic peripheral neuropathic pain; Fibro = fibromyalgia; GAD = general anxiety disorder; HR = heart rate; MDD = major depressive disorder; PBO = placebo; SUI = stress urinary incontinence; UI = urinary incontinence
Source: LOECGVH1

Table 10.3.3 ECG parameters corrected for the sponsor's concern regarding imbalance of baseline values for GAD safety data base [compilation of multiple sponsor table].

Heart Rate

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Duloxetine	447	68.0	10.9	67.0	45.0	107.0	70.52	11.07	69.0	43.0	106.0	2.51	10.18	3.0	-34.0	44.0
Placebo	343	68.5	10.8	67.0	39.0	105.0	67.20	10.99	66.0	42.0	112.0	-1.27	10.05	-1.0	-52.0	43.0

PR Interval

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Duloxetine	447	155.3	21.0	153.0	106.0	268.0	152.14	21.22	150.0	104.0	288.0	-3.16	11.97	-3.0	-62.0	41.0
Placebo	343	157.1	22.6	155.0	106.0	246.0	156.09	24.37	154.0	0.0	257.0	-0.97	16.82	-1.0	-213.0	34.0

RR Interval

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Duloxetine	447	904.7	144.2	895.5	560.7	1333.3	871.80	136.71	869.6	566.0	1395.3	-32.93	128.62	-30.0	-540.7	393.3
Placebo	343	898.8	146.7	895.5	571.4	1538.5	916.26	146.94	909.1	535.7	1428.6	17.42	125.92	13.6	-439.6	560.6

QRS Interval

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Duloxetine	447	97.8	9.6	97.0	69.0	144.0	97.65	10.28	97.0	73.0	152.0	-0.11	7.96	0.0	-29.0	27.0
Placebo	343	98.9	11.5	98.0	75.0	156.0	99.55	11.63	98.0	73.0	155.0	0.69	8.65	1.0	-33.0	25.0

QT Interval

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Duloxetine	447	387.8	27.9	387.0	317.0	484.0	384.98	27.87	384.0	311.0	470.0	-2.78	23.25	-2.0	-89.0	84.0
Placebo	343	391.3	29.8	390.0	307.0	509.0	393.55	29.92	391.0	329.0	498.0	2.24	24.51	2.0	-93.0	85.0

QTc Bazetts Interval

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Duloxetine	447	409.7	20.5	409.0	343.0	476.0	414.25	20.68	414.0	357.0	474.0	4.54	18.20	5.0	-50.0	59.0
Placebo	343	414.9	22.8	413.0	351.0	520.0	413.21	22.07	414.0	360.0	483.0	-1.67	18.35	-2.0	-83.0	63.0

QTc Fredericias Interval

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Duloxetine	447	402.0	17.9	401.6	350.2	452.4	404.00	18.38	403.3	351.0	471.6	2.03	14.76	2.2	-50.9	42.5
Placebo	343	406.5	20.4	404.6	348.8	492.7	406.25	19.75	405.6	353.8	473.3	-0.30	15.96	0.1	-60.5	42.8

QTc Regression Interval

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Duloxetine	447	405.6	18.3	404.1	346.8	461.7	408.84	18.78	408.2	353.7	473.4	3.24	15.70	3.9	-45.9	50.5
Placebo	343	410.4	20.9	409.0	352.3	505.1	409.52	20.14	409.0	356.9	478.1	-0.93	16.49	-0.4	-57.7	48.8

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/s/

Roberta Glass
1/29/2007 09:13:40 PM
MEDICAL OFFICER

Ni Aye Khin
1/30/2007 01:12:58 PM
MEDICAL OFFICER
I agree that this sNDA (duloxetine in GAD) be considered for approval; see memo to file for additional comments.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-427 / S-011

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
OFFICE OF NEW DRUG QUALITY ASSESSMENT

POST-MARKETING EVALUATION
CMC ASSESSMENT FORM

APPLICANT: LILLY	**NDA NUMBER: 021427**	**DOC TYPE: SE1**	**SEQ NUMBER: 011**	**SUBMISSION TYPE: ORIGINAL**
PROPRIETARY NAME: CYMBALTA(DULOXETINE HCL)20,30,40,6OMG	**ESTABLISHED NAME: DULOXETINE HCL**			
DOSAGE FORM: CAP	**STRENGTH/POTENCY: 20 MG, 30 MG, 40 MG, 60**	**PHARMACOLOGICAL CATEGORY:**		
LETTER DATE: 4/27/2006	**STAMP DATE: 4/27/2006**	**PDUFA GOAL DATE: 2/27/2007**	**SUBMISSION (CHECK ONE) FIRM: PA FINAL: PA**	
DIVISION IV BRANCH: VII	**OND DIVISION: 130**	**MANAGED BY: OND**	**PAL: Brown**	**MEDIA SUBMISSION: Electronic**
SUPPLEMENT PROVIDES FOR: the use of Cymbalta in the treatment of Generalized Anxiety Disorder.				
BUNDLED: No				
CHANGE CATEGORY: Efficacy Supplement				
LABELING INVOLVED: Yes - Both PI & Label	**PAT: No**	**COMPARABILITY PROTOCOL: No**	**PHASE 4 COMMITMENT:**	
REVIEW PATH: 3 - Moderate Risk - Minimal Review				
CONSULTS:				

JUSTIFICATION/COMMENTS: 1/17/2007 - BROWNJA

1. A Finding of No Significant Impact (FONSI) has been issued for Duloxetine Hydrochloride in support of NDA 21-427/S-011. The Center for Drug Evaluation and Research has concluded that the product can be used and disposed without any expected adverse environmental effects. Refer to the EA review by Raanan Bloom on 17-Jan-2007.

2. The applicant has referred to NDA 21-427 (Cymbalta) for information on the CMC for the drug substance and drug product to be used in the treatment for Generalized Anxiety Disorder (GAD). There are no CMC changes to the approved application to support the new indication. Lilly plans to utilize the 30 mg and 60 mg approved drug product for the treatment of GAD.

3. There are no CMC labeling changes.

4. From a CMC standpoint, this supplement can be approved.

PAL ACTION: Recommend Approval

BRANCH CHIEF: James Vidra

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Janice Brown
1/17/2007 01:26:33 PM
CHEMIST

Jim Vidra
1/17/2007 02:41:15 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-427 / S-011

ENVIRONMENTAL ASSESSMENT

REVIEW OF

ENVIRONMENTAL ASSESSMENT

for

Duloxetine Hydrochloride, delayed release 20, 30, 40 and 60 mg gelatin capsules

NDA 21-427
S-011

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products

Date Completed: January 16, 2007

EA Review – NDA 21-427 S-011 Duloxetine hydrochloride

EXECUTIVE SUMMARY – ENVIRONMENTAL ASSESSMENT

A Finding of No Significant Impact (FONSI) is recommended.
The information provided in this EA is substantially the same as provided in the original NDA

Duloxetine will enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW) and the terrestrial environment through land application of sludge containing adsorbed duloxetine. The Expected Introduction Concentration ($EIC_{aquatic}$) is 0.5 ppb assuming no metabolism and 78% removal due to adsorption to sludge. The Expected Environmental Concentration (EEC) in the aquatic environment is less than 0.05 ppb. It was calculated using 78% for removal on sludge and a dilution factor of 10 for wastewater effluents discharged into the receiving waters. Hydrolysis and photolysis are expected depletion mechanisms for duloxetine in the aquatic environment. A small amount of available sludge from POTW may be applied to soil. In this case, the maximum expected concentration of duloxetine in the top 15 cm of this soil is less than 5 ppb.

Environmental effect data were generated for aquatic species. It is unlikely that duloxetine represents a risk to the aquatic environment based on the available data.

	Duloxetine (free base) Effects Testing Data	
Activated sludge respiration rate	3 hour EC_{50} = 36,500 ppb	3 hour NOEC = 2000 ppb
Daphnia, acute	48 hour EC_{50} = 2400 ppb	48 hour NOEC = 1100 ppb
Rainbow trout	96 hour LC_{50} = 1300 ppb	96 hour NOEC = 450 ppb
Green Alga (Microbial Inhibition)	72 hour, biomass end point EC_{50} = 64 ppb NOEC = 11 ppb	72 hour, growth rate end point EC_{50} = 200 ppb NOEC = 29 ppb
Daphnia magna, (21 day test per OECD 211)	Full life Cycle Toxicity Test Lowest observed effect concentration (LOEC) = 37 ppb No observed effect concentration (NOEC) = 11 ppb Maximum allowable toxicant concentration (MATC) = 20 ppb Calculated 21-day survival ($EC_{survival}50$) = 450 ppb Calculated 21 day reproduction ($EC_{reproduction}50$) = 280 ppb	

No significant environmental impact is anticipated based on the data submitted.

Raanan Bloom, Ph.D. 1/16/2007

REVIEW of ENVIRONMENTAL ASSESSMENT

1. **Date:** April 27, 2006

2. **Name of applicant/petitioner:** Eli Lilly and Co.

   ADEQUATE

3. **Address:** Lilly Corporate Center, Indianapolis, IN 46285

   ADEQUATE

4. **Description of the proposed action:**

   a. **Requested Approval:**

   Duloxetine hydrochloride is be marketed as 20, 30, 40 and 60 mg gelatin capsules. Lilly filed NDA 21-427 pursuant to section 505(b) of the Federal, Food, Drug and Cosmetic Act for the use in treating major depressive disorder [redacted]. This supplement proposed the use of duloxetine hydrochloride as a treatment for generalized anxiety disorder. The EA was submitted pursuant to 21 CFR 25.31a (a), following the Center for Drug Evaluation and Research "Guidance for Industry for the Submission of an Evironmental Assessment" dated July 1998. b(4)

   ADEQUATE

   b. **Need for Action:**

   Duloxetine inhibits the uptake of serotonin and norepinephrine and lacks affinity for neurotransmitter receptors. It is proposed as a treatment for major depressive disorder stress urinary incontinence, and generalized anxiety disorder.

   ADEQUATE

   c. **Expected Locations of Use (Drug Product):**

   Duloxetine hydrochloride will be used primarily in the patient's home and workplace. It will be used throughout the U.S.

   ADEQUATE

d. Disposal Sites

Empty or partially empty packages containing duloxetine hydrochloride will be disposed by a community's solid waste management system, which may include landfills, incineration and recycling. Minimal quantities of unused drug may be disposed in the sewer system.

ADEQUATE

5. **Identification of chemicals that are the subject of the proposed action:**

a. Nomenclature
   i. Established Name (USAN): duloxetine hydrochloride
   ii. Proposed Trade Name: Cymbalta
   iii. Chemical Name: (+)-N-methyl-γ-(1-naphthalenyloxy)-2-thiophenepropanamine hydrochloride
b. Chemical Abstracts Service (CAS) Registration Number: 136434-34-9
c. Molecular Formula: $C_{18}H_{19}NOS \cdot HCl$
d. Molecular Weight: 333.88
e. Chemical Structure is in the EA, Volume 1.6, page 5

ADEQUATE

6. **Environmental Issue:**

a. Environmental Fate of Released Substances

i. Identification of Substances of Interest

The firm states that
humans extensively metabolize duloxetine hydrochloride. A clinical study (SAAZ) identified 2 predominant (>10%) human metabolites namely, 5-hydroxy-6-methoxy duloxetine (~ 17%) and 4-hydroxy duloxetine (~ 28%). These metabolites are excreted in the urine as either glucuronide or sulfate conjugates. Additionally, 4-hydroxy duloxetine is excreted in the feces in an unconjugated form. Four percent (4%) of the administered dose is excreted in the feces as the parent compound. Duloxetine hydrochloride is a valid environmental tracer for assessing fate and effects because the human metabolites are less active than the parent compound.

ADEQUATE

ii. Physical and Chemical Characterization

[redacted] conducted testing according to OECD Guidelines and in compliance with Good Laboratory Practice. Acceptable. b(4)

Duloxetine exists as a cation in the environmental pH range. (pKa = 9.34)

Its solubility at 20°C is enhanced at low pH ranging from 0.331 mg/L at pH 9 to 21.6 g/L at pH 4.

The log of the n-octanol / water partition coefficient (P_{ow}) is 0.781 at pH 4, 1.54 at pH 7 and 3.35 at pH 9. The probability for bioaccumulation is low because P_{ow} is less than 3.5.

The duloxetine will adsorb to particulate matter, humic acids, suspended sediments and sediments because P_{ow} is greater than 3.0.

K_d characterizes the adsorption of duloxetine to solids following incubation with sewage sludge for 4 hours. K_d as a function of the concentration of solids is 1166 (2500 mg solids per liter), 1269 (1250 mg solids per liter), 1197 (625 mg solids per liter) and 1731 (313 mg solids per liter). K_d normalized for the amount of organic carbon in the sludge gives K_{oc} 2893 to 4296. Sludge solids are expected to bind duloxetine tightly.

Vapor pressure was not determined because there is no weight loss when duloxetine is heated up to 160°C. Therefore, vaporization into the atmosphere is not expected.

ADEQUATE

iv. Environmental Depletion Mechanisms

[redacted] conducted testing according to OECD Guidelines and in compliance with Good Laboratory Practice. b(4)

Duloxetine hydrochloride hydrolyzes slowly at temperatures below 30°C (half-life 2.5 ± 1.0 months). Based on its UV absorption spectrum, photolysis is expected to be complete within 1 month. While neither depletion mechanism is rapid, both mechanisms provide an effective means for eliminating duloxetine hydrochloride in the environment.

Sorption to wastewater solids will reduce the amount of duloxetine that would otherwise be in POTW effluent and subsequently released into the environment. Duloxetine does not biodegrade significantly when incubated with activated sludge for 8 days. However, testing according to OECD Guideline 302A demonstrated the slow appearance (approximately 1.5 % after 8 days) of a biodegradation product.

ADEQUATE

iv. Environmental Concentration, aquatic

The total amount of duloxetine free base required in the peak market is not more than 100,000 kg/year. (Lilly provided this information in the public part of the EA)

The Expected Introduction Concentration ($EIC_{aquatic}$) of duloxetine (expressed as free base) entering into the external aquatic environment is NMT 2.3 ppb (0.0023 mg/L). This assumes no metabolism and no removal on solids in the POTW. Adjusting for sorption to solids, $EIC_{aquatic}$ = 0.5 ppb is predicted. This is the concentration used in the risk assessment for effects on microorganisms and acute toxicity studies.

Adjusting $EIC_{aquatic}$ for sorption on solids and 10 fold dilution when duloxetine is introduced into the aquatic compartment gives the Expected Environmental Concentration, EEC = 0.05 ppb. [EEC is sometimes called the Predicted Environmental Concentration (PEC).] This is the concentration used in the risk assessment for the chronic daphnia study. To be conservative, EICs and EEC were not adjusted for removal by photolysis or hydrolysis.

ADEQUATE

v. Environmental Concentration, continued, solids

Assuming no metabolism, the maximum expected introduction concentration (EIC) of duloxetine entering the publicly owned treatment works (POTW) is NMT 2.3 µgrams per liter (2.3 ppb). Following equilibration with 3 grams solids per liter, 78% or 1.8 µgrams are bound to the solids. Therefore, the concentration of duloxetine in sludge is 600 µgrams per kilogram.

A small amount of available sludge from publicly owned treatment works (POTW) may be applied to soil. If the maximum rate for applying sludge (biosolids containing approximately 3% nitrogen) to soil is 18 metric tons per 10,000 m^2, the concentration of duloxetine in the top 15 cm of the soil compartment is 4.8 ppb. This concentration is below the 100 ppb level stated in the 2000 VICH Guideline that triggers the need for terrestrial ecotoxicity testing for veterinary medicinal products.

ADEQUATE

vi. Summary

Lilly states that use and disposal of duloxetine after approval of this NDA will produce a negligible concentration of duloxetine and associated metabolites in the environment. Duloxetine will enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW). Duloxetine is not volatile and therefore will not enter the air compartment. Generally, only a fraction of sludge from POTWs would be applied to soil. Based on the $K_{d\ sludge}$ for duloxetine, sludge applied to cropland results in an insignificant concentration of duloxetine in the soil compartment.

Lilly states that duloxetine is not expected to be persistent in the environment due to its potential for degradation, hydrolysis and photolysis.

ADEQUATE

b. Environmental Effects

The environmental effect data were generated on aquatic species. _____ conducted testing according to OECD Guidelines and in compliance with Good Laboratory Practice. b(4)

Duloxetine (free base) Effects Testing Data

Activated sludge respiration rate	3 hour EC_{50} = 36,500 ppb	3 hour NOEC = 2000 ppb
Daphnia, acute	48 hour EC_{50} = 2400 ppb	48 hour NOEC = 1100 ppb
Rainbow trout	96 hour LC_{50} = 1300 ppb	96 hour NOEC = 450 ppb
Green Alga (Microbial Inhibition)	72 hour, biomass end point EC_{50} = 64 ppb NOEC = 11 ppb	72 hour, growth rate end point EC_{50} = 200 ppb NOEC = 29 ppb
Daphnia magna, (21 day test per OECD 211)	Full life Cycle Toxicity Test Lowest observed effect concentration (LOEC) = 37 ppb No observed effect concentration (NOEC) = 11 ppb Maximum allowable toxicant concentration (MATC) = 20 ppb Calculated 21-day survival ($EC_{survival}50$) = 450 ppb Calculated 21 day reproduction ($EC_{reproduction}50$) = 280 ppb	

i. Tier 1, Activated sludge respiration test (3 hour): This test was performed instead of a microbial inhibition test to assess the potential for disruption of the waste treatment processes. Results show that duloxetine hydrochloride does not inhibit sewage microorganisms significantly and therefore it is not expected to disrupt wastewater treatment process. The NOEC is 2000 ppb duloxetine free base.

ADEQUATE

ii. Tier 2, Ecotoxicity Testing (Daphnia Magna): EC_{50} at 48 hours is 2400 ppb; NOEC at 48 hours is 1100 ppb.

Tier 2, Ecotoxicity (Rainbow Trout): LC_{50} at 96 hours is 1300 ppb; NOEC at 96 hours is 450 ppb.

Tier 2, Ecotoxicity (Green Alga, pseudokirchneriella subcapitata): EC_{50} (biomass endpoint) at 72 hours is 64 ppb; NOEC (biomass endpoint) at 72 hours is 11 ppb.

ADEQUATE

iii. Tier 3, Chronic toxicity was determined using daphnia magna in a full life-cycle test with end-points of size, survival and reproduction. Reproduction is the most sensitive characteristic. EC_{50} = 280 ppb and the NOEC is 11 ppb.

Duloxetine is a selective serotonin re-uptake inhibitor (SSRI). Invertebrates appear to be sensitive to SSRIs. Indeed normal physiological events regulated by serotonin may be disrupted. Therefore, the chronic toxicity study was conducted with the invertebrate *Daphnia Magna* to probe for effects that would not be noticed easily in microbiological test systems

ADEQUATE

c. Summary

The firm concludes that introduction of the duloxetine to sewage treatment plants and into the environment through use and disposal of the product does not pose an environmental risk.

Duloxetine hydrochloride does not inhibit sewage microorganisms at concentrations expected in wastewater treatment plants and therefore it is not expected to disrupt wastewater treatment process.

The applicant performed acute toxicity testing in algae, daphnia magna and rainbow trout. The EC_{50} or LC_{50} to MEEC (maximum expected environmental concentration) ratio was greater than 100 and the NOEC was greater than MEEC for each study indicating that no effects would be expected.

Typically testing would end after the acute testing phase. However there is evidence in the literature that selective serotonin re-uptake inhibitors (SSRI) have sub-lethal reproductive effects on aquatic organisms. Duloxetine is a SSRI. Therefore, the chronic toxicity study described above was conducted with the invertebrate *Daphnia Magna* to probe for effects that would not be noticed easily in other test systems. The EC_{50} to MEEC ratio is greater than 10 and the NOEC is greater than the MEEC indicating that no effects would be expected.

A small amount of available sludge from publicly owned treatment works (POTW) may be applied to soil. If the maximum rate for applying sludge (biosolids containing approximately 3% nitrogen) to soil is 18 metric tons per 10,000 m^2, the concentration of duloxetine in the top 15 cm of the soil compartment is 4.8 ppb. This concentration is below the 100 ppb level stated in the 2000 VICH Guideline that triggers the need for terrestrial ecotoxicity testing for veterinary medicinal products. The applicant's focus on testing of aquatic species is appropriate.

Based on the data, a FONSI can be recommended.

ADEQUATE

7. Mitigation Measures

No adverse environmental effects have been identified.
No mitigation measures are required.

ADEQUATE

8. Alternatives to the proposed action

No potential effects have been identified for this proposed action.
No alternatives to the proposed action are required.

ADEQUATE

9. List of Preparers

Names and professional experience are provided in the non-confidential appendix to the EA.

ADEQUATE

10. References

References are provided.

ADEQUATE

11. Appendices

The EA contains data tables and report summaries in the non-confidential appendices. Three confidential appendices include information about metabolites, consultants and full study reports.

ADEQUATE

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/s/

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1/17/2007 10:30:43 AM
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1/22/2007 04:26:58 PM
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ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Duloxetine Hydrochloride, delayed release 20, 30, 40 and 60 mg gelatin capsules

NDA 21-427 S-011

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products

Date Completed: January 16, 2007

FINDING OF NO SIGNIFICANT IMPACT

NDA 21-427

Duloxetine Hydrochloride
Delayed release 20, 30, 40 and 60 mg gelatin capsules

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

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 its new drug application for Duloxetine Hydrochloride, delayed release 20, 30, 40 and 60 mg gelatin capsules, Eli Lilly & Co prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal from use of the product.

Duloxetine hydrochloride is a chemically synthesized drug that is indicated for the treatment of major depressive disorder, stress urinary incontinence and generalized anxiety disorder.

Duloxetine hydrochloride may enter the environment from patient use and disposal. It is expected to enter into the aquatic and terrestrial environments. Data indicate that the drug will adsorb to sludge and is susceptible to hydrolysis and photolysis. The toxicity of duloxetine hydrochloride to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at expected environmental concentrations.

Empty or partially empty packages will be disposed by a community's solid waste management system that may include landfills, incineration and recycling. Minimal quantities of the unused drug may be disposed in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

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Attachment: Environmental Assessment
Appended Electronic Signature Page

REVIEW OF

ENVIRONMENTAL ASSESSMENT

for

Duloxetine Hydrochloride, delayed release 20, 30, 40 and 60 mg gelatin capsules

NDA 21-427
S-011

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products

Date Completed: January 16, 2007

Environmental Assessment

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Environmental Assessment for the Use of Duloxetine Hydrochloride

Description of the Proposed Action

Requested Approval

Eli Lilly and Company has filed a supplement to NDA for duloxetine hydrochloride pursuant to the Federal Food, Drug, and Cosmetic Act. Duloxetine hydrochloride will be marketed as gelatin capsules (20, 30, 40, and 60 mg) packaged in opaque, white HDPE bottles and in 2 mm thick Aclar® blister packs with aluminum foil backing. An Environmental Assessment has been submitted pursuant to 21 CFR part 25.

An environmental assessment of duloxetine hydrochloride was submitted with the original NDA 21-427. The current proposed supplement is not categorically excluded from assessment of environmental impact as dictated in the Federal Register (July 29, 1997, 21 CFR 25.31) due to the estimated concentration at the point of entry into the aquatic environment and due to the predicted increased use of duloxetine hydrochloride in the United States with the proposed new indication. The use of duloxetine hydrochloride will result in one major pathway to the environment: sewage treatment facilities receiving influent from the general public. Wastes generated from production facilities are regulated by Federal, State and local environmental protection agencies and are not considered in this environmental assessment.

Need for Action

Duloxetine hydrochloride, a naphthyl ether amine, inhibits the uptake of serotonin and norepinephrine and lacks affinity for neurotransmitter receptors. In the current application, duloxetine hydrochloride is being proposed as a treatment for generalized anxiety disorder.

Locations of Use

The location of the use of duloxetine hydrochloride will be primarily in the patient's home and workplace. There is no reason to expect use to be concentrated in a particular geographic region.

Disposal Sites

Empty or partially empty packages containing duloxetine hydrochloride will typically be disposed of by a community's solid waste management system, which may include landfills, incineration, and recycling, although minimal quantities of unused drug could be disposed of in the sewer system.

Identification of the Chemical Substance

The identification of the chemical substance has not changed from that described in the original Environmental Assessment filed with NDA 21-427.

Nomenclature

Established Name (USAN):

(+)-N-methyl-γ-(1-naphthalenyloxy)-2-thiophenepropanamine hydrochloride

Brand/Proprietary Name/Tradename

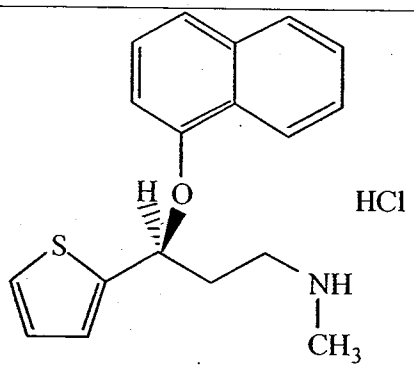
Cymbalta

Chemical Name (Uninverted)

(+)-(S)-N-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride

Chemical Abstracts Index Name (Inverted)

2-Thiophenepropanamine, N-methyl-γ-(1-naphthalenyloxy)-, hydrochloride, (S)-

Chemical Abstracts Service Number:	136434-34-9
Molecular Formula:	$C_{18}H_{19}NOS \cdot HCl$
Molecular Weight:	333.88
Structural Formula:	

Environmental Issues

Environmental Fate of Released Substances

The environmental fate of the released substance has not changed from that described in the original Environmental Assessment filed with NDA 21-427. Additionally, while the total use of duloxetine is expected to increase with the new indication, it will still be below the maximum total amount estimated in the original Environmental Assessment. Thus the expected environmental concentrations will remain the same.

Physical and Chemical Characterization

Duloxetine is extensively metabolized by humans; less than 10% of the administered dose is excreted as parent compound (Confidential Appendix O). The water solubility of duloxetine hydrochloride was determined to be 21.6, 2.74, and 0.331 g/L at pH 4, 7, and 9, respectively (Appendix B). The dissociation constant (pK_a) of duloxetine hydrochloride was determined to be 9.34 (Appendix C). At pH 4, 7, and 9 the log of the n-octanol/water partition coefficient (log P_{ow}) of duloxetine hydrochloride was determined to be 0.781, 1.54, and 3.35, respectively (Appendix D). The K_d was measured in sewage sludge and ranged between 1166 to 1731 (Appendix E). The K_d can be normalized for the amount of organic carbon in the sludge to calculate a K_{oc} of 2893 to 4296 for duloxetine hydrochloride.

Characteristic	Duloxetine Hydrochloride		
pK_a		9.34	
K_{oc}		2893 to 4296	
K_d		1166 to 1731	
	pH 4	pH 7	pH 9
Solubility g/L	21.6	2.74	0.331
Log P_{ow}	0.781	1.54	3.35

The log P_{ow} at pH 9 is less than 3.5 indicating that the probability for bioaccumulation is low. However, it is greater than 3 suggesting that sorption to biosolids will occur. Indeed, the K_{oc} confirms that duloxetine hydrochloride will sorb to biosolids in wastewater treatment plants.

Vapor pressure of duloxetine hydrochloride was not determined because thermogravimetric analysis of duloxetine hydrochloride showed no weight loss below 160°C. Above this temperature, decomposition and melting occurs. Thus, in the environment, release to the atmosphere is not expected.

Environmental Depletion Mechanisms

Duloxetine hydrochloride hydrolyzes slowly at temperatures lower than or equal to 30°C, with a half-life ranging from approximately 1.5 to 3.5 months at 30°C (Appendix F). Based on its ultraviolet-visible absorption spectrum, the theoretical phototransformation of duloxetine hydrochloride is estimated to be 100% within one month (Appendix G). Duloxetine hydrochloride was not significantly biodegraded when incubated with activated sewage sludge for 8 days (Appendix E). However, the presence of a small non-duloxetine radioactive peak indicates that there is potential for transformation of duloxetine. Thus, the primary depletion mechanisms of duloxetine hydrochloride from the aqueous environment are sorption, hydrolysis, and photolysis.

It is not expected that duloxetine will persist in the environment. Its extensive metabolism in humans and the presence of a transformation product in the biodegradation study suggest that duloxetine will be subjected to biodegradation. In addition, duloxetine will slowly hydrolyze in the aqueous environment.

Environmental Concentrations

Expected Introduction Concentration (EIC) in water

Even with the increase in use expected with the supplemental indication, the maximum amount used annually in the United States is still predicted to be less than 100,000 kg of duloxetine (free base). From this forecast, the expected introduction concentration (EIC) of duloxetine at the point of entry into the aquatic environment is calculated as follows:

$$EIC_{aquatic}\,(ppb) = \frac{100{,}000kg \times 1{,}000{,}000{,}000\mu g/kg}{1.214x10^{11}\,L/day \times 365days} = 2.3\mu g/L$$

where $1.214x10^{11}$ L/day is the volume of water entering publicly owned treatment works in the United States. This calculation assumes that all duloxetine produced in a year is used and enters the publicly owned treatment works system, drug product usage occurs throughout the United States in proportion to population and the amount of wastewater generated, and there is no human metabolism or microbial degradation.

This $EIC_{aquatic}$ can be adjusted for sorption to biosolids. The measured K_d for sorption to biosolids at 2.5 g/L was 1166. K_d is defined as:

$$K_d = \frac{\left(\frac{Duloxetine_{biosolids}}{Mass_{biosolids}}\right)}{\left(\frac{Duloxetine_{water}}{Mass_{water}}\right)}$$

where $Duloxetine_{water}$ and $Duloxetine_{biosolids}$ are the amounts of duloxetine in water and biosolids, respectively. If the total amount of duloxetine in the water and the sludge is $Duloxetine_{total}$, then the above equation can be rearranged to give:

$$Duloxetine_{water} = \frac{Duloxetine_{total} \times Mass_{water}}{Mass_{biosolids} \times \left(K_d + \frac{Mass_{water}}{Mass_{biosolids}}\right)}$$

A typical water treatment facility has a biosolids concentration in the aerator basin of 3 to 6 g/L (Metcalf & Eddy, 1991). Using the more conservative number, in one liter of water, $Duloxetine_{total}$ is 2.3 µg, $Mass_{water}$ is 1000 g (or 1000 mL) and $Mass_{biosolids}$ is 3 g. Solving for $Duloxetine_{water}$, the expected introduction concentration (EIC) in the aqueous phase adjusted for sorption to solids is:

$$EIC_{aquatic} = 0.5\mu g / L$$

Expected Environmental Concentration (EEC) in water

The Expected Environmental Concentration, EEC, can be calculated for the aquatic environment after consideration of dilution of treatment facility effluent by receiving waters. Based on dilution factors for treatment facilities available from the EPA, a dilution factor of 10 is appropriate. This concentration is considered for long-term exposure scenarios.

$$EEC_{aquatic\,(afterdilution)} = 0.05\mu g / L$$

Expected Introduction Concentration (EIC) in solids

It is also possible to determine the amount of duloxetine bound to the biosolids in a wastewater facility. The total duloxetine in one liter is 2.3 µg so in this case, the amount that must be sorbed to 3 g of biosolids is 1.8 µg. Thus:

$$EIC_{biosolids} = 600\mu g / kg$$

The residence time for sludge in wastewater facilities is 5 to 10 days. Appendix E describes a biodegradation study with duloxetine hydrochloride in which it was observed that after 8 days in contact with sludge, at least one degradation product of duloxetine was detected. The lag time to detection of a degradation product may indicate that microorganisms must become adapted in order to use duloxetine as a food source. In a wastewater treatment plant, it is assumed that the duloxetine concentration will be constant and thus the microorganisms will be continually exposed to duloxetine. This could result in greater biodegradation than observed in the study described in

Appendix E. Therefore, it is not unreasonable to assume that, in a wastewater facility, some degradation of duloxetine will occur.

Biosolids from treatment facilities are often applied to land as fertilizer and the majority of the application is to cropland. The rate of application is limited by the quantity of pollutants in the biosolids and by the nitrogen concentration. The total amount of nitrogen in biosolids ranges from 3 to 8% on a dry weight basis (Sullivan, 1998). The total nitrogen includes ammonium nitrogen and organic nitrogen. Ammonium nitrogen is immediately available for crop use but is also susceptible to loss through volatilization upon application. The organic nitrogen is available following mineralization by soil microbes. For this assessment it is assumed that all of the nitrogen is essentially available to the crops. Therefore, the least amount of nitrogen in biosolids would be 3% on a dry weight basis. Corn silage utilizes a maximum rate of nitrogen at 480 pounds/acre (539 kg/ha, Hammond et al., 1994). Using this application rate of nitrogen, a maximum rate of application of biosolids to agricultural land can be calculated.

$$\frac{539\text{kg}_{\text{Nitrogen}}}{\text{ha}} \times \frac{100\text{kg}_{\text{biosolids}}}{3\text{kg}_{\text{Nitrogen}}} = 17{,}967\text{kg}_{\text{biosolids}}/\text{ha} = 18\text{metrictons}_{\text{biosolids}}/\text{ha}$$

An incorporation depth of 15 cm into the top layer is typical in land application of biosolids (EPA, 1993). Assuming that the mass of soil is 1500 kg/m^3, the concentration of duloxetine in the soil after application of biosolids with 600 µg duloxetine/kg concentration is estimated to be:

$$\frac{18{,}000\text{kg}_{\text{biosolids}} \times 600\mu\text{g}_{\text{duloxetine}}/\text{kg}_{\text{biosolids}}}{10{,}000\text{m}^2 \times 0.15\text{m} \times 1500\text{kg}_{\text{soil}}/\text{m}^3} = 4.8\mu\text{g}_{\text{duloxetine}}/\text{kg}_{\text{soil}}$$

Summary

Duloxetine hydrochloride will enter the environment through its use by the general population. While human metabolism of duloxetine is extensive, estimations of concentrations of duloxetine in the environment were calculated based on total elimination as the parent compound. The Expected Introduction Concentration in the aqueous environment ($EIC_{aquatic}$) could be as high as 2.3 µg/L. The primary depletion mechanism of duloxetine from the aqueous environment is sorption to biosolids at water treatment facilities. Consideration of this depletion mechanism is used to calculate an adjusted $EIC_{aquatic}$ of 0.5 µg/L. The concentration in biosolids could be as high as 600 µg/kg. If biosolids are applied to land, then duloxetine may enter the terrestrial environment at a concentration in the soil ($EIC_{terrestrial}$) of 4.8 µg/kg. Duloxetine is not expected to volatilize and therefore will not enter the atmospheric environment. Duloxetine is not expected to be persistent in the environment due to its potential for degradation.

Environmental Effects of Released Substances

The environmental effects of duloxetine hydrochloride in aquatic organisms were investigated in a battery of toxicity studies conducted according to OECD guidelines. Since the original Environmental Assessment was submitted with NDA 21-427, an additional toxicity study has been conducted in earthworms. The results of all the toxicity studies are summarized below.

Microbial Inhibition (Tier One)

The effect of duloxetine hydrochloride on sewage microorganisms was tested by incubating activated sludge with duloxetine for 3 hours (Appendix H). The endpoint measured was respiration rate. The no-observed-effect concentration (NOEC) was 2 mg/L and the EC50 was determined to be 36.5 mg/L (expressed as duloxetine free base).

Fish Acute Toxicity (Tier Two)

The acute toxicity of duloxetine hydrochloride to rainbow trout was determined in juvenile fish following exposure to the compound for 96 hours (Appendix I). The endpoint measured was mortality. The NOEC was 0.45 mg/L and the 96-hour LC50 was estimated to be 1.3 mg/L (expressed as duloxetine free base).

Invertebrate Acute Toxicity (Tier Two)

The acute toxicity of duloxetine hydrochloride to *Daphnia magna* was determined following exposure to the compound for 48 hours (Appendix J). The endpoint measured was immobilization. The NOEC was determined to be 1.1 mg/L and the 48-hour EC50 was estimated to be 2.4 mg/L (expressed as duloxetine free base).

Algal Toxicity (Tier Two)

The acute toxicity of duloxetine hydrochloride to green algae was determined using the species *Psuedokirchneriella subcapitata* (Appendix K). The algal cells were exposed for 72 hours and the endpoints measured were inhibition of biomass and average growth rate. Biomass, the area under the growth curve, was sensitive to duloxetine with a 72-hour EC50 of 0.064 mg/L and a NOEC of 0.011 mg/L (expressed as duloxetine free base).

Earthworm Toxicity (Tier Two)

The acute toxicity of duloxetine hydrochloride to *Eisenia fetida* was determined following exposure to the compound incorporated in an artificial soil for 14 days (Appendix L). The endpoints measured were mortality and growth (weight change). The NOEC was determined to be 1000 mg/kg (the highest concentration tested) and the 14-day LC50 was > 1000 mg/kg (expressed as duloxetine free base).

Chronic Toxicity (Tier Three)

The chronic toxicity of duloxetine hydrochloride was determined using *Daphnia magna* in a full life-cycle test with endpoints of size, survival, and reproduction (Appendix M). Along with body length, the most sensitive endpoint in the study was reproduction. The EC50 and NOEC values of 0.28 mg/L and 0.011 mg/L (expressed as duloxetine free base), respectively, were determined.

Risk Assessment

To assess the environmental risk of duloxetine in the environment, the median effect concentration was compared to the Maximum Expected Environmental Concentration, or MEEC. To protect all species, the quotient of the two numbers (the Assessment Factor) must be above 1000 for Tier One screening, above 100 for Tier Two, and above 10 for Tier Three screening as suggested by guidance from the FDA.

Effects Concentrations compared to expected environmental concentrations.

Aquatic Environment					
Species	NOEC (µg/L free base)	LC50 or EC50 (µg/L free base)	MEEC (µg/L free base)	LC50 or EC50 ÷ MEEC	Required Assessment Factor
Sewage microorganisms (3 hours)	2000	36,500	0.5	73,000	≥1000
Rainbow trout (96 hours)	450	1300	0.5	2600	≥100
Daphnia magna (48 hours)	1100	2400	0.5	4800	≥100
Pseudokirchneriella subcapitata (72 hours)	11	64	0.5	128	≥100
Daphnia magna (21 days)	11	280	0.05*	5600	≥10
Terrestrial Environment					
Species	NOEC (µg/kg free base)	LC50 (µg/kg free base)	MEEC (µg/kg free base)	LC50 ÷ MEEC	Required Assessment Factor
Eisenia fetida (14 days)	1000000	>1000000	4.8	>208333	≥100

*Note: for chronic exposure a dilution factor of 10 was utilized.

The calculated assessment factors in all cases are greater than the required factors and in no case were sublethal effects observed at concentrations equal to the MEEC. These results indicate that duloxetine release to sewage treatment plants and the environment does not pose an environmental risk.

Other Issues

Effects of Serotonin Reuptake Inhibitors on Aquatic Organisms

There is evidence in the literature that serotonin reuptake inhibitors can have sublethal effects on fish. Many studies have used selective serotonin reuptake inhibitors (SSRIs) as tools to probe the normal physiological role of serotonin in aquatic organisms. For example, Khan and Thomas (1992) demonstrated that fluoxetine (a potent SSRI) itself had no effect on the release of gonadotropin or on gonadotropin releasing hormone's stimulation of gonadotropin in Atlantic croaker (10 mg/kg by injection). With co-administration of serotonin by injection, 10 mg/kg fluoxetine did potentiate serotonin's increase of gonadotropin releasing hormone's stimulation of gonadotropin. In goldfish, as well, injected fluoxetine had no effect on gonadotropin levels itself, but did potentiate the effect of serotonin (Somoza et al., 1988). Foran et al. (2004) reported, however, that exposure to low levels of fluoxetine in water (nominally 0.1 to 5 µg/L) had no effect on reproductive endpoints (fecundity, fertilization, hatching response) in medaka (*Oryzias latipes*).

SSRIs can also have sublethal effects on aquatic invertebrate species. Fluoxetine has been shown to increase gonadal development in crustaceans with injections of 15 mg/kg in crayfish (Kulkarni et al., 1992) and about 18 mg/kg in crabs (Sarojini, 1993). Bivalves appear to be very sensitive to the effects of fluoxetine and other SSRIs on physiological endpoints. Ram et al. (1993) showed that serotonin (in water or by injection) induces zebra mussels to spawn within hours. Fong (1998) demonstrated that 5 µM (1.5 mg/L) fluoxetine in water caused spawning in 100% of male mussels while 0.05 µM (0.015 mg/L) was the lowest effective concentration and induced 20% of male mussels to spawn. Fluoxetine has been reported to have reproductive effects in cladocerans. Flaherty and Dodson (2005) reported increased fecundity in *Daphnia magna* following chronic exposure to 0.036 mg/L fluoxetine. Fecundity was slightly (<10% compared to control) increased at 0.056 mg/L fluoxetine and decreased at concentrations of 0.11 mg/L and greater in *Ceriodaphnia dubia* (Brooks et al. 2003). Henry et al. (2004) reported that concentrations of fluoxetine greater than 0.089 mg/L decreased *C. dubia* fecundity.

Like fluoxetine, duloxetine also has serotonin reuptake inhibitory activity. In a chronic toxicity study with *D. magna*, both body length and reproduction were affected by duloxetine exposure as summarized in this assessment. The NOEC for both body length and reproduction was 0.011 mg/L; fecundity was reduced at higher concentrations. This NOEC concentration for duloxetine in *D. magna* is more than 20 times greater than the maximum concentration of duloxetine expected to be discharged into surface water.

Potential Effects on Humans

If a human were to drink two liters of surface water at the maximum EEC of 0.05 µg/L duloxetine, the dose would be 0.1 µg. This dose would be at least 200,000 times less than the therapeutic dose of duloxetine. Thus, it is not expected that humans will be adversely affected by environmental concentrations of duloxetine.

Summary

Duloxetine and related metabolites in the environment originate from wastewater facilities. In wastewater facilities, duloxetine is expected to partition to the solids resulting in a reduction of the aqueous concentration. The expected duloxetine environmental concentration in water is not expected to affect aquatic organisms based on the toxicity of duloxetine to fish, invertebrates and algae. Duloxetine is not expected to persist in the aquatic environment because it is subject to degradation, hydrolysis, and photolysis. The maximum concentration of duloxetine expected in soil resulting from agricultural land application of biosolids is not expected to affect terrestrial organisms based on the lack of toxicity of duloxetine to earthworms. The amount of duloxetine that humans could be exposed to by drinking surface water with the maximum expected environmental concentration of duloxetine would be substantially less than the therapeutic dose range. In summary, no adverse environmental effects have been identified from the use of duloxetine in the treatment of human populations.

Mitigation Measures

As no adverse environmental effects have been identified in this environmental assessment from the use of duloxetine in the treatment of major depressive disorder and generalized anxiety disorder, no mitigation measures are needed. This action has no known effects on endangered or threatened species or historic properties.

Alternatives to the Proposed Action

As no adverse environmental effects have been identified from the use of duloxetine in the treatment of major depressive disorder and generalized anxiety disorder, there is no need for alternatives to the proposed action.

List of Preparers

Authors

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See Appendix N for curriculum vitae

Consulting Agencies

See Confidential Appendix P for contract testing laboratories

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Nonconfidential Appendices

Appendix A: Duloxetine Data Summary Table

DULOXETINE DATA SUMMARY TABLE	
PHYSICAL/CHEMICAL CHARACTERIZATION	
Water Solubility	At pH 4 21.6 g/L At pH 7 2.74 g/L At pH 9 0.331 g/L
Dissociation Constant	$pK_a = 9.34$
Log Octanol/Water Partition Coefficient	Log P_{ow} At pH 4 0.781 At pH 7 1.54 At pH 9 3.35
Vapor Pressure or Henry's Law Constant	Not determined, assumed to be nonvolatile. Thermogravimetric analysis indicates decomposition and melting do not occur until 160°C.
Sorption/Desorption (K_{OC})	2893 to 4296

DEPLETION MECHANISMS	
Hydrolysis	Half life at temperatures equal to or lower than 30°C is 1.5 to 3.5 months
Aerobic Biodegradation	No significant degradation in 8 days. Small radioactive degradation product indicates eventual degradation.
Soil Biodegradation	Not determined
Photolysis	Theoretical phototransformation is 100% loss within one month in pH 4, 7 and 9 aqueous buffers.
Metabolism	Human metabolism is extensive, <10% excreted as parent compound.

ENVIRONMENTAL EFFECTS	
Microbial Inhibition	EC50 36.5 ppm NOEC 2 ppm
Acute Toxicity	*Daphnia magna* (48 hr) EC50: 2.4 ppm NOEC: 1.1 ppm *Oncorhynchus mykiss* (96 hr) EC50: 1.3 ppm NOEC: 0.45 ppm *Pseudokirchneriella subcapitata* (72 hr) $EC_{biomass}50$: 0.064 ppm $NOEC_{biomass}$: 0.011 ppm $EC_{growthrate}50$: 0.20 ppm $NOEC_{growthrate}$: 0.029 ppm *Eisenia fetida* (14 days) LC50: >1000 mg/kg NOEC: 1000 mg/kg
Chronic Toxicity	Full Life-Cycle Toxicity Test with *Daphnia magna* (21 days) LOEC: 0.037 ppm NOEC: 0.011 ppm MATC: 0.020 ppm $EC_{survival}50$: 0.45 ppm $EC_{reproduction}50$: 0.28 ppm

Appendix B: Report Summary - Study #: 1982.6114

Report Title: Duloxetine Hydrochloride - Determination of the Water Solubility of a Test Substance Following OECD Guideline 105

Study #: 1982.6114

Study date: June 2001

Methods:

The aqueous solubility of duloxetine hydrochloride was determined in pH 4, 7, and 9 aqueous buffers. Duloxetine hydochloride was added to 250 mL round bottomed flasks containing 100 mL of the buffer solutions. Test samples were agitated on a shaker table in a 30°C environmental chamber for equilibration periods of 24, 48 or 72 hours. After the equilibration period, the flasks were moved to an environmental chamber at 20°C for 24 hours with continued shaking. Duplicate samples were taken from the flasks and centrifuged at 25,848 g for 20 minutes. The supernatants were analyzed for duloxetine by HPLC.

Results:

The length of the equilibration time at 30°C did not affect the water solubility. Solubility decreased with increasing pH.

	Mean water solubility of duloxetine hydrochloride at 20°C (g/L)
pH 4	21.6
pH 7	2.74
pH 9	0.331

Appendix C: Report Summary - Study #: 1982.6115

Report Title: Duloxetine Hydrochloride - Determination of the Dissociation Constant for a Test Substance Following OECD Guideline 112

Study #: 1982.6115

Study date: June 2001

Methods:

The dissociation constant of duloxetine was determined at 20°C by a titration method using a Brinkman Titrino Workcell Version 4.0, Metrohm titrator. Two concentrations of duloxetine hydrochloride were prepared in CO_2-free water: 2.98 mM and 0.596 mM. The 2.98 mM solution was titrated with 0.150 mL aliquots of 0.1 M hydrochloric acid. The 0.596 mM solution was titrated with 0.020 mL aliquots of 0.1 M sodium hydroxide. The software program recorded the cumulative milliliters added and the resulting pH after each addition.

Results:

The dissociation constant (pK_a) was determined from the titration curve with 0.1 M sodium hydroxide. Titration with 0.1 M hydrochloric acid did not result in a titration curve. The mean pK_a for duloxetine hydrochloride was determined to be 9.34 at 20°C.

Appendix D: Report Summary - Study #: 1982.6127

Report Title: Duloxetine Hydrochloride – Determining the Partitioning Coefficient (n-Octanol/Water) of a Test Substance by the Flask-Shaking Method Following OECD Guideline 107

Study #: 1982.6127

Study date: June 2001

Methods:

The octanol/water partition coefficient (P_{ow}) of duloxetine hydrochloride was determined at pH 4, 7, and 9. A stock concentration of 201 mg/L duloxetine hydrochloride was prepared in buffer-saturated n-octanol. Solutions were prepared in duplicate for each pH using the volume ratios of 1:16, 1:8, and 1:4 of n-octanol-saturated buffer to duloxetine n-octanol stock. The mixtures were placed in centrifuge tubes with Teflon®-lined caps and rotated for five minutes at 20°C, centrifuged and re-equilibrated. Each phase was then analyzed by HPLC.

Results:

The partition coefficients were dependent on pH but independent of concentration.

	Mean P_{ow} (range)	Log P_{ow}
pH 4	6.05 (5.76 to 6.39)	0.781
pH 7	34.7 (33.2 to 36.3)	1.54
pH 9	2250 (2110 to 2320)	3.35

Appendix E: Report Summary - Study #: 1982.6123

Report Title: Duloxetine hydrochloride - Determination of the Inherent Biodegradability and Adsorption of a Test Substance by the SCAS Test, Modified from OECD Guideline 302A

Study #: 1982.6123

Study date: June 2001

Methods:

[^{14}C]Duloxetine hydrochloride was used to determine the kinetics of adsorption to sewage sludge and the aerobic biodegradability of duloxetine in activated sludge.

For adsorption determination, duplicate 500 mL flasks containing 200 mL 0.01 M $CaCl_2$ and 2500, 1250, 625, or 313 mg/L sludge solids were incubated with 1.01 mg/L [^{14}C]duloxetine hydrochloride. The flasks were stirred in an environmental chamber at 22 ± 3°C for four hours. At timepoints 0, 1, 2, and 4 hours, 30 mL homogenous samples were taken from each flask. Samples were split with one portion being extracted and analyzed for parent material by HPLC/RAM and LSC and the other portion centrifuged to isolate the supernatant for assay of parent material. The organic carbon content of the sludge was also determined.

For assessment of biodegradation potential, duplicate 500 mL flasks containing 250 mL of sewage sludge with 2500 mg/L solids were incubated with 1.00 mg/L of [^{14}C]duloxetine hydrochloride. The flasks were stirred in an environmental chamber at 22 ± 3°C. The flasks were stoppered and connected to a volatiles trapping system. Samples (20 mL) were taken from the flasks at 0, 8, 24, 72, 96, 120, 144, and 192 hours. The volatiles traps were sampled at 96 and 192 hours. Sludge samples were analyzed by HPLC/RAM following extraction of the whole sample. Volatile trap samples were assayed by LSC.

Results:

Adsorption of duloxetine hydrochloride to solids reached a plateau by 2 hours incubation with the sewage sludge. The adsorption coefficients ($K_{d(sludge)}$) at 4 hours were calculated to be 1166, 1269, 1197, and 1731 for 2500, 1250, 625, and 313 mg solids/L, respectively. The adsorption coefficients expressed as a function of the organic carbon content ($K_{oc(sludge)}$) of the activated sludge were calculated to be 2893, 3150, 2970, and 4296.

During the biodegradation study, duloxetine concentrations dropped from 91.3% at 0 hour to 62.1% by 8 hours. There was no further decline in duloxetine concentration over the remaining 8 days. Therefore, this initial decline is most likely attributable to extraction inefficiency as duloxetine becomes more tightly bound to the sludge solids. After 8 days, a small degradation peak was observed accounting for approximately 1.5% of the total radioactivity. The presence of this degradation product indicates the eventual biodegradability of duloxetine.

Appendix F: Report Summary - Study #: 1982.6120

Report Title: Duloxetine Hydrochloride – Determination of the Abiotic Degradation of the Test Substance by Hydrolysis at Three Different pH Values Following OECD Guideline 111

Study #: 1982.6120

Study date: June 2001

Methods:

Preliminary Test:

A hydrolysis study with duloxetine was conducted in three aqueous buffers, pH 4, 7, and 9. Duloxetine hydrochloride was added to the buffers for a final concentration of 10 mg/L (expressed as duloxetine free base). Aliquots of each solution were incubated in 50 mL volumetric flasks in a 50°C water bath for 5 days. All flasks were wrapped in foil. Analysis for duloxetine concentration was performed on days 0 and 5.

Definitive Test:

A hydrolysis study with duloxetine was conducted in the same three aqueous buffers above. Two 200 mL aliquots of each solution containing 10 mg/L duloxetine were incubated in volumetric flasks for 28 days in a 40°C water bath. A third 200 mL aliquot was incubated for 35 days at 30°C. All flasks were wrapped in foil. At days 0, 3, 7, 10, 12, 14, 17, 20 and 28 samples were removed from the 40°C incubation for analysis. Samples were taken from the 30°C incubation at days 0, 3, 7, 10, 12, 17, 28, and 35.

Results:

Preliminary Test:

The percent duloxetine remaining after 5 days at pH 4, 7, and 9 was 56.4%, 75.9%, and 60.7%, respectively.

Definitive Test:

The following first order hydrolysis rate characteristics for duloxetine were calculated.

pH	°C	Initial [Duloxetine] on Day 0 (mg/L)	[Duloxetine] at end of test (mg/L)	Hydrolysis Rate Constant (Day^{-1})	Half Life (Days)
4	30	10.4	6.07	0.0165	41.88
7	30	10.0	8.05	0.0069	100.62
9	30	10.0	7.43	0.0096	72.48
4	40	9.98	2.92	0.0440	15.73
7	40	10.2	5.67	0.0219	31.69
9	40	9.84	4.21	0.0306	22.64

Appendix G: Report Summary - Study #: 1982.6130

Report Title: Duloxetine Hydrochloride - Determination of the Ultraviolet-Visible Absorption Spectrum in Aqueous Solution Following OECD Proposed Guideline for Phototransformation of Chemicals in Water

Study #: 1982.6130

Study date: June 2001

Methods:

Solutions of 0.0015 M duloxetine hydrochloride were prepared in pH 4 and pH 7 buffers and in unbuffered pure reagent water. A solution of 0.0003 M duloxetine hydrochloride was prepared in pH 9 buffer. The absorption spectra of the test solutions were measured using a Hewlett-Packard Model 8453 UV-Vis spectrophotometer. Absorbance peaks recorded in the wavelength range for natural sunlight (i.e. 295 to 800 nm) were used to calculate the propensity for phototransformation of duloxetine.

Results:

Absorbance peaks were observed in the range of 295 to 325 nm. The molar absorption coefficient was determined for each peak and using these values it was calculated that within 30 days, 100% of duloxetine would be phototransformed at pH 4, 7, and 9 and in pure reagent water.

Appendix H: Report Summary - Study #: 1982.6126

Report Title: Duloxetine Hydrochloride - Activated Sludge Respiration Inhibition Following OECD Guideline 209

Study #: 1982.6126

Study date: June 2001

Methods:

Duloxetine hydrochloride was incubated with synthetic sewage feed and activated sludge (1.5 g/L solids concentration) in a volume of 500 mL in 1000 mL beakers. There were five treatment levels consisting of one replicate each. Four treatment levels of 3,5-dichlorophenol were incubated as above as a reference control for the study. There were two controls consisting of synthetic sewage feed and activated sludge only and an abiotic control with synthetic sewage feed only. The nominal concentrations of duloxetine (expressed as free base) were 2, 6, 18, 54, and 162 mg/L. The stock solution (500 mg/L) used to make the test concentrations was analyzed by HPLC and determined to be 498 mg/L duloxetine (free base). The nominal concentrations of 3,5-dichlorophenol were 3.0, 10, 30 and 100 mg/L. After 3 hours and 25 minutes of incubation during which the test systems were aerated, homogenous samples from each replicate and control were collected. The pH was measured and the dissolved oxygen was monitored over 10 minutes in a Strathkelvin Instruments oxygen system while the samples were continuously stirred in a water bath. From these measurements, the oxygen consumption rate was calculated for each treatment level and control.

Results:

The temperature of the test solutions was maintained between 18.5 and 21.9°C during the incubation and the water bath used during the oxygen measurements was maintained at approximately 21°C. The pH in all treatments was between 7.27 and 7.59. The respiration rates for the control vessels were 29.3 and 31.1 mg O_2/L/hr. The abiotic control respiration rate was -1.8 mg O_2/L/hr. The respiration rates for the reference compound were 26.9, 15.4, 3.5 and 0.6 mg O_2/L/hr for 3.0, 10, 30, and 100 mg/L, respectively. The EC50 of 3,5-dichlorophenol was calculated to be 11.1 mg/L which is within the acceptable limits (5.0 to 30 mg/L) as specified in the OECD 209 Guideline. Respiration rates for the treatment levels were 30.7, 21.8, 26.0, 7.7 and -0.8 mg O_2/L/hr for 2, 6, 18, 54, and 162 mg/L duloxetine, respectively. The no-observed effect concentration for duloxetine was 2 mg/L and the EC50 was calculated to be 36.5 mg/L.

Appendix I: Report Summary - Study #: 1982.6125

Report Title: Duloxetine Hydrochloride - Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static-Renewal Conditions

Study #: 1982.6125

Study date: June 2001

Methods:

The acute toxicity of duloxetine to rainbow trout was assessed according to OECD guideline 203. Juvenile trout (mean weight 0.75 g, mean length 42 mm) were exposed to mean measured concentrations of duloxetine of 0 (control), 0.45, 0.89, 1.9, 3.8, 8.6, and 17 mg/L (here and below expressed as duloxetine free base) for 96 hours. A total of 10 fish were exposed to each treatment level in a volume of 15 L. At 48 hours, the fish were transferred to fresh exposure solutions. Daily mortality and behavioral changes were recorded.

Results:

Temperature in the test system was maintained between 13 and 14°C. The pH and dissolved oxygen ranged from 6.7 to 7.4 and 6.2 to 10.2 mg/L, respectively. At 96 hours the cumulative mortality at concentrations ≥1.9 mg/L was 100%. There was no mortality in lower treatment levels or the control. Lethargic swimming behavior was observed in the 0.89 mg/L. The 96 hour LC50 was determined to be 1.3 mg/L duloxetine with 95% confidence intervals of 0.89 to 1.9. The 96 hour no-observed-effect concentration was 0.45 mg/L duloxetine.

Appendix J: Report Summary - Study #: 1982.6116

Report Title: Duloxetine Hydrochloride - Acute Toxicity to Daphnids (*Daphnia magna*) Under Static Conditions

Study #: 1982.6116

Study date: June 2001

Methods:

The acute toxicity of duloxetine to daphnids was assessed according to OECD guideline 202. Daphnids (≤24 hours old) were exposed to mean measured concentrations of duloxetine of 0 (control), 0.10, 0.52, 1.1, 2.1, 4.2 and 8.5 mg/L (expressed as duloxetine free base) for 48 hours. Four replicates were included at each treatment level. Each replicate contained five animals in 200 mL of test solution. The test solutions were prepared with fortified well water (initially pH 8.0, conductance 550 µmhos/cm, total hardness as $CaCO_3$ 180 mg/L, and total alkalinity as $CaCO_3$ 120 mg/L). At 24 and 48 hours, water quality measurements were made and the number of immobilized daphnids in each replicate was recorded.

Results:

During the testing period the temperature ranged from 19 to 21°C, the pH from 7.9 to 8.2 and the dissolved oxygen from 8.6 to 10.3. No immobilization or other adverse effects (e.g. lethargy) were observed in treatment levels ≤1.1 mg/L duloxetine and the control. Immobilization occurred in 35, 100 and 100% of daphnids exposed to 2.1, 4.2 and 8.5 mg/L duloxetine, respectively. The surviving daphnids in the 2.1 mg/L group were observed to be lethargic. The 48-hour EC50 and 95% confidence limits were calculated to be 2.4 mg/L and 1.1 to 4.2 mg/L duloxetine, respectively. The no-observed-effect concentration was 1.1 mg/L duloxetine.

Appendix K: Report Summary - Study #: 1982.6118

Report Title: Duloxetine hydrochloride - Acute Toxicity to the Freshwater Green Alga *Pseudokirchneriella subcapitata*, Following OECD Guideline #201

Study #: 1982.6118

Study date: June 2001

Methods:

A static toxicity test was conducted to evaluate the effects of duloxetine hydrochloride on the green alga, *Pseudokirchneriella subcapitata*. There were six treatment levels containing duloxetine hydrochloride and three replicates at each treatment. The initial measured concentrations in the treatments were 0.0053, 0.011, 0.029, 0.070, 0.20 and 0.47 mg/L duloxetine (concentrations and all results below are expressed as the free base). There were six replicates for the control. To each replicate, approximately one million algal cells were added to 100 mL of appropriately treated Algal Assay Procedure medium in sterile 250 mL flasks to give an initial cell concentration of 10,000 cells/mL. The cells were cultured under continuous illumination at 400 to 490 footcandles and continuous shaking for 72 hours. The pH and conductivity during the test ranged from 7.4 to 8.2 and 80 to 90, respectively. The temperature was 24°C. At 24, 48, and 72 hours, a sample was removed from each flask and the cells were counted using a hemocytometer. These measurements were used to calculate the growth rate and biomass for each replicate.

Results:

After 72 hours, the concentration of duloxetine in all treatments was <10% of the nominal concentration. An additional replicate in the 0.029 mg/L treatment in which no cells were added also contained less than 10% of the initial concentration after 72 hours. Thus the disappearance of duloxetine was probably due in large part to photolysis. There is no established method to maintain constant exposure concentrations in algal toxicity studies if test material declines over the study. After 72 hours the control growth rate was 1.61 $days^{-1}$ (standard deviation = 0.020) and for treatment concentrations ≥0.070 mg/L the rate was significantly reduced (≤1.51 $days^{-1}$). Thus, the no-observed-effect concentration (NOEC) for growth rate was 0.029 mg/L. The median effective duloxetine concentration on reduction of growth rate (EC50) was 0.20 mg/L with 95% confidence limits of 0.088 to 0.31 mg/L. After 72 hours, the biomass (the area under the growth curve) of the control cells was 10,500 cells·days/mL. At 0.47 mg/L duloxetine biomass was significantly reduced. Based on these results, the NOEC for biomass would be 0.20 mg/L. However, duloxetine concentrations ≥0.029 mg/L duloxetine caused >10% reduction of biomass. Thus, the NOEC for biomass was considered to be 0.011 mg/L rather than 0.20 mg/L. The EC50 at 72 hours was calculated to be 0.064 mg/L with 95% confidence limits of 0.019 to 0.23 mg/L. Biomass was the most sensitive endpoint and, therefore, the most conservative EC50 and NOEC for this study were initial duloxetine concentrations of 0.064 and 0.011 mg/L, respectively.

Appendix L: Report Summary - Study #: 1982.6133

Report Title: Duloxetine Hydrochloride - Acute Toxicity to Earthworms (*Eisenia fetida*) following OECD Guideline #207

Study #: 1982.6133

Study date: February 2002

Methods:

The acute toxicity of duloxetine to earthworms was assessed according to OECD guideline 207. Adult earthworms (300-600 mg) were exposed to 63, 130, 250, 500 and 1000 mg/kg duloxetine (as free base) in artificial soil for 14 days. Four replicates of ten earthworms each were exposed to each concentration and a blank control in 750 g (wet weight) of amended artificial soil. Mortality and observations of surviving earthworms were recorded on days 7 and 14. On day 14 the surviving earthworms were collectively weighed on a per replicate basis after being rinsed with deionized water and blotted dry.

Results:

Temperature, pH and moisture content in the test system ranged from 19 to 21°C, 5.8 to 6.5, and 21 to 39%, respectively. There was 100% survival in all treatment levels and controls. The 14-day NOEC was 1000 mg/kg and the LC50 was >1000 mg/kg. After 14 days, the mean change in body weight of earthworms exposed to 63, 130, 250, 500 and 1000 mg/kg duloxetine was -16.0%, -16.0%, -16.3%, 17.2%, and 26.8%, respectively. The mean weight change in the control group was -14.2%.

Appendix M: Report Summary - Study #: 1982.6129

Report Title: Duloxetine Hydrochloride - Full Life-Cycle Toxicity Test with Water Fleas, *Daphnia magna* Under Flow-Through Conditions, Following FIFRA Guideline 72-4, OECD Guideline #211, and OPPTS Draft Guideline 850.1300.

Study #: 1982.6129

Study date: June 2001

Methods:

Daphnia magna, ≤24 hours old, were exposed to duloxetine hydrochloride for 21 days in a flow-through exposure system. There were six treatment levels and a control with four replicate vessels in each treatment. Each replicate vessel held 10 daphnids in a volume of 1.4 L. Test solutions were delivered to the vessels at a rate of six vessel volumes per 24-hour period to provide a 90% solution replacement rate of approximately 9 hours. The mean measured concentrations in the treatments were 0 (control), 0.011, 0.037, 0.080, 0.14, 0.26 and 0.50 mg/L duloxetine (expressed here and below as the free base) prepared in fortified well water. Conditions during the exposure were 19 to 22°C and a light:dark cycle of 16:8 hours at 30 to 70 footcandles. The number of immobilized adult daphnids and observations of abnormal behavior were recorded daily. Assessments of offspring released were determined beginning on day 7 and three times per week through day 21.

Results:

Water quality parameters monitored during the test included pH (7.9 to 8.2), conductivity (500 µmhos/cm), total hardness (180 mg/L as $CaCO_3$), and total alkalinity (110 to 120 mg/L as $CaCO_3$). After 21 days mean percent survival in the treatments was 95, 100, 93, 93, 100, 100, and 38% in the control, 0.011, 0.037, 0.080, 0.14, 0.26 and 0.50 mg/L duloxetine, respectively. The EC50 for survival was calculated to be 0.45 mg/L. After 21 days, the mean body length of daphnids exposed to ≥0.037 mg/L duloxetine was significantly reduced from the control average of 5.1 mm. The mean dry weight of daphnids exposed to ≥0.14 mg/L was significantly reduced compared to the control average of 1.1 mg. After 21 days the mean cumulative number of offspring released per female daphnid in the treatments was 161, 166, 140, 131, 113, and 72 for control, 0.011, 0.037, 0.080, 0.014, and 0.26 mg/L duloxetine, respectively. The reproduction for the 0.50 treatment was not analyzed in the statistics because of the significant survival effect. Offspring numbers in treatment levels ≥0.037 were significantly different from the control. The no-observed-effect concentration and the EC50 for reproduction were calculated to be 0.011 and 0.28 mg/L duloxetine, respectively.

Appendix N: Curriculum Vitae of Preparers

Alison Nimrod Perkins

Lilly Research Laboratories, Indianapolis, IN

Ph.D.	Pharmacology/Toxicology, University of Mississippi	1996
B.S.	Chemistry, Tulane University	1988

Previous Experience: Research Scientist, University of Mississippi in the National Center for Natural Products Research (1997 to 1999). Supervised technical staff of the Biological Core. This group was responsible for screening extracts and pure compounds from natural products for various biological activities. Primary effort included development of new assays. Author on several publications and abstracts in the natural products arena as well as environmental toxicology. Guest lecturer for undergraduate and graduate level courses in pharmacology and toxicology.

Current Responsibility: Research Scientist, Health, Safety and Environmental. Prepares environmental risk assessments for animal and pharmaceutical products for submission to the FDA and Europe. Prepares guidelines for production facilities for containment of active products.

Professional Activities:

Editorial Board: Environmental Toxicology and Chemistry
Member: Society of Environmental Toxicology and Chemistry
Reviewer: ETC, Journal of Natural Products, Journal of Biomolecular Screening

Roger D. Meyerhoff

Lilly Research Laboratories, Greenfield, IN

Ph.D.	Fisheries/Pharmacology & Toxicology, Oregon St. Univ.	1980
M.S.	Fisheries/Limnology & Water Pollution, Oregon St. Univ.	1976
B.S.	Fisheries and Wildlife Biology, Univ. Calif. at Davis	1974

Previous Experience: Senior Toxicologist up to Research Advisor and Head of Environmental Science and Hazard Communications (1980 to 2004). Conducted acute and chronic environmental toxicology studies with over 20 aquatic and terrestrial species and coordinated aquatic and terrestrial field studies. Author of a number of abstracts, papers, and chapters on the results of these studies and lecturer on environmental risk assessment to undergraduates and graduate students at several universities. Has prepared risk assessments for pesticides, animal products, and pharmaceutical products to support submissions to the EPA, FDA, Europe, Australia and Japan since 1982. As Head of Environmental Science and Hazard Communications, was responsible for personnel and operations supporting environmental safey at production facilities, registration of new products (conduct of inhalation, aquatic, wildlife, microbial, and environmental chemistry studies), and workplace safety (material safety data sheets, caution statements, and risk assessments for human exposure).

Current Responsibility: Senior Research Advisor for Health, Safety and Environmental in Lilly Research Laboratories. Responsible for human and environmental risk assessments to support product registrations, workplace safety, product safety, and environmental safety at production facilities.

Professional Activities:
Chairman (1993-1995), SETAC Foundation for Environmental Education
President (1991-1992), Society of Environmental Toxicology & Chemistry (SETAC)
Board of Directors (1987-1993), SETAC
Member (1991-Present), PhRMA Environmental Working Group
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-427 / S-011

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY MEMO TO THE FILE

NDA 21-417.
Submission SE-011, letter-dated 4/27/06, stamp-dated 4/27/06.

Drug: Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules.
Sponsor: Eli Lilly and Company.
Currently-proposed Indication: Generalized Anxiety Disorder (GAD).
[This formulation has already been approved for treatment of Major Depressive Disorder and for Diabetic Peripheral Neuropathic Pain.]

Reviewer: Linda H. Fossom, Ph.D., Pharmacologist.
HFD-130, Division of Psychiatry Products.

RE: This is an efficacy supplement for treatment of the new indication of Generalized Anxiety Disorder.

Background: Duloxetine hydrochloride has already been approved as delayed-release capsules (Cymbalta® Delayed-release Capsules) for treatment of Major Depressive Disorder (MDD) under NDA 21-427 (approved 8/3/04), with a maximum recommended human dose (MRHD) of 60 mg per day; and for treatment of Diabetic Peripheral Neuropathic Pain under NDA 21-733 (approved 9/3/04), with a MRHD of 120 mg per day.

The current submission: The current submission contains clinical studies to support the proposed claim for use of duloxetine hydrochloride (as the same formulation and strengths that have already been approved) for treatment of Generalized Anxiety Disorder (GAD), with a maximum recommended human dose probably set at 60 mg per day (apparently the higher dose of 120 mg did not offer additional benefits, based on the Clinical review of this submission, by Roberta Glass, M.D., finalized 1/30/07).

In this submission, the Sponsor re-submitted all the non-clinical studies that had originally supported the approval of duloxetine for treatment of MDD under this NDA. Additionally, they provided 26 new non-clinical studies that had not previously been submitted to this NDA (the Sponsor identified these new studies in an amendment to SE-011, BP, letter-dated 9/21/06, stamp-dated 9/25/06). Of these 26 studies, the 6 ADME studies and all but 8 of the toxicology studies have been previously reviewed under NDA 21-733 (approved for treatment of Diabetic Peripheral Neuropathic Pain).

Discussion: No new non-clinical studies are required to support the use of Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules for the treatment of GAD. This is a similar patient population to that for the already-approved indication of MDD; the MRHD of 60 mg is the same as that for MDD (although the higher dose of 120 mg is

acknowledged to have been shown to be effective for GAD); and the drug formulation and strengths are the same as have already been approved. Consequently, the newly submitted non-clinical studies are not being reviewed at this time; however, a list of these new studies is provided in an appendix to this memo.

The Sponsor does not appear to have changed the non-clinical sections of labeling. It should be noted that safety margins for clinical doses of both 60 and 120 mg per day are already provided in labeling for appropriate animal toxicology findings (i.e., for reproductive and carcinogenicity studies).

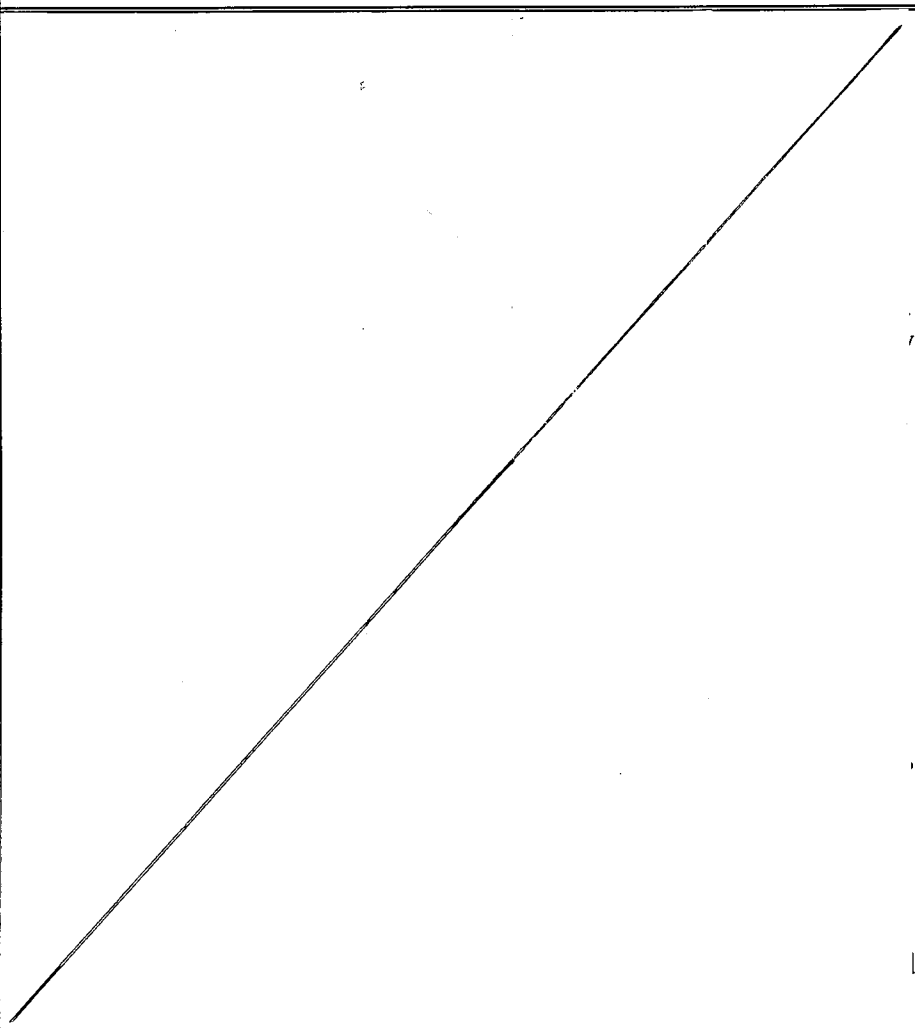
Conclusions/recommendations: From a Pharmacology/Toxicology perspective, this efficacy supplement for the use of duloxetine hydrochloride for the treatment of GAD may be approved.

Linda H. Fossom, Ph.D., Pharmacologist *{see appended electronic signature page}*
Barry Rosloff, Ph.D., Supervisor *{see appended electronic signature page}*

APPENDIX:

Listing of the 26 non-clinical studies that have not been previously submitted to this NDA (copied from submission SE-011, BP, letter-dated 9/21/06, stamp-dated 9/25/06). All but 8 toxicology studies have been reviewed under NDA 21-733 (approved for treatment of Diabetic Peripheral Neuropathic Pain.)

REVIEWED UNDER NDA 21-733?	REPORTS
yes	New Non Clinical Pharmacology Studies in GAD submission: 1. ADME Report 79 Quantitation of LY248686 (Duloxetine) in Rabbit Plasma Using LC/MS/M 2. ADME Report 93 Quantification of 550408 and 581920 in Rabbit, Rat and Mouse Plasma Using TurboIon Spray LC/MS/MS 3. ADME Report 96 Quantification of 550408 and 581920 in Rabbit, Rat and Mouse Plasma Using TurboIon Spray LC/MS/MS - Stability Report 4. ADME Report 92 Plasma Exposure of Duloxetine (LY248686) and Metabolites in Pregnant New Zealand White Rabbits Following Multiple Oral Doses of 2, 10, or 45 mg Duloxetine/kg as the Hydrochloride Salt on Gestation Day 7 through Gestation Day 19 5. ADME Report 94 Plasma Exposure of CD-1Mice to Duloxetine and the Glucuronide Conjugate of 4-Hydroxy Duloxetine Following Daily Dietary Doses of 0.01%, 0.03%, or 0.08% of the Diet as Duloxetine in the Hydrochloride Form for 1 Month 6. ADME Report 95 Plasma Exposure of Fisher 344 Rats to Duloxetine and the Glucuronide Conjugate of 4-Hydroxy Duloxetine Following Daily Dietary Doses of 0.01%, 0.02%, 0.05%, or 0.08% of the Diet as Duloxetine in the Hydrochloride Form for 1 Month
no	[redacted] b(4)

REVIEWED UNDER NDA 21-733?	REPORTS
	 b(4)
yes	9. NCPR 55: Effect of Duloxetine (LY248686 Hydrochloride) on the Norepinephrine, Serotonin, and Dopamine Transporter Binding Site 10. NCPR 56: Effect of S-Duloxetine (LY248686 Hydrochloride) on N-Methyl Scopolamine (NMS) Binding to Human Muscarinic M1 Through M5 Receptors 11. NCPR 59: Effect of S-Duloxetine (LY248686 Hydrochloride) on N-Methyl Scopolamine (NMS) Binding to Human Muscarinic M1 Through M5 Receptors

REVIEWED UNDER NDA 21-733?	REPORTS
	12. CNS 455: Occupancy of the Serotonin and Norepinephrine Transporters by Duloxetine Hydrochloride in Rat Cortex 13. NCPR 63: Comparison of Effects of Duloxetine and Other Dual Transporter Inhibitors on Extracellular Monoamine Levels in Rats 14. NCPR 60: LY248686 Hydrochloride Occupancy of Cortical Serotonin Transporter Sites in Sprague Dawley Rats Measured Using Citalopram as a Tracer 15. NCPR 58: In Vivo Occupancy of Striatal Dopamine Reuptake Sites by Oral LY248686 Hydrochloride Administration in Sprague Dawley Rats 16. NCPR 57: Blockade of the a-Methyl-m-Tyrosine-Induced Depletion of Rat Cortical Norepinephrine Concentrations by Duloxetine 17. NCPR 61: Effect of Duloxetine Hydrochloride (LY248686) on Extracellular Levels of 5-Hydroxytryptamine and Noradrenaline in the Rat Medial Prefrontal Cortex 18. CNS 465: Update on Effects of Duloxetine.HCl (LY246916) in the Partial Sciatic Nerve Ligation and L5/L6 Spinal Nerve Ligation Models of Neuropathic Pain in Sprague Dawley Rats 19. CNS 466: Additional Studies on Effects of Acute Systemic and Central Administration of Duloxetine.HCl (LY246916) in the Formalin Test of Persistent Pain and the Rotorod Test in Rats 20. CNS 467: Effects of Duloxetine.HCl (LY246916) in a Model of Acute Nociceptive Pain in Sprague Dawley Rats

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/s/

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2/23/2007 11:43:11 AM
PHARMACOLOGIST

Barry Rosloff
2/26/2007 12:41:07 PM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-427 / S-011

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	21-427 / SE-011
Drug Name:	Cymbalta (duloxetine)
Indication(s):	Generalized anxiety disorder
Applicant:	Eli Lilly
Date(s):	April 27, 2006
Review Priority:	Standard Review
Biometrics Division:	Division of Biometrics I (HFD-710)
Statistical Reviewer:	George Kordzakhia, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D.; Kooros Mahjoob, Ph.D.
Medical Division:	Division of Psychiatry Products (HFD-130)
Clinical Team:	Roberta Glass, M.D.; Ni Khin, M.D.
Project Manager:	Ms. Felicia Curtis

Keywords: ANCOVA, repeated measures analysis.

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1. EXECUTIVE SUMMARY

The sponsor has submitted the efficacy findings of one fixed dose and two flexible dose studies on the efficacy of Duloxetine in the treatment of generalized anxiety disorder (GAD) in adult outpatients. The studies were conducted in the United States, Europe and South Africa.
All three studies have demonstrated statistically significant treatment effect in the pre-specified primary efficacy endpoint.

1.1 Conclusions and Recommendations

Duloxetine in doses 60 mg/day, 120 mg/day and 60 to 120 mg/day was effective in the treatment of generalized anxiety disorder in adult outpatients. The effect of higher dose (120 mg/day) was not found to be better than the effect of the lower dose (60 mg/day).

1.2 Brief Overview of Clinical Studies

The proposed new indication was to be supported by the results of three studies: F1J-MC-HMBR, F1J-MC-HMDT, and F1J-MC-HMDU. These studies were multi-center, randomized, double-blind, placebo-controlled Phase 3 studies. Studies HMBR and HMDT had a single-blind placebo lead-in and a double-blind drug-tapering phase. Study HMDU was not only placebo-controlled but also included an active comparator. Patients enrolled in all studies were at least 18 years of age presenting with GAD as defined by DSM-IV Criteria.

Study HMBR was a fixed dose study with two treatment arms (60 mg/day and 120 mg/day) and 9-week acute therapy phase. The study was performed in seven countries and involved 513 patients. Studies HMDT and HMDU were 10-week flexible dose US studies with duloxetine treatment arm: 60 to 120 mg/day. Overall, there were respectively 327 and 487 patients involved in the studies. The primary efficacy variable for all three studies was change in Hamilton Depression Rating Scale (HAMA) total score from baseline to endpoint visit.

1.3 Statistical Issues and Findings

The three studies have demonstrated that duloxetine in doses 60 mg/day, 120 mg/day and 60 to 120 mg/day was effective in the treatment of generalized anxiety disorder in adult outpatients. In all studies, the primary efficacy endpoint- HAMA has shown statistically significant efficacy of duloxetine compared with placebo. The fixed-dose study HMBR indicated that there was no additional benefit of 120 mg arm over 60 mg arm, although primary comparison was 120 mg versus placebo.

2. INTRODUCTION

2.1 Overview

The clinical development program for duloxetine in generalized anxiety disorder consisted of three randomized, double-blind, placebo-controlled studies in outpatients with GAD. The studies were conducted in the United States, Europe, South Africa. Table 1 lists an overview of the studies.

Table 1. Reviewer's overview of the randomized studies

Study	Treatment Duration	Duloxetine Doses (mg/day)	Comparator(s)
HMBR-US/EU	9 weeks	Fixed 60 and 120	Placebo
HMDT-US	10 weeks	Flexible 60 to 120	Placebo
HMDU-US	10 weeks	Flexible 60 to 120	Venlafaxine/Placebo

2.2 Data Sources

All documents reviewed for this NDA submission are in electronic form. The path to CDER Electronic Document Room for this submission is listed below:
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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Description of Studies HMBR, HMDT, HMDU

3.1.1.1 Objectives of the Studies

Primary Objective: To evaluate efficacy of duloxetine hydrochloride compared with placebo in the treatment of generalized anxiety disorder (GAD) as measured by the Hamilton Anxiety Rating Scale (HAMA). For study HMBR the targeted dose of duloxetine was 120 mg once daily. In studies HMDT and HMDU, flexible dose of duloxetine 60 mg to 120mg once daily was compared with placebo.

Key Secondary Objective: To assess whether duloxetine hydrochloride is superior to placebo as measured by Sheehan Disability Scale (SDS) Global Functional Impairment Score (120 mg/day for study HMBR; flexible dose 60 mg to 120 mg for studies HMDT and HMDU).

Reviewer's Remark: Note that although Study HMBR included 60mg and 120mg of duloxetine, the main objective of the study was the efficacy of 120mg of duloxetine.

3.1.1.2 Design of the Studies

All three studies were multi-center, randomized, double-blind, placebo-controlled Phase 3 studies. Patients who met criteria for GAD as defined by the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) were eligible to participate in the studies. Patients had a disease severity of at least moderate intensity as defined by a Hospital Anxiety and Depression Scale (HADS) anxiety subscale score > 9, and a Covi Anxiety Scale(CAS) score >8. To exclude patients with severe depression conditions, it was required that no item in the Raskin Depression Scale (RDS) scale was >3. The CAS score was required to be greater than the RDS score. In addition, patients had to have Clinical Global Impressions of Severity (CGI-Severity) score >3 at Visit 1 and Visit2.

Study HMBR was designed to assess the acute effect of 120 mg once daily dose of duloxetine (primary objective) in the treatment of generalized anxiety disorder. Secondary objective was to compare duloxetine 60 mg (QD) with placebo. There were 639 patients enrolled in the study at Visit 1. Following a 3- to 30-day screening phase (Study Period 1) and a 5- to 9-day single-blind placebo lead-in (Study Period 2), eligible patients were randomly assigned at Visit 3 to receive treatment with duloxetine 60 mg QD, 120 mg QD, or placebo. There were 168, 170 and 175 patients receiving the respective treatments. The acute therapy phase (Study Period 3) lasted 9 weeks and was followed by a 2-week drug-tapering phase (Study Period 4) that began at the completion of Visit 8.

Study HMDT was designed to test the efficacy of duloxetine 60 mg to 120 mg once daily (QD) versus placebo. There were 515 patients enrolled in the study at Visit 1. Following a 3- to 30-day screening phase (Study Period 1) and a 5- to 9-day single-blind placebo lead-in (Study Period 2), eligible patients were randomly assigned at Visit 3 to receive treatment with duloxetine 60 to 120 mg QD, or placebo. There were 168 and 159 patients receiving the respective treatments. The acute therapy phase (Study Period 3) lasted 10 weeks and was followed by a drug-tapering phase (Study Period 4).

Study HMDU was designed to assess whether duloxetine 60 mg to 120 mg once daily (QD) is superior to placebo. There were 707 patients enrolled in the study at Visit 1. Following a 3- to 30-day screening phase (Study Period 1), eligible patients were randomly assigned at Visit 2 to receive treatment with duloxetine 60 mg to 120 mg QD, venlafaxine extended release 75 mg to 225 mg (active comparator) or placebo. There were 162, 164 and 161 patients receiving the respective treatments. The acute therapy phase (Study Period 2) lasted 10 weeks and was followed by a drug-tapering phase (Study Period 3).

3.1.1.3 Efficacy Variables and Statistical Methods.

For all three studies, the primary efficacy endpoint was the mean change from baseline to the end of the acute therapy phase in the HAMA total score. The HAMA stands for Hamilton Depression Rating Scale. It is a 14-item self rating scale for assessing severity of generalized anxiety disorder in scores 0 to 4 for each item. Thus, the HAMA total score is the sum of all 14 items and ranges from 0 to 56. Higher scores indicate a greater degree of symptom severity. For Study HMBR, the duloxetine 120 mg QD group vs. placebo group was to be conducted on the primary endpoint. For Studies HMDT and HMDU, the duloxetine 60 mg to 120 mg QD group was compared with placebo group. The key secondary efficacy endpoint was the mean change from baseline to endpoint in the Sheehan Disability Scale (SDS) Global Functional Impairment score.

All analyses were conducted on an intent-to-treat basis, meaning that data were analyzed by treatment groups to which patients were randomly assigned, even if the patient did not take the assigned treatment, did not receive the correct treatment, or did not comply with the protocol. For each efficacy variable, the analysis included all randomized patients with baseline and at least one post-baseline observation.

The primary analysis for the primary and secondary efficacy endpoints was ANCOVA under LOCF data set. The model contained the main effects of treatment and investigator and baseline covariate. Type III sum-of-squares for the least-squares means was used for the statistical comparison. The primary efficacy endpoint (mean change in HAMA score) had to show statistical significance in favor of duloxetine compared with placebo to establish efficacy. The secondary statistical analysis was based on mixed model with repeated measures (MMRM).

A gatekeeper strategy was employed for testing the key secondary hypothesis to be eligible for possible inclusion in the label. The key secondary objective was to evaluate the efficacy of duloxetine (120 mg/day for study HMBR; flexible dose 60 mg to 120 mg for studies HMDT and HMDU) compared with placebo on the Sheehan Disability Scale Global Functional Impairment score. Since the sponsor planned to use the sequential testing procedure with pre-specified sequence of testing, no adjustment for alpha is necessary.

When computing total scores for efficacy measures with missing items the following procedures were used. If less than 20% of the items were missing, the mean score for all other items was imputed as the score for the missing items when computing the total. If more than 20% of the items were missing, then the total was considered missing. Sensitivity analysis on the imputation methods was performed on the primary endpoint (HAMA total score) only. Method 1: If any of the individual items on the HAMA were missing, then the HAMA score was considered missing. If less than 1% of the data differed between the primary method of imputation and Method 1, no additional sensitivity analyses were performed. Otherwise Method 2 was used: If less than 20% of the items were missing, then the item scores from previous visit were used when computing the total score. If more than 20% of the items were missing, then the total was considered missing.

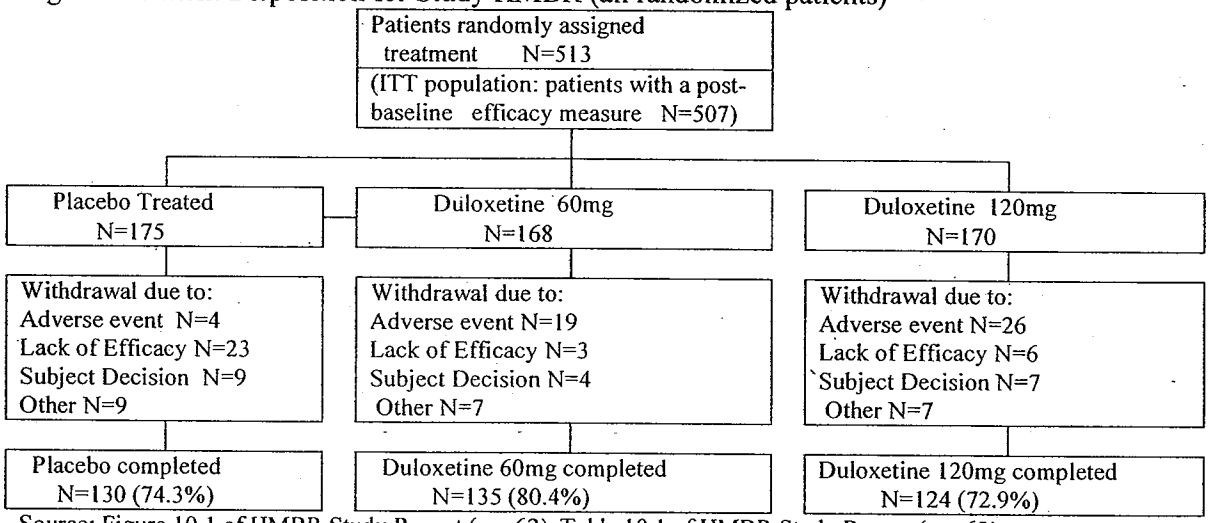
3.1.2 Patient Disposition, Demographic and Baseline Characteristics.

3.1.2.1 Patient Disposition.

Study HMBR

Study HMBR was conducted in 41 study centers in seven countries (Finland, France, Germany, South Africa, Spain, Sweden and United States). In this study, a total of 513 patients were randomized and received study medication. During the course of study, 124 patients discontinued due to adverse events, lack of efficacy or administrative reasons. A total of 507 patients who had a post-baseline efficacy assessment constituted intent-to treat population. Figure 1 presents the patient disposition.

Figure 1. Patient Disposition for Study HMBR (all randomized patients)

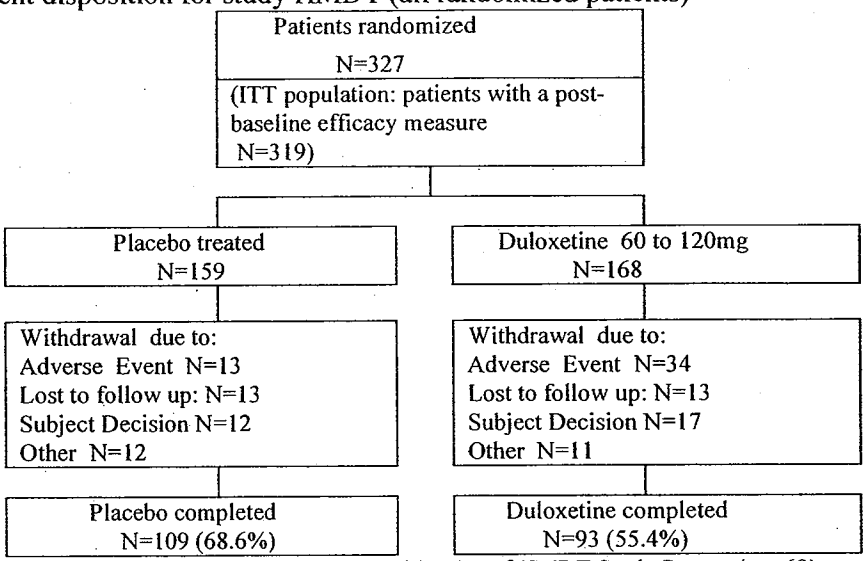


Source: Figure 10.1 of HMBR Study Report (pg. 62), Table 10.1 of HMBR Study Report (pg. 63).

Study HMDT

Study HMDT was conducted at 28 study centers in the United States. A total of 327 patients were randomly assigned to receive study medication:168 were assigned to duloxetine and 159 were assigned to placebo. A total of 319 patients constituted intent-to treat population. 202 were able to complete the study.

Figure 2. Patient disposition for study HMDT (all randomized patients)

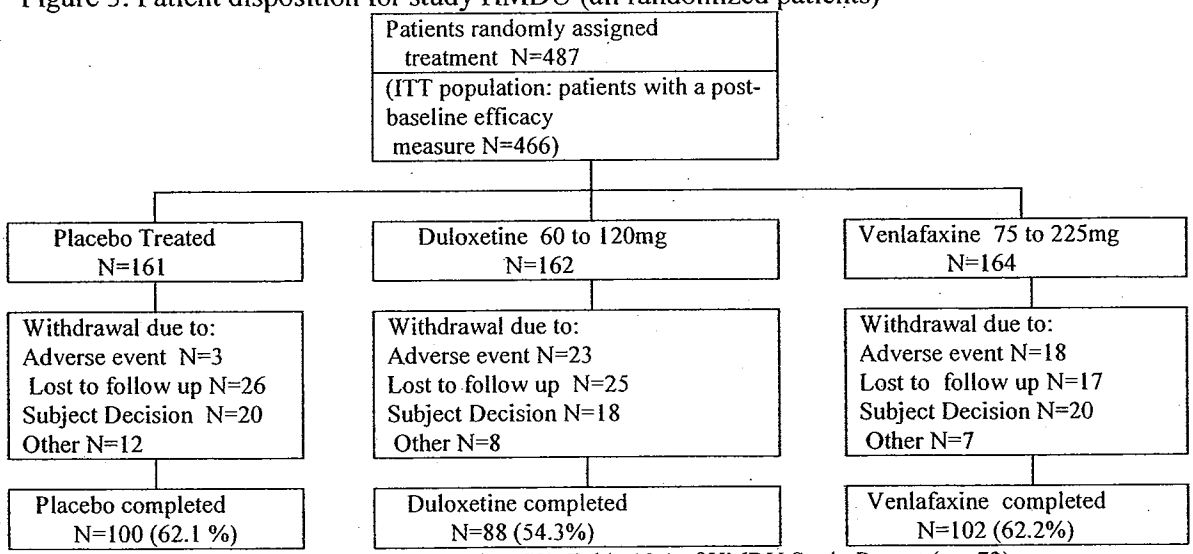


Source: Figure 10.1 of HMDT Study Report (pg. 67), Table 10.1 of HMDT Study Report (pg. 68).

Study HMDU

Study HMDU was conducted at 42 study centers in the United States. In this study, 162 patients were randomly assigned to receive duloxetine, 164 were randomly assigned to venlafaxine, 161 were assigned to placebo (total of 487). A total of 466 patients had a post-baseline efficacy assessment. During the course of study, 197 patients discontinued due to adverse events, subject decision or administrative reasons, and 290 patients were able to complete the study.

Figure 3. Patient disposition for study HMDU (all randomized patients)



Source: Figure 10.1 of HMDU Study Report (pg. 70), Table 10.1 of HMDU Study Report (pg. 72)

3.1.2.2 Patients Demographic and Baseline Characteristics

In all studies, treatment groups appeared to be comparable for race, age, gender and baseline characteristics. The following tables present patients demographic and baseline characteristics by treatment groups.

Study HMBR

Table 2. Study HMBR: Demographic and Baseline Characteristics for ITT population

Patient Status	Placebo	Duloxetine 60mg	Duloxetine 120mg
No Patients	173	165	169
Age (years)			
Mean (S.D.)	44.27 (13.37)	42.99 (12.90)	44.03 (12.65)
Gender, N (%)			
Female	115 (66.47%)	105 (63.63%)	122 (72.18%)
Male	58 (33.52%)	60 (36.36%)	47 (27.81%)
Race, N (%)			
Caucasian	172 (99.42%)	160 (98.15%)	168 (98.24%)
Other	1 (0.57%)	3 (1.84%)	3 (1.75%)
Baseline HAMA Total Score			
Mean (SD)	25.82 (7.66)	25.05 (7.18)	25.13 (7.24)

Source: Table 11.10 (pg. 101), Table 14.20 (pg. 287-288) of HMBR Study Report

Study HMDT

Table 3. Study HMDT: Demographic and Baseline Characteristics for ITT population

Patient Status	Placebo	Duloxetine 60-120mg
No Patients	158	161
Age (years)		
Mean (S.D.)	41.07 (14.18)	42.18 (13.72)
Gender, N (%)		
Female	99 (62.65%)	99 (61.49%)
Male	59 (37.34%)	62 (38.50%)
Race, N (%)		
Caucasian	123 (77.84%)	128 (79.50%)
Other	35 (22.15%)	33 (20.49%)
Baseline HAMA Total Score		
Mean (SD)	23.49 (7.91)	22.54 (7.44)

Source: Table 11.10 (pg. 111), Table 14.8 (237-238) of HMDT Study Report

Study HMDU

Table 4. Study HMDU: Demographic and Baseline Characteristics for ITT population

Patient Status	Placebo	Duloxetine 60-120 mg	Venlafaxine
No Patients	158	149	159
Age (years)			
Mean	42.12 (14.17)	40.48 (13.64)	40.25 (13.23)
Gender, N (%)			
Female	98 (62.02%)	96 (64.42%)	99 (62.26%)
Male	60 (37.97%)	53 (35.57%)	60 (37.73%)
Race, N (%)			
Caucasian	110 (69.62%)	99 (66.44%)	115 (72.32%)
Other	48 (30.37%)	49 (32.88%)	44 (27.67%)
HAMA Total Score			
Mean (SD)	24.98 (5.82)	25.77 (5.66)	24.92 (5.48)

Source: Table 11.11 (pg. 129), Table 14.20 (pg. 286-287) of HMDU Study Report

3.1.3 Efficacy results for studies HMBR, HMDT, HMDU

3.1.3.1 Primary Analysis on the Primary Efficacy Endpoint

This reviewer confirmed the sponsor's analysis results for primary endpoint HAMA. Treatment group differences were evaluated using the ANCOVA model with treatment and principal investigator terms and baseline covariate by LOCF method. Table 5 lists the primary efficacy results of the three studies. The findings indicate that all of the duloxetine treatment arms (60mg/day, 120mg/day for study HMBR, and a flexible dose 60-120 mg/day for studies HMDT and HMDU) were statistically significantly ($p<0.001$) superior to placebo in reducing Hamilton Anxiety Rating Scale total score of the patients with generalized anxiety disorder (GAD). For study HMBR, the effect of higher dose (120mg/day) did not appear to be better than the effect of the lower dose (60mg/day).

Table 5. Mean change in HAMA total score from Baseline to Endpoint visit

Study Treatment	Number of patients	Baseline Mean (SD) (raw data)	Endpoint Mean (SD) (raw data)	LS Change Mean (SE)	p-value when compared with Placebo
Study HMBR					
Placebo	173	25.82 (7.66)	17.19 (9.96)	-8.38 (0.67)	
DLX 60mg	165	25.05 (7.18)	12.32 (8.79)	-12.8 (0.68)	< 0.001
DLX 120mg	169	25.13 (7.24)	12.74 (9.55)	-12.5 (0.67)	< 0.001
Study HMDT					
Placebo	158	23.49 (7.91)	17.00 (10.24)	-5.89 (0.70)	
DLX60-120mg	161	22.54 (7.44)	14.27 (9.58)	-8.12 (0.70)	0.023
Study HMDU					
Placebo	158	24.98 (5.82)	16.06 (9.29)	-9.19 (0.67)	
DLX60-120mg	149	25.77 (5.66)	13.95 (8.55)	-11.8 (0.69)	0.007
VEN 75-225mg	159	24.92 (5.48)	12.90 (8.95)	-12.4 (0.67)	<0.001

Source: Table 11.10 of HMBR Study Report (pg. 101), Table 11.10 of HMDT Study Report (pg. 111), Table 11.11 of HMDU Study Report (pg. 129).

This reviewer also performed treatment comparisons at each visit time as an exploratory analysis for all three studies. The purpose of the comparisons was to explore whether effects were consistent across the visits. The results are summarized in tables below. It is to be noted that the reported p-values are nominal p-values and are not adjusted for multiplicity.

Study HMBR

Table 6. Study HMBR: Mean change in HAMA total score by visit

Visit (week)	Placebo (N=173)	DLX 60 (N=165)	DLX120 (N=169)	p-value when compared with Placebo	
				DLX 60	DLX 120
4 (1)	-2.998(0.427)	-2.904 (0.429)	-3.035 (0.429)	0.875	0.951
5 (2)	-5.186 (0.523)	-8.283 (0.536)	-7.258 (0.527)	<0.0001	0.004
6 (4)	-6.538 (0.583)	-10.474 (0.598)	-10.132 (0.587)	<0.0001	<0.0001
7 (6)	-7.834 (0.632)	-12.120 (0.648)	-11.929 (0.636)	<0.0001	<0.0001
8 (9)	-8.376 (0.667)	-12.761 (0.683)	-12.469 (0.671)	<0.0001	<0.0001

Source: Reviewer's results
Note: the reported p-values are nominal p-values and are not adjusted for multiplicity.

Study HMDT

Table 7. Study HMDT: Mean change in HAMA total score by visit

Visit (week)	Placebo (N=158)	DLX 60-120 (N= 161)	p-value when compared with Placebo
4(1)	-3.084 (0.447)	-3.516 (0.443)	0.488
5(2)	-4.496 (0.514)	-6.175 (0.510)	0.0198
6(4)	-5.463 (0.580)	-7.236 (0.575)	0.029
7(7)	-6.077 (0.652)	-7.824 (0.646)	0.052
8 (10)	-5.893 (0.702)	-8.119 (0.695)	0.0234

Source: Reviewer's results
Note: the reported p-values are nominal p-values and are not adjusted for multiplicity.

Study HMDU

Table 8. Study HMDU: Mean change in HAMA total score by visit

Visit (week)	Placebo (N=158)	DLX 60-120 (N=149)	VEN 75-225 (N=159)	p-value when compared with Placebo	
				DLX 60-120	VEN 75-125
3 (1)	-4.173 (0.436)	-5.437 (0.447)	-5.297 (0.433)	0.0416	0.0647
4 (2)	-6.139 (0.486)	-8.195 (0.501)	-8.261 (0.485)	0.0031	0.0019
5 (4)	-7.851 (0.553)	-9.566 (0.570)	-10.369 (0.552)	0.0298	0.0012
6 (7)	-8.589 (0.641)	-11.473 (0.661)	-12.033 (0.639)	0.0017	0.0001
7 (10)	-9.185 (0.673)	-11.775 (0.694)	-12.335 (0.671)	0.007	0.0009

Source: Reviewer's results
Note: the reported p-values are nominal p-values and are not adjusted for multiplicity.

3.1.3.2 Sensitivity Analysis on the Imputation Methods on the Primary Endpoint.

In studies HMBR and HMDT, there were no missing item scores for any patients (if the scheduled visit was not missing). Thus, there were no differences in the calculation of the total score using the pre-specified imputation methods. For study HMDU, only one patient had differences in the calculation of the total score using the primary imputation method and Method 1.

3.1.3.3 Secondary Analysis on the Primary Endpoint

The efficacy results presented in this section represent those reported by the sponsor and confirmed by the reviewer. Tables 13, 14 and 15 show results from the repeated measures analysis of the HAMA total score for the studies HMBR, HMDT and HMDU respectively. In all three studies, the results were consistent with those from primary analysis (ANCOVA).

Study HMBR

Table 9. Study HMBR: Repeated measures analysis on HAMA total score

Visit (week)	Study Treatment	Number of patients	LS Change Mean (SE)	p-value when compared with Placebo
	Study HMBR			
4 (1)	Placebo	173	-3.11 (0.42)	
4 (1)	DLX 60 mg	165	-3.03 (0.43)	0.882
4 (1)	DLX 120 mg	169	-3.14 (0.42)	0.961
5 (2)	Placebo	164	-5.38 (0.50)	
5 (2)	DLX 60 mg	150	-8.95 (0.52)	< 0.001
5 (2)	DLX 120 mg	157	-7.84 (0.51)	< 0.001
6 (4)	Placebo	157	-6.83 (0.54)	
6 (4)	DLX 60 mg	146	-11.37 (0.56)	< 0.001
6 (4)	DLX 120 mg	145	-11.34 (0.56)	< 0.001
7 (6)	Placebo	145	-8.49 (0.57)	
7 (6)	DLX 60 mg	141	-13.34 (0.59)	< 0.001
7 (6)	DLX 120 mg	135	-13.65 (0.59)	< 0.001
8 (9)	Placebo	135	-9.17 (0.62)	
8 (9)	DLX 60 mg	137	-13.98 (0.63)	< 0.001
8 (9)	DLX 120 mg	130	-14.28 (0.64)	< 0.001

Source: Table 11.12 of HMBR Study Report (pg. 108)
Note: the reported p-values are nominal p-values and are not adjusted for multiplicity.

Study HMDT

Table 10. Study HMDT: Repeated measures analysis on HAMA total score

Visit (week)	Study Treatment	Number of patients	LS Change Mean (SE)	p-value when compared with Placebo
	Study HMDT			
4 (1)	Placebo	158	-3.00 (0.43)	
4 (1)	DLX 60-120 mg	161	-3.45 (0.43)	0.464
5 (2)	Placebo	156	-4.41 (0.49)	
5 (2)	DLX 60-120 mg	139	-6.83 (0.51)	<0.001
6 (4)	Placebo	141	-5.57 (0.56)	
6 (4)	DLX 60-120 mg	126	-8.41 (0.59)	<0.001
7 (7)	Placebo	129	-6.58 (0.66)	
7 (7)	DLX 60-120 mg	114	-9.63 (0.69)	0.001
8 (10)	Placebo	116	-6.29 (0.73)	
8 (10)	DLX 60-120 mg	100	-10.1 (0.78)	<0.001

Source: Table 11.12 of HMDT Study Report (pg. 118)
Note: the reported p-values are nominal p-values and are not adjusted for multiplicity.

Study HMDU

Table 11. Study HMDU: Repeated measures analysis on HAMA total score

Visit (week)	Study Treatment	Number of patients	LS Change Mean (SE)	p-value when compared with Placebo
	Study HMDU			
3 (1)	Placebo	157	-4.20 (0.42)	
3 (1)	DLX 60-120 mg	149	-5.46 (0.43)	0.036
3 (1)	VEN 75-225 mg	159	-5.32 (0.42)	0.057
4 (2)	Placebo	150	-6.29 (0.47)	
4 (2)	DLX 60-120 mg	133	-8.65 (0.50)	<0.001
4 (2)	VEN 75-225 mg	147	-8.56 (0.48)	< 0.001
5 (4)	Placebo	139	-8.00 (0.55)	
5 (4)	DLX 60-120 mg	119	-10.21 (0.59)	0.006
5 (4)	VEN 75-225 mg	133	-10.96 (0.56)	< 0.001
6 (7)	Placebo	123	-9.06 (0.66)	
6 (7)	DLX 60-120 mg	106	-13.03 (0.71)	< 0.001
6 (7)	VEN 75-225 mg	125	-13.11 (0.66)	< 0.001
7 (10)	Placebo	106	-10.00 (0.72)	
7 (10)	DLX 60-120 mg	94	-13.54 (0.77)	< 0.001
7 (10)	VEN 75-225 mg	110	-13.91 (0.72)	< 0.001

Source: Table 11.13 of HMDU Study Report (pg. 136)
Note: the reported p-values are nominal p-values and are not adjusted for multiplicity.

3.1.3.4 Primary Analysis on the Key Secondary Endpoint

This reviewer confirmed the sponsor's analysis results for key secondary end point Sheehan Disability Scale Global Functional Impairment score (SDS). Table 12 displays efficacy results for the key secondary endpoint. Based on the ANCOVA model, all duloxetine treatment arms were statistically significantly superior to placebo. For study HMBR, the effect of higher dose (120mg/day) did not appear to be better than the effect of the lower dose (60mg/day).

Table 12. Mean change in Sheehan Disability Scale global score from Baseline to Endpoint visit

Study Treatment	Number of patients	Baseline Mean (SD) (raw data)	Endpoint Mean (SD) (raw data)	LS Change Mean (SE)	p-value when compared with Placebo
Study HMBR					
Placebo	163	15.05 (7.29)	11.39 (8.12)	-3.83 (0.56)	
DLX 60 mg	156	15.26 (7.40)	7.38 (6.79)	-7.76 (0.58)	< 0.001
DLX 120 mg	160	14.97 (7.51)	8.08 (8.27)	-7.04 (0.57)	< 0.001
Study HMDT					
Placebo	141	14.64 (7.78)	11.42 (8.71)	-3.11 (0.66)	
DLX60-120mg	144	14.26 (7.24)	8.42 (7.96)	-5.78 (0.66)	0.004
Study HMDU					
Placebo	125	17.52 (5.82)	12.08 (7.53)	-5.42 (0.68)	
DLX60-120mg	122	17.41 (6.44)	9.49 (7.92)	-8.03 (0.69)	0.007
VEN 75-225mg	139	17.55 (5.43)	9.57 (8.06)	-7.97 (0.64)	0.006

Source: Table 11.11 of HMBR Study Report (pg.103), Table 11.11 of HMDT Study Report (pg. 113), Table 11.12 of HMDU Study Report (pg.131).

3.1.3.5 Exploratory Secondary Efficacy measures

The main exploratory secondary efficacy measures were the Anxiety and Depression Subscales Score of the Hospital Anxiety and Depression Scale (HADS), HAMA Psychic Factor Score and the Somatic Factor Score, Clinical Global Impression-Improvement (CGI-Improvement) Scale, Patient Global Impression-Improvement (PGI-Improvement) Scale. The secondary efficacy variables were analyzed by ANCOVA, ANOVA and repeated measures analysis. The sponsor reported the following analyses results:

Study HMBR

All secondary efficacy measures demonstrated significant improvement of duloxetine 60mg and duloxetine 120 mg arms compared with placebo.

Study HMDT

All secondary efficacy measures except HADS Depression Subscale Score demonstrated significant improvement of flexible dose of duloxetine (60 mg to 120 mg) compared with placebo.

Study HMDU

All secondary efficacy measures except HAMA Somatic Anxiety Factor Score demonstrated significant improvement of flexible dose of duloxetine (60 mg to 120 mg) compared with placebo.

Reviewer's comment: These were the sponsor's exploratory analyses and the results are considered exploratory only.

3.1.3.6 Results and Conclusions

For all three studies, this reviewer confirmed the sponsor's analysis results for the primary and key secondary endpoints. In these studies, the primary efficacy measure, HAMA total score, and the key secondary efficacy measure, SDS Global Functional Impairment score, demonstrated efficacy of each dose group of duloxetine.

In the fixed dose study HMBR, the 120 mg arm of duloxetine did not appear to demonstrate better effect compared to 60 mg arm (based on the primary and key secondary efficacy endpoints). Per sponsor's SAP, the primary objective was to compare 120 mg to placebo with respect to HAMA total score. Although comparison of 60 mg to placebo on this efficacy measure was initially considered as one of the primary objectives, it was removed from the final SAP.

3.2 Evaluation of Safety

The statistical reviewer did not perform the evaluation of safety for this application. Please see the clinical review for this evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Tables below present reviewer's efficacy results from exploratory subgroup analyses by gender, race and age. Analysis by race was not performed for study HMBR since there were only two non-Caucasian patients in placebo group and one such patient in duloxetine 120mg group. The results coincide with the sponsor' results. For study HMDU, this reviewer noticed that female patients accounted for about 2/3 of the total set of ITT population, but they did not seem to show numerical difference between the duloxetine and placebo groups in change from baseline to endpoint in HAMA total score. In general, the treatment effect appeared to be numerically in favor of duloxetine (when compared with placebo) among all subgroups in all three studies except non-Caucasian subgroup in study HMDT.

Study HMBR

Table 13. Study HMBR: Subgroup Analysis. Mean change in HAMA total score from Baseline to Endpoint visit

HMBR	Placebo N=173	DLX 60mg N=165	DLX 120mg N=169
Gender, mean, 95% CI			
Male N=165	-7.783, (-9.684, -5.883) N=58	-12.192, (-14.060, -10.323) N=60	-14.276, (-16.386, -12.166) N=47
Female N=342	-8.660, (-10.398, -6.922) N=115	-13.258, (-15.075,-11.441) N=105	-11.843, (-13.530, -10.157) N=122
Age, Mean, 95% CI			
<55 years N=399	-8.760, (-10.309, -7.210) N=132	-13.131, (-14.657, -11.605) N=136	-13.120, (-14.674, -11.566) N=131
>=55 years N=108	-7.033, (-9.512, -4.555) N=41	-11.879, (-14.825, -8.932) N=29	-10.345, (-12.920, -7.770) N=38

Corresponds to Table 14.20 of HMBR Study Report (pg. 286-288)
Note: the reported 95% CIs are nominal CIs and are not adjusted for multiplicity.

Study HMDT

Table 14. Study HMDT: Subgroup Analysis. Mean change in HAMA total score from Baseline to Endpoint visit

HMDT	Placebo N=158	DLX 60-120mg N=161
Gender, Mean, 95 % CI		
Male N=121	-6.814, (-9.174, -4.454) N=59	-7.854, (-10.154, -5.553) N=62
Female N=198	-6.108, (-7.841, -4.375) N=99	-8.730, (-10.462, -6.997) N=99
Race, Mean, 95% CI		
Caucasian N=251	-5.769, (-7.355, -4.182) N=123	-9.213, (-10.768, -7.659) N=128
Other N=68	-8.110, (-10.881, -5.339) N=35	-5.609, (-8.463, -2.755) N=33
Age, Mean, 95% CI		
<55 years N=260	-6.262 (0.791) N=129	-8.000 (0.785) N=131
>=55 N=59	-6.333, (-9.392, -3.274) N=29	-10.610, (-13.616, -7.605) N=30

Corresponds to Table 14.8 of HMDT Study report (pg. 236-238)
Note: the reported 95% CIs are nominal CIs and are not adjusted for multiplicity.

Study HMDU

Table 15. Study HMDU: Subgroup Analysis. Mean change in HAMA total score from Baseline to Endpoint visit

HMDU	Placebo N=158	DLX 60-120mg N=149	VEN 75-225mg N=159
Gender, Mean, 95% CI			
Male N=173	-6.925, (-8.997, -4.854) N=60	-12.772, (-14.978, -10.567) N=53	-10.958, (-13.035, -8.881) N=60
Female N=293	-10.342, (-12.079, -8.604) N=98	-10.863, (-12.618, -9.108) N=96	-12.783, (-14.509, -11.057) N=99
Race, Mean, 95% CI			
Caucasian N=324	-8.531, (-10.098, -6.965) N=110	-11.931, (-13.583, -10.279) N=99	-12.072, (-13.604, -10.539) N=115
Other N=142	-10.153, (-12.734,-7.572) N=48	-10.794, (-13.323, -8.264) N=50	-12.202, (-14.888, -9.516) N=44
Age, Mean, 95% CI			
<55 years N=391	-9.207, (-10.716, -7.697) N=129	-11.813, (-13.354, -10.271) N=124	-12.409, (-13.869, -10.948) N=138
>=55 N=75	-8.278, (-11.120, -5.437) N=29	-10.116, (-13.179, -7.052) N=25	-10.190, (-13.521, -6.860) N=21

Corresponds to Table 14.15 of HMDU Study Report (pg. 285-287)
Note: the reported 95% CIs are nominal CIs and are not adjusted for multiplicity.

4.2 Other Special/Subgroup Populations

For studies HMBR, HMDT and HMDU, this reviewer confirmed the sponsor's results of exploratory subgroup analysis by anxiety severity at baseline and by previous use of benzodiazepines (existing medication used for GAD treatment). For the patients with less severe anxiety conditions at baseline, not all studies showed numerical trend in favor of duloxetine (refer to Table 18).

Study HMBR

Table 16. Study HMBR: Special Subgroup Analysis. Mean change in HAMA total score from Baseline to Endpoint visit

HMDU	Placebo	DLX 60mg	DLX 120mg
Anxiety severity, Mean, 95% CI			
score <22 N=162	-5.850, (-7.821, -3.879) N=56	-7.129, (-9.194, -5.064) N=51	-6.941, (-8.929, -4.953) N=55
score >=22 N=345	-9.548, (-11.252, -7.845) N=117	-15.552, (-17.275, -13.828) N=114	-15.121, (-16.841, -13.401) N=114
Previous benzo use, Mean, 95% CI			
Yes N=103	-8.927, (-11.707, -6.147) N=42	-14.004, (-17.353, -10.656) N=29	-8.966, (-12.136, -5.795) N=32
No N=404	-8.173, (-9.670, -6.675) N=131	-12.674, (-14.144, -11.204) N=136	-13.318, (-14.782, -11.853) N=137

Corresponds to Table 14.20 of HMBR Study Report (pg. 289-290)
Note: the reported 95% CIs are nominal CIs and are not adjusted for multiplicity.

Study HMDT

Table 17. Study HMDT: Special Subgroup Analysis. Mean change in HAMA total score from Baseline to Endpoint visit

HMDT	Placebo N=158	DLX 60-120mg N=161
Anxiety severity, Mean, 95% CI		
score <22 N=133	-4.133, (-5.913, -2.353) N=64	-6.079, (-7.792, -4.365) N=69
score >= 22 N=186	-7.786, (-9.785, -5.787) N=94	-10.240, (-12.260, -8.219) N=92
Previous benzo use, Mean, 95% CI		
Yes N=41	-8.221, (-12.375, -4.066) N=22	-13.112, (-17.585, -8.639) N=19
No N=278	-6.018, (-7.494, -4.543) N=136	-7.813, (-9.256, -6.369) N=142

Corresponds to Table 14.8 of HMDT Study report (pg. 239-240)
Note: the reported 95% CIs are nominal CIs and are not adjusted for multiplicity.

Study HMDU

Table 18. Study HMDU: Special Subgroup Analysis. Mean change in HAMA total score from Baseline to Endpoint visit

HMDU	Placebo N=158	DLX 60-120mg N=149	VEN 75-225mg N=159
Anxiety severity, Mean, 95% CI			
score <22 N=134	-6.338, (-8.391, -4.284) N=48	-5.864, (-8.115, -3.612) N=40	-8.808, (-10.903, -6.713) N=46
score >=22 N=332	-10.129, (-11.817, -8.441) N=110	-13.759, (-15.457, -12.061) N=109	-13.398, (-15.065, -11.730) N=113
Previous benzo use, Mean, 95% CI			
Yes N=71	-7.353, (-11.250, -3.456) N=22	-13.118, (-17.321, -8.915) N=19	-11.365, (-14.694, -8.036) N=30
No N=395	-9.318, (-10.742, -7.893) N=136	-11.259, (-12.720, -9.798) N=130	-12.317, (-13.781, -10.854) N=129

Corresponds to Table 14.15 of HMDU Study Report (pg. 288-289)
Note: the reported 95% CIs are nominal CIs and are not adjusted for multiplicity.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The three studies have demonstrated that duloxetine in the dose range of 60 mg to 120 mg was effective in the treatment of symptoms of Generalized Anxiety Disorder in adult patients. The fixed-dose study HMBR indicated that there was no additional benefit of 120mg arm over 60 mg arm, although primary comparison was 120 mg versus placebo.

5.2 Conclusions and Recommendations

All three studies demonstrated statistically significant treatment effect in the symptoms of Generalized Anxiety Disorder. Even though in study HMBR the 120 mg dose was considered as primary dose, the lower dose should be used for treatment of GAD unless there is some additional evidence in support of the 120 mg dose vs. 60 mg dose.

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/s/

George Kordzakhia
1/9/2007 02:26:11 PM
BIOMETRICS
I am thankful to Dr. Yeh-Fong Chen for her active involvment in my first NDA review.

Peiling Yang
1/9/2007 04:55:03 PM
BIOMETRICS

James Hung
1/11/2007 01:51:25 PM
BIOMETRICS

Supplemental New Drug Application
Efficacy Supplement
OCP Review

NDA:	21-427
Serial Number:	SES-011
Type of Submission:	Standard Efficacy Supplement
Generic Name:	Duloxetine HCl Capsules Delayed Release Pellets
Brand Name:	Cymbalta
Formulation(s); Strength(s); Route(s)	Capsules 20, 30, 60 mg po
Sponsor:	Lilly Indianapolis, IN
Submission Dates:	April 27, 2006
Reviewer:	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
Team Leader	Raman Baweja, Ph.D.
OCPB Division	Division of Clinical Pharmacology 1 (DCP1) HFD-860
ORM Division	Division of Psychiatry Drug Products (DPDP) HFD-130

1 BACKGROUND

Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) that is approved for the treatment of major depressive disorder at dosages up to 60 mg per day (30 mg bid or 60 mg qd) and for the pain of diabetic neuropathy at doses up to 120 mg/day.

As a post-marketing phase IV commitment for the approval of Yentreve® for the treatment of Stress Urinary Incontinence (SUI) in the European Union (EU), Lilly has conducted a study of the excretion of duloxetine into human breast milk. Duloxetine is approved as a dose of 40 mg bid for SUI in the EU.

The present submission includes the study report from this breast milk excretion study and changes to the labeling based on the results.

This submission also contains pharmacokinetic information on the effect of ethnicity, gender, smoking, CYP1A2 inhibition, and receptor binding, along with bioequivalence data for a different capsule shell and a manufacturing site change.

2 OCP FINDINGS

Fluvoxamine 100 mg qPM increased the AUCτ over 6 fold after duloxetine 40 mg bid in CYP2D6 poor metabolizers due to inhibition of CYP1A2. However, as the dose of duloxetine is higher than is typically used clinically, the degree of increase will be even greater in subjects receiving a typical labeled dose. In addition, as exposures in poor metabolizers are already twice as high as in extensive metabolizers the AUCs in these PMs in the presence of a CYP1A2 inhibitor are actually around 13 fold higher than the AUCs seen in the typical uninhibited CYP2D6 extensive metabolizer who comprise the bulk of the safety

database. These subjects may also be at a greater risk for metabolic shunting via duloxetine epoxide and thus may be at a greater risk for hepatotoxicity.

The average increase in theophylline AUC∞ is 20% with a range of -6% to approximately 60% using a duloxetine dose that will mimic exposures in Female CYP2D6 poor metabolizers.

Based on the results of study SBCR there may be a clinically significant inhibition of CYP1A2 by duloxetine under steady-state conditions, especially in female CYP2D6 poor metabolizers. The true extent of this interaction cannot be determined by the present study, as the study was designed and reported in such a way as to minimize the ability to detect or recognize the presence of any interaction even with a single dose of aminophylline.

There was insufficient information to tell if there's an effect of Chinese or Southern Asian ethnicity or not.

Studies HMEE, HMCE, and HMDS all show higher duloxetine exposures in women compared with men.

As expected, smokers had lower exposures to duloxetine than non-smokers in both studies HMDS and HMCE.

Results of positron emission studies of thalamic serotonin receptor binding indicate that doses above 40 mg daily are unlikely to add additional clinical benefit.

Duloxetine 60 mg capsules manufactured at Lilly del Caribe, Inc., Carolina, Puerto Rico (test) are bioequivalent to those manufactured at the Indianapolis, Indiana facility.

Duloxetine 20 mg capsules using HPMC capsules are bioequivalent to duloxetine 20 mg capsules using gelatin capsules.

Study SBCS regarding the effect of lactation and duloxetine excretion in breast milk was reviewed under labeling supplement N21-427 SLR-009 submitted January 23rd, 2006. OCP labeling recommendations for the sponsor were included in the review for SLR-009 and the reader is referred to that review for more details.

3 OCP RECOMMENDATIONS

OCP finds the studies submitted adequate to justify labeling changes.

4 OCP COMMENTS

4.1 Comments for Review Team

OCP finds that duloxetine 60 mg capsules manufactured at Lilly del Caribe, Inc., Carolina, Puerto Rico (test) are bioequivalent to those manufactured at the Indianapolis, Indiana facility.

Although the sponsor provided bioequivalence data for a manufacturing site change, the sponsor has not made an explicit request for the addition of this site nor has the sponsor provided information on either manufacturing or equipment changes. In addition no dissolution or stability data has been provided.

4.2 Comments to be sent to the Sponsor

Labeling comments shown in §6 Labeling Recommendations should be forwarded to the sponsor as appropriate.

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6 LABELING RECOMMENDATIONS

The sponsor's proposed changes are shown in yellow highlighting.

The sponsor's proposed deletions are indicated by single line ~~strike outs in red text.~~

The sponsor's proposed additionss are indicated by single underlines in blue text.

OCP proposed changes are shown in [redacted].

OCP proposed deletions are indicated by double line ~~strike outs in red text~~.

OCP proposed additions are indicated by double underlines in blue text.

11 Page(s) Withheld

√ Trade Secret / Confidential (b4)

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Withheld Track Number: Pharm/Tox- 1

7 OCP REVIEW

7.1 Intrinsic Factors

7.1.1 Effect of Ethnicity

There was insufficient information to tell if there's an effect of Chinese or Southern Asian ethnicity or not.

7.1.1.1 Chinese – Studies HMEE & HMCE

Study HMEE was a double- blind, randomized, placebo-controlled, single period, single and multiple dose safety/tolerability and pharmacokinetic study in healthy male and female Chinese healthy subjects 20 to 45 years of age conducted in Beijing China.

Duloxetine was administered 60 mg (2 x 30 mg capsules) were administered on day 1 and then for 6 days from days 4 to 9.

Results are shown in Table 1 and Table 2, without a comparator group the results are difficult to interpret although by visual inspection they appear to be around the values reported for Caucasians and Japanese in the original NDA.

7.1.1.2 Indian – Study HMCE

Study HMCE was a bioequivalence study for a manufacturing site change. Subjects included Chinese, Indian, a Pakastani, and a Malaysian. There are too few subjects to tell if there are higher exposures in Indians or not, see Table 2.

7.1.2 Effect of Gender - Study HMCE

Studies HMEE, HMCE, and HMDS all show higher duloxetine exposures in women compared with men, (see Table 1, Table 2, Table 14, and Table 17).

Table 1 Duloxetine Single and Multiple Dose Pharmacokinetic Metrics - Study HMEE

SD/ MD	Gender	N	Tlag (h)	Tmax (h)	Cmax (ng/ml)	Cmin,ss (ng/ml)	Cav,ss (ng/ml)	AUC∞ (ng/ml x hr^{-1})[a]	% Extrap	t½ (h)	CL/F (L/h)	Vz/F (L)	RA (ng/ml)	LI (ng/ml x hr^{-1})
SD	M & F	23	0.9 ± 0.8 (84.6) 0.0 - 2.0 [1.0]	5.4 ± 1.4 (26.1) 4.0 - 8.0 [6.0]	39.7 ± 17.0 (42.8) 13.0 - 74.8 [34.8]	–	–	683 ± 365 (53.3) 117 - 1630 [621]	2.80 ± 1.96 (69.8) 0.863 - 9.46 [2.32]	10.5 ± 2.1 (20.1) 6.33 - 16.3 [10.4]	122 ± 97.0 (79.2) 36.8 - 513 [96.7]	1660 ± 856 (51.5) 760 - 4680 [1480]	–	–
	M	13	1.1 ± 0.8 (77.3) 0.0 - 2.0 [1.0]	5.2 ± 1.5 (29.4) 4.0 - 8.0 [4.0]	39.5 ± 17.7 (44.7) 13.0 - 74.8 [34.8]	–	–	666 ± 335 (50.3) 117 - 1320 [621]	2.9 ± 2.2 (78.2) 1.1 - 9.5 [2.0]	10.3 ± 2.1 (20.3) 6.3 - 13.6 [10.6]	132.5 ± 122.8 (92.7) 45.4 - 513.0 [96.7]	1722 ± 1018 (59.1) 801 - 4680 [1480]	–	–
	F	10	0.7 ± 0.7 (96.4) 0.0 - 2.0 [1.0]	5.6 ± 1.3 (22.6) 4.0 - 8.0 [6.0]	40.1 ± 17.0 (42.6) 19.5 - 71.6 [38.3]	–	–	706 ± 417 (59.1) 334 - 1630 [599]	2.7 ± 1.6 (59.8) 0.9 - 5.4 [2.6]	10.7 ± 2.2 (20.6) 8.5 - 16.3 [10.3]	109.3 ± 50.5 (46.2) 36.8 - 180.0 [104.9]	1586 ± 629 (39.7) 759 - 2700 [1510]	–	–
MD	M & F	21	–	5.0 ± 1.2 (24.2) 4.0 - 8.0 [4.0]	58.9 ± 25.9 (43.9) 19.0 - 115.0 [59.7]	16.3 ± 8.7 (53.4) 2.3 - 39.5 [14.1]	32.3 ± 14.5 (44.8) 7.76 - 66.9 [30.0]	774 ± 347 (44.8) 186 - 1610 [720]	–	11.2 ± 2.5 22.4 6.36 - 17.8 [10.6]	101 ± 66.3 (65.9) 37.4 - 322 [83.3]	1720 ± 796 (46.4) 794 - 3630 [1400]	1.64 ± 0.74 (45.2) 1.11 - 4.44 [1.41]	1.24 ± 0.58 (46.6) 0.770 - 3.36 [1.07]
	M	12	–	5.0 ± 1.0 (20.9) 4.0 - 6.0 [5.0]	47.6 ± 18.2 (38.1) 19.0 - 72.1 [51.5]	13.6 ± 7.0 (51.5) 2.3 - 25.4 [13.5]	26.6 ± 11.3 (42.7) 7.8 - 42.4 [27.7]	638 ± 273 (42.8) 186 - 1020 [664]	–	10.9 ± 2.5 (22.7) 6.4 - 15.3 [10.6]	121.3 ± 78.3 (64.6) 58.9 - 322.0 [90.4]	2022 ± 879 (43.4) 1120 - 3630 [1610]	1.3 ± 0.2 (14.2) 1.1 - 1.8 [1.3]	1.0 ± 0.2 (21.4) 0.8 - 1.6 [1.0]
	F	9	–	4.9 ± 1.4 (29.6) 4.0 - 8.0 [4.0]	73.9 ± 27.8 (37.7) 31.2 - 115.0 [68.5]	19.8 ± 9.8 (49.4) 8.4 - 39.5 [19.1]	39.8 ± 15.3 (38.3) 19.6 - 66.9 [41.3]	957 ± 367 (38.4) 470 - 1610 [992]	–	11.7 ± 2.7 (22.8) 9.0 - 17.8 [11.7]	73.1 ± 32.3 (44.3) 37.4 - 128.0 [60.5]	1306 ± 438 (33.5) 794 - 2160 [1220]	2.0 ± 1.0 (48.7) 1.1 - 4.4 [1.7]	1.5 ± 0.8 (50.5) 0.9 - 3.4 [1.3]

a Metric for steady-state dosing is AUCτ

Table 2 Duloxetine Single Dose Pharmacokinetic Metrics in Subjects grouped by Ethnicity and Gender – Study HMCE

Ethnicity	Chinese				Indian		Malay		Pakistani	
Gender	Male		Female		Male		Male		Male	
Rx	Ref	Test	Ref	Test	Ref	Test	Ref	Test	Ref	Test
N	17	17	2	2	3	3	1	1	1	1
Wt (kg)	71.7 ± 10.2 (14.3) 54.5 - 89.3 [70.5]	71.7 ± 10.2 (14.3) 54.5 - 89.3 [70.5]	62.2 ± 12.2 (19.6) 53.6 - 70.8 [62.2]	62.2 ± 12.2 (19.6) 53.6 - 70.8 [62.2]	67.5 ± 10.0 (14.8) 56 - 73.5 [73]	67.5 ± 10.0 (14.8) 56 - 73.5 [73]	65	65	84.1	84.1
Tmax (hrs)	6.4 ± 1.1 (16.6) 4 - 8 [6]	6.0 ± 1.4 (23.5) 4 - 8 [6]	6.0 ± 0.0 (0.0) 6.0 - 6.0 [6.0]	6.0 ± 0.0 (0.0) 6.0 - 6.0 [6.0]	6.0 ± 0.0 (0.3) 6 - 603 [6]	7.3 ± 1.2 (15.7) 6 - 8 [8]	8	8	6	6
Cmax (ng/ml)	33.5 ± 13.9 (41.5) 9.8 - 61.3 [33.7]	34.7 ± 13.6 (39.3) 12.7 - 57.8 [31.5]	76.4 ± 27.0 (35.4) 57.3 - 95.5 [76.4]	80.8 ± 54 (66.9) 42.6 - 119 [80.8]	56.1 ± 43.3 (77.2) 28.2 - 106 [34.1]	54.1 ± 42.4 (78.5) 27.3 - 103 [31.9]	35.4	32.3	16.5	14
AUCt (ng/ml x hr^{-1})	536 ± 261 (48.7) 156 - 1060 [465]	517 ± 225.2 (43.5) 242 - 1140 [467]	1366 ± 754 (55.2) 833 - 1900 [1366.5]	1352 ± 860 (63.6) 744 - 1960 [1352.0]	1062 ± 960 (90.4) 472 - 2170 [545]	1118 ± 1038 (92.8) 416 - 2310 [628]	666	642	257	202
AUCinf /ml x hr^{-1}	589 ± 351 (59.6) 161 - 1610 [484]	534 ± 227 (42.5) 248 - 1170 [494]	1412 ± 775 (54.9) 864 - 1960 [1412.0]	1386 ± 868 (62.6) 773 - 2000 [1386.5]	1114 ± 1019 (91.4) 492 - 2290 [561]	1188 ± 1124 (94.6) 440 - 2480 [643]	682	652	269	214
AUCextrap (%)	6.1 ± 8.6 (141.8) 1.13 - 38.3 [3.79]	3.4 ± 2.1 (60.0) 1.08 - 8.99 [2.99]	3.3 ± 0.5 (15.2) 3.0 - 3.7 [3.3]	3.0 ± 1.0 (31.7) 2.3 - 3.7 [3.0]	4.0 ± 1.2 (31.1) 2.78 - 5.26 [3.93]	4.9 ± 2.3 (47.7) 2.26 - 6.71 [5.59]	2.39	1.42	4.43	5.8
CL/F (L/hr)	136.2 ± 80.8 (59.3) 36.8 - 372 [124]	130.5 ± 50.8 (38.9) 51.4 - 241 [121]	50.0 ± 27.4 (54.9) 30.6 - 69.4 [50.0]	54 ± 34 (62.6) 29.9 - 77.4 [53.7]	85.1 ± 51.5 (60.6) 26.2 - 122 [107]	84.8 ± 56.9 (67.0) 24.2 - 137 [93.3]	87.9	92.1	222	281
Vz (L)	2093 ± 1031 (49.3) 925 - 4830 [1820]	1929 ± 716 (37.1) 917 - 3850 [1810]	830 ± 312 (37.6) 609 - 1050 [829.5]	806 ± 345 (42.8) 562 - 1050 [806.0]	1467 ± 750 (51.1) 631 - 2080 [1690]	1474 ± 768 (52.1) 621 - 2110 [1690]	1590	1420	3310	4370
$t_{1/2}$ (hrs)	12.8 ± 10.9 (85.3) 6.7 - 54.8 [10.3]	10.5 ± 1.7 (16.2) 6.55 - 12.7 [10.4]	12.2 ± 2.3 (19.2) 10.5 - 13.8 [12.2]	11.2 ± 2.5 (22.7) 9.4 - 13.0 [11.2]	13.3 ± 3.6 (26.9) 9.58 - 16.7 [13.5]	13.7 ± 3.7 (26.8) 10.7 - 17.8 [12.6]	12.6	10.7	10.3	10.8

7.2 Extrinsic Factors

7.2.1 Effect of Smoking – Studies HMDS and HMCE

The effect of smoking was not formally studied however both studies HMDS and HMCE included smoking status, as expected smokers had lower exposures to duloxetine than non-smokers.

Study HMDS examined the effect of CYP1A2 inhibition by fluvoxamine on Duloxetine pharmacokinetics. Unfortunately there were only 2 smokers so no conclusions can be drawn, see Table 8 - Table 13.

Study HMCE examined the bioequivalence of duloxetine manufactured at two manufacturing sites. As expected smokers had much lower AUCs; indicative of enzyme induction of CYP1A2, see Table 3.

Table 3 Effect of Smoking Status on Duloxetine Pharmacokinetics - Study HMDS

Smoking Status	Non-Smokers		Smokers	
Rx	Ref	Test	Ref	Test
N	13	13	11	11
Wt (kg)	69.5 ± 10.2 (14.7) 53.6 - 86.5 [70.8]	69.5 ± 10.2 (14.7) 53.6 - 86.5 [70.8]	71.9 ± 10.6 (14.8) 54.5 - 89.3 [70.5]	71.9 ± 10.6 (14.8) 54.5 - 89.3 [70.5]
Tmax (hrs)	6.5 ± 0.9 (13.5) 6 - 8 [6]	6.6 ± 1.3 (19.1) 4 - 8 [6]	6.2 ± 1.1 (17.4) 4 - 8 [6]	5.8 ± 1.4 (24.0) 4 - 8 [6]
Cmax (ng/ml)	45.0 ± 28.7 (63.8) 9.8 - 106 [34.3]	46.4 ± 31.4 (67.7) 12.7 - 119 [36.8]	32.4 ± 11.9 (36.8) 16.5 - 58.9 [33.7]	32.4 ± 12.6 (39.1) 14 - 57.8 [31.5]
AUCt (ng/ml x hr^{-1})	811.6 ± 609.3 (75.1) 156 - 2170 [545]	804.8 ± 639.3 (79.4) 242 - 2310 [628]	491.2 ± 184.8 (37.6) 257 - 802 [465]	475.7 ± 172.5 (36.3) 202 - 717 [421]
AUCinf (ng/ml x hr^{-1})	887.4 ± 669.2 (75.4) 161 - 2290 [561]	835.2 ± 674.6 (80.8) 248 - 2480 [643]	509.3 ± 185.0 (36.3) 269 - 811 [484]	492.1 ± 171.6 (34.9) 214 - 728 [436]
AUCextrap (%)	6.6 ± 9.8 (148.9) 1.18 - 38.3 [3.66]	3.5 ± 2.3 (65.6) 1.45 - 8.99 [2.64]	3.9 ± 1.6 (40.3) 1.13 - 5.96 [3.96]	3.8 ± 1.8 (48.2) 1.08 - 6.29 [4.16]
CL/F (L/hr)	116.2 ± 96.5 (83.1) 26.2 - 372 [107]	109.7 ± 64.9 (59.2) 24.2 - 241 [93.3]	133.7 ± 50.7 (37.9) 74 - 222 [124]	138.8 ± 58.4 (42.1) 82.4 - 281 [137]
Vz (L)	1898.8 ± 1234.3 (65.0) 609 - 4830 [1620]	1666.2 ± 862.0 (51.7) 562 - 3850 [1660]	1987.3 ± 737.5 (37.1) 1010 - 3310 [1820]	2086.4 ± 937.0 (44.9) 1300 - 4370 [1810]
t½ (hrs)	14.7 ± 12.3 (84.1) 6.7 - 54.8 [11.1]	11.5 ± 2.7 (23.8) 6.55 - 17.8 [12.2]	10.4 ± 1.0 (9.8) 8.98 - 12.6 [10.3]	10.4 ± 0.8 (8.2) 8.59 - 11.6 [10.4]

7.2.2 Drug-Drug Interactions

7.2.2.1 Effect of CYP1A2 Inhibition on Duloxetine – Study HMDS

Fluvoxamine 100 mg qPM increased the AUCτ over 6 fold after duloxetine 40 mg bid in CYP2D6 poor metabolizers. First as the dose of duloxetine is higher than is typically used clinically, the degree of increase will be even greater in subjects receiving a typical labeled dose. In addition, as exposures in poor metabolizers are already twice as high as in extensive metabolizers the AUCs in these PMs in the presence of a CYP1A2 inhibitor are actually around 13 fold higher than the AUCs seen in the typical uninhibited extensive metabolizer who comprise the bulk of the safety database.

In the original NDA review the effect of CYP1A2 inhibition on duloxetine pharmacokinetics was not examined. Yet the original review concluded that inhibition by common CYP1A2 inhibitors such as fluroquinilones or cimetidine could result in excessive exposures and adverse effects, especially in CYP2D6 poor metabolizers. Alternatively, as with duloxetine, this could result in shunting to a toxic metabolite. This is typically of concern when starting or stopping a medication. If the offending co-medication is one that is commonly taken in combination, the interaction may be more easily managed. However in the present case these drugs are of additional concern as both fluroquinilones and cimetidine may be taken acutely and not chronically, and may be prescribed by different physicians than those prescribing duloxetine, and in the case of cimitidine is available as a non-prescription drug.

Study HMDS was a randomized, un-blinded multiple-dose study of the effect of CYP1A2 inhibition by fluvoxamine on duloxetine pharmacokinetics in 15 healthy men (n = 3) and women (n = 10) 21 – 59 years of age who are CYP2D6 poor metabolizers, two of whom were smokers.

Duloxetine 40 mg bid was given alone on Days 1-4 and in the morning of Day 5, and then in combination with fluvoxamine from the evening of Day 5 through the morning of Day 19. Fluvoxamine was given once daily in the evening at a dose of 50 mg on Days 5 and 6, then at a dose of 100 mg on Days 7 – 18 in combination with duloxetine. After the last dose of duloxetine in the morning of Day 19, fluvoxamine was continued at a dose of 100 mg daily in the evenings of Day 19 and Day 20 and then at a dose of 50 mg daily in the evenings of Day 21 and Day 22.

Plasma samples to determine concentrations of duloxetine and two metabolites, 4-hydroxy-duloxetine glucuronide and 5-hydroxy, 6-methoxy-duloxetine sulfate, were obtained on the last day of duloxetine-only dosing, (Day 5), and on the last day of duloxetine-fluvoxamine dosing, (Day 19), Samples were collected from each subject at approximately 2, 4, 6, 8, 10, and 12 hours after the morning dose of duloxetine.

According to the sponsor, *'In subjects not taking fluvoxamine, duloxetine has a mean 12-hour half-life and reaches steady state within 3 days of dosing. In a single CYP2D6 PM subject enrolled in Study HMCC, the half-life of duloxetine when taken alone was comparable at 13.7 hours. During combined dosing with duloxetine and fluvoxamine in this PM subject, the half life of duloxetine was 97.4 hours. Based on this extended half-life, 90% of steady state was expected within 14 days of combined dosing. Therefore, with duloxetine 40 mg twice daily and fluvoxamine 100 mg once daily, at least 90% of duloxetine steady state was expected to be reached by Day 19.*

With at least 7 CYP2D6 PM subjects, there will be between 80% and 85% probability that the 90% confidence interval of the ratio of geometric means (combined fluvoxamine and duloxetine versus duloxetine only) around a 5.2-fold increase in steady-state AUC for duloxetine will fall between 4.0 and 8.4. This is based upon a within-subject coefficient-of-variation (CV) of 17% for duloxetine AUC. The mean 5.2-fold increase assumes an additive effect of dual inhibition of CYP2D6 and CYP1A2, based on studies F1J-FW-SBAG and F1J-LC-HMCC, respectively.'

Results

Table 4 shows that the both the Cmax and AUCτ of duloxetine increase over 6 fold in CYP2D6 poor metabolizers in the presence of a CYP1A2 inhibitor. In addition, the formation of 4-hydroxy-duloxetine glucuronide and 5-hydroxy, 6-methoxy-duloxetine sulfate decreased by approximately 50% and 60% respectively.

A 6.4 fold increase indicates that total clearance decreased by 85%. Since, the subjects are CYP2D6 poor metabolizers the degree of decrease in clearance is greater than is expected in extensive metabolizers, but the exposure relative to the typical subject making up the safety database is higher. That is a typical subject in the database is an extensive metabolizer whose CYP1A2 is not blocked. Since, exposures in poor metabolizers are twice as high as in extensive metabolizers the expected exposure relative to the typical subject is expected to be around 13 fold higher. This is also consistent with the 1.6 fold increase in AUC seen in the presence of the CYP2D6 inhibitor paroxetine, e.g. 1.6 x 6.4 = an expected 10.24 fold increase, and is also consistent with predictions made during the IND phase based on *in vitro* and mass balance data.

Another indication that this is correct is by examination of AUCs in the present study in the presence of fluvoxamine compared to AUCs under similar conditions in another study in the absence of CYP1A2 inhibitors. If we use study HMAR from the original NDA we can find that the maximum AUCτ at a dose of 40 mg bid was around 1000 ng/ml x hr^{-1}, whereas in the present study the maximum observed AUCτ was 13300 ng/ml x hr^{-1}.

From the mass balance study in the original NDA on average 3.2% of a dose in eliminated via the reactive epoxide intermediary. Consequently, a 10-12 fold increase in shunting to this pathway means approximately 1/3 of the dose is eliminated via this pathway when both CYP1A2 and CYP2D6 are inhibited.

Since the typical approved dose of duloxetine in depression in 60 mg per day and in diabetic peripheral neuropathy up to 120 mg per day we expect upward of 40 mg per day to be eliminated via the potentially hepatotoxic epoxide intermediate when both CYP1A2 and CYP2D6 are blocked. Consequently, patients who have diminished elimination via both CYP2D6 and CYP1A2 have diminished hepatic reserve and who are likely to have decreased glutathione stores are likely to be at the most risk or hepatotoxicity.

Safety

'Subject 001-1006, a 54-year-old Caucasian male without significant medical problems, discontinued from the study due to an adverse event of orthostatic hypotension. The subject was noted to have asymptomatic orthostatic hypotension during screening. However, after receiving a total of 17 doses of duloxetine 40 mg and four doses of fluvoxamine (two doses of 50 mg and two doses of 100 mg) per the study schedule, the subject presented on study Day 9, 11 November 2003, with symptomatic orthostasis. He was encouraged to increase his oral fluid intake and get up from the supine position slowly.

On [redacted], *at approximately 0400 when subject went to the restroom, he had a syncopal event, suffering an orbital laceration with hematoma. He was evaluated in the Indiana University Hospital Emergency Department and released back to care in the Clinical Research Unit. The subject was given the option to withdraw from the study, but he volunteered to continue and agreed to take precautions to prevent further falls. On 17 November 2003, after a consultation with the sponsor, the investigator initiated termination of the subject from the study because of documented orthostatic hypotension. The investigator decided to discontinue the study drug duloxetine and to taper fluvoxamine for 2 days. This subject continued to present with symptomatic orthostasis until 27 November 2003.* b(6)

He was discharged from the protocol on 02 December 2003, when he reported that he felt "back to normal" and all adverse events had abated. It is the investigator's impression that this subject may have had predrug exposure evidence of asymptomatic postural orthostatic tachycardia syndrome based on the changes of his resting heart rate from a supine to standing position noted at screening. This potentially underlying condition may have been exacerbated by duloxetine.'

Table 4 Summary of Duloxetine and Metabolite Pharmacokinetic Geometric Means in the Presence and Absence of Fluvoxamine in CYP2D6 Poor Metabolizers by Subpopulation – Study HMDS

Analyte	Sub-Population	N	Cmax			AUC		
			Geometric Means		Geometric Mean Ratio (90% CI)	Geometric Means		Geometric Mean Ratio (90% CI)
Duloxetine	*All*	13	112	650	5.71 (4.63 - 7.04)	1080	7000	6.4 (5.13 - 7.97)
	Non-Smokers	11	112	628	5.61	1080	6770	6.26
	Smokers[a]	2	113	687	6.07	1060	8430	7.95
	Females	10	122	718	5.88	1190	7660	6.43
	Male	3	89.5	468	5.23	847	5210	6.15
4-OH-Duloxetine Glucuronide	*All*	13	179	82	0.47 (0.35 - 0.61)	1840	884	0.49 (0.37 – 0.64)
	Non-Smokers	11	172	80.2	0.47	1780	872	0.49
	Smokers[a]	2	231	92.3	0.40	2290	952	0.42
	Females	10	197	82.5	0.42	2020	878	0.43
	Male	3	142	80	0.56	1450	903	0.62
5-OH-6-MeO-Duloxetine Sulfate	*All*	13	160	61.1	0.38 (0.28, 0.52)	1540	603	0.39 (0.29 - 0.52)
	Non-Smokers	11	156	59.2	0.38	1510	593	0.39
	Smokers[a]	2	188	72.6	0.39	1750	658	0.38
	Females	10	170	57.7	0.34	1620	560	0.35
	Male	3	137	74	0.54	1370	768	0.56

a. All smokers are female

Table 5 **Duloxetine Pharmacokinetic Metrics in the Presence and Absence of Fluvoxamine in CYP2D6 Poor Metabolizers - All Subjects – Study HMDS**

	Summary Statistics		Geometric Mean ± SD		Geometric Mean Ratio 90% CI
Rx Day	Duloxetine Alone 5	Duloxetine & Fluvoxamine 19	Duloxetine Alone 15	Duloxetine & Fluvoxamine 19	(19) / (15) Fluvoxamine
N	14	13	14	13	
Tmax (h)	NC ± NC (NC) 2.00 - 10.07 [6.00]	NC ± NC (NC) 0.00 - 11.83 [6.00]	NC ± NC	NC ± NC	
Cmax (ng/mL)	129 ± 75.3 (58.5) 54.9 - 307.1 [100.4]	688 ± 236 (34.3) 349.7 - 1185.4 [696.7]	112 ± 1.70 111.82	650 ± 1.43 638.39	5.71 4.63 - 7.04
Clast (ng/mL)	88.1 ± 60.2 (68.4) 32.8 - 231.0 [66.4]	587 ± 217 (36.9) 288.1 - 998.2 [584.1]	73.9 ± 1.80	550 ± 1.47	
Cmin (ng/mL)	83.4 ± 58.2 (69.8) 25.9 - 231.0 [63.9]	550 ± 206 (37.4) 283.5 - 998.2 [544.4]	69.6 ± 1.82	517 ± 1.45	
Cavg (ng/mL)	104 ± 63.7 (61.0) 41.9 - 263.8 [79.3]	622 ± 220 (35.4) 310.6 - 1114.7 [598.2]	90.4 ± 1.71	587 ± 1.43	
AUCT (h•ng /mL)	1250 ± 765 (61.3) 503 - 3170 [945]	7420 ± 2620 (35.3) 3730 - 13300 [7180]	1080 ± 1.71 1079.0	7000 ± 1.43 6900.77	6.40 5.13 - 7.97
CL/F (L/h)	41.8 ± 19.6 (47.0) 12.6 - 79.5 [42.4]	6.06 ± 2.25 (37.2) 3.01 - 10.7 [5.57]	37.1 ± 1.71	5.71 ± 1.43	
RA		6.81 ± 2.98 (43.8) 2.38 - 14.0 [6.71]		6.24 ± 1.57	

Table 6 **4-Hydroxy-Duloxetine Glucuronide Pharmacokinetic Metrics in the Presence and Absence of Fluvoxamine in CYP2D6 Poor Metabolizers – All Subjects – Study HMDS**

	Summary Statistics		Geometric Mean ± SD		Geometric Mean Ratio 90% CI (1) (2)
Rx Day	Duloxetine Alone 5	Duloxetine & Fluvoxamine 19	Duloxetine Alone 5	Duloxetine & Fluvoxamine 19	Fluvoxamine
N	14	13	14	13	
Tmax (h)	NC ± NC (NC) 0.00 – 12.00 [6.00]	NC ± NC (NC) 0.00 – 12.00 [10.00]	NC ± NC	NC ± NC	
Cmax (ng/mL)	195 ± 87.6 (44.8) 77.20 – 418.40 [176.05]	99.3 ± 76.1 (76.6) 25.85 – 321.50 [71.93]	179 ± 1.53 179.35	82.0 ± 1.85 83.53	0.47 0.35 - 0.61
Clast (ng/mL)	152 ± 92.6 (60.7) 54.40 – 418.40 [132.00]	97.0 ± 77.0 (79.5) 21.23 – 321.50 [70.04]	133 ± 1.70	78.4 ± 1.93	
Cmin (ng/mL)	142 ± 77.7 (54.8) 54.40 – 354.50 [132.00]	79.4 ± 53.0 (66.7) 21.23 – 231.90 [64.48]	125 ± 1.66	67.7 ± 1.77	
Cavg (ng/mL)	170 ± 81.1 (47.7) 67.36 – 378.97 [159.79]	88.1 ± 63.5 (72.1) 23.53 – 274.43 [68.44]	154 ± 1.57	74.1 ± 1.80	
AUCT (h•ng /mL)	2030 ± 972 (47.9) 808 – 4550 [1920]	1050 +763 (72.5) 280 – 3290 [823]	1840 ± 1.57 1841.1	884 ± 1.81 901.14	0.49 0.37 - 0.64
CL/F (L/h)					
RCmax		0.53 ± 0.26 (48.2) 0.16 - 0.99 [0.46]			
RAUCinf		0.56 ± 0.27 (47.9) 0.16 - 1.06 [0.49]			

Table 7 **5-Hydroxy-6-Methoxy-Duloxetine Sulfate Pharmacokinetic Metrics in the Presence and Absence of Fluvoxamine in CYP2D6 PoorTable 14 Metabolizers – All Subjects – Study HMDS**

	Summary Statistics		Geometric Mean ± SD		Geometric Mean Ratio (90% CI)
	Duloxetine Alone	Duloxetine & Fluvoxamine	Duloxetine Alone	Duloxetine & Fluvoxamine	(3) : (2) Fluvoxamine
Rx Day	5	19	5	19	
N	14	13			
Tmax (h)	NC ± NC (NC) 0.00 – 12.00 [6.00]	NC ± NC (NC) 10.00 – 12.02 [11.87]	NC ± NC	NC ± NC	
Cmax (ng/mL)	165 ± 46.4 (28.1) 117.8 – 283.6 [152.50]	74.0 ± 49.2 (66.5) 21.18 – 202.50 [52.49]	160 ± 1.28 160.03	61.1 ± 1.92 60.61	0.38 (0.28, 0.52)
Clast (ng/mL)	119 ± 32.5 (27.3) 79.76 – 190.0 [113.05]	73.1 ± 49.2 (67.2) 19.48 – 202.50 [51.83]	116 ± 1.28	60.2 ± 1.93	
Cmin (ng/mL)	103 ± 27.2 (26.3) 77.76 – 177.8 [98.20]	48.9 ± 29.0 (59.3) 13.55 – 121.50 [40.09]	101 ± 1.26	41.7 ± 1.83	
Cavg (ng/mL)	133 ± 38.6 (28.9) 94.07 – 235.62 [121.12]	60.2 ± 38.0 (63.0) 17.07 – 157.77 [44.44]	129 ± 1.29	50.5 ± 1.87	
AUC_T (h•ng /mL)	1590 ± 461 (28.9) 1130 – 2830 [1440]	719 ± 456 (63.3) 203 – 1890 [526]	1540 ± 1.28 1542.39	603 ± 1.87 602.09	0.39 (0.29, 0.52)
CL/F (L/h)					
R_{Cmax}		0.44 ± 0.23 (51.8) 0.11 - 0.79 [0.34]			
R_{AUCinf}		0.45 ± 0.21 (47.9) 0.12 - 0.73 [0.39]			

Table 8 **Duloxetine Pharmacokinetic Metrics in the Presence and Absence of Fluvoxamine in CYP2D6 Poor Metabolizers - Non-Smokers – Study HMDS**

Rx Day	Summary Statistics		Geometric Mean ± SD		Geometric Mean Ratio 90% CI
	Duloxetine Alone 5	Duloxetine & Fluvoxamine 19	Duloxetine Alone 5	Duloxetine & Fluvoxamine 19	(1) (2) Fluvoxamine
N	12	11	12	11	
Tmax (h)	NC ± NC (NC) 2.00 – 10.07 [6.00]	NC ± NC (NC) 0.00 – 11.83 [6.07]	NC ± NC	NC ± NC	
Cmax (ng/mL)	131 ± 80.9 (61.9) 54.9 – 307.1 [100.4]	665 ± 237 (35.5) 349.7 – 1185.4 [696.7]	112 ± 1.77	628 ± 1.44	5.61
Clast (ng/mL)	88.7 ± 64.8 (73.1) 32.8 – 231.0 [64.9]	562 ± 204 (36.3) 288.1 – 998.2 [584.1]	72.7 ± 1.87	528 ± 1.47	
Cmin (ng/mL)	85.6 ± 62.7 (73.2) 25.9 – 231.0 [63.9]	531 ± 201 (37.8) 283.5 – 998.2 [544.4]	69.8 ± 1.90	499 ± 1.45	
Cavg (ng/mL)	107 ± 68.5 (64.3) 41.9 – 263.8 [79.3]	602 ± 221 (36.7) 310.6 – 1114.7 [598.2]	90.5 ± 1.78	567 ± 1.44	
AUCτ (h•ng /mL)	1270 ± 822 (64.5) 503 – 3170 [945]	7190 ± 2630 (36.6) 3730 – 13300 [7180]	1080 ± 1.78	6770 ± 1.44	6.26
CL/F (L/h)	42.4 ± 21.0 (49.7) 12.6 – 79.5 [42.4]	6.27 ± 2.34 (37.3) 3.01 – 10.7 [5.57]	37.0 ± 1.78	5.91 ± 1.44	
RA		6.61 ± 3.22 (48.7) 2.38 – 14.0 [6.71]		5.97 ± 1.61	

Table 9 **4-Hydroxy-Duloxetine Glucuronide Pharmacokinetic Metrics in the Presence and Absence of Fluvoxamine in CYP2D6 Poor Metabolizers – Non-Smokers – Study HMDS**

Parameter / Rx Day	Summary Statistics: Duloxetine Alone Day 5	Summary Statistics: Duloxetine + Fluvoxamine Day 19	Geometric Mean ± SD: Duloxetine Alone Day 5	Geometric Mean ± SD: Duloxetine + Fluvoxamine Day 19	Geometric Mean Ratio (90% CI) (Day 19) / (Day 5) Fluvoxamine
N	12	11	12	11	
Tmax (h)	NC ± NC (NC) 0.00 – 12.00 [6.00]	NC ± NC (NC) 0.00 – 12.00 [8.05]	NC ± NC	NC ± NC	
Cmax (ng/mL)	189 ± 93.4 (49.3) 77.20 – 418.40 [153.70]	99.6 ± 82.0 (82.4) 25.85 – 321.50 [71.93]	172 ± 1.57	80.2 ± 1.92	0.47
Clast (ng/mL)	151 ± 101 (66.7) 54.40 – 418.40 [110.40]	96.7 ± 83.1 (85.8) 21.23 – 321.50 [70.04]	128 ± 1.77	76.1 ± 2.01	
Cmin (ng/mL)	138 ± 83.9 (60.7) 54.40 – 354.50 [105.76]	79.7 ± 57.2 (71.8) 21.23 – 231.90 [64.48]	120 ± 1.71	66.6 ± 1.85	
Cavg (ng/mL)	166 ± 87.4 (52.7) 67.36 – 378.97 [131.21]	89.0 ± 68.8 (77.3) 23.53 – 274.43 [68.44]	148 ± 1.62	73.0 ± 1.88	
AUCT (h•ng /mL)	1980 ± 1050 (52.9) 808 – 4550 [1560]	1060 ± 826 (77.6) 280 – 3290 [823]	1780 ± 1.62	872 ± 1.89	0.49
CL/F (L/h)					
RCmax		0.55 ± 0.27 (48.9) 0.16 - 0.99 [0.46]			
RAUCinf		0.58 ± 0.28 (48.4) 0.16 - 1.06 [0.49]			

Table 10 5-Hydroxy-6-Methoxy-Duloxetine Sulfate Pharmacokinetic Metrics in the Presence and Absence of Fluvoxamine in CYP2D6 Poor Metabolizers – Non-Smokers – Study HMDS

Rx Day	Summary Statistics: Duloxetine Alone 6	Summary Statistics: Duloxetine & Fluvoxamine 19	Geometric Mean ± SD: Duloxetine Alone 6	Geometric Mean ± SD: Duloxetine & Fluvoxamine 19	Geometric Mean Ratio 90% CI (D+F) / D Fluvoxamine
N	12	11	12	11	
Tmax (h)	NC ± NC (NC) 0.00 – 12.0 [6.00]	NC ± NC (NC) 10.00 – 12.02 [11.83]	NC ± NC	NC ± NC	
Cmax (ng/mL)	161 ± 49.0 (30.4) 117.8 – 283.6 [150.25]	73.4 ± 52.4 (71.5) 21.18 – 202.5 [52.49]	156 ± 1.30	59.2 ± 1.99	0.38
Clast (ng/mL)	118 ± 34.7 (29.3) 79.8 – 190.0 [113.05]	72.3 ± 52.4 (72.4) 19.5 – 202.5 [51.83]	114+1.30	58.1 ± 2.00	
Cmin (ng/mL)	102 ± 29.3 (28.7) 77.76 – 177.80 [95.92]	49.2 ± 31.3 (63.6) 13.55 – 121.50 [40.09]	99.1 ± 1.28	41.0 ± 1.91	
Cavg (ng/mL)	131 ± 41.4 (31.6) 94.07 – 235.62 [118.08]	60.5 ± 40.7 (67.3) 17.07 – 157.77 [44.44]	126 ± 1.30	49.7 ± 1.95	
AUCT (h•ng /mL)	1570 ± 496 (31.6) 1130 – 2830 [1410]	724 ± 489 (67.6) 203 – 1890 [526]	1510 ± 1.30	593 ± 1.95	0.39
CL/F (L/h)					
RCmax		0.40 ± 0.17 (41.4) 0.29 - 0.52 [0.40]			
RAUCinf		0.40 ± 0.18 (44.2) 0.27 - 0.52 [0.40]			

Table 11 Duloxetine Pharmacokinetic Metrics in the Presence and Absence of Fluvoxamine in CYP2D6 Poor Metabolizers - Smokers – Study HMDS

	Summary Statistics		Geometric Mean ± SD		Geometric Mean Ratio 90% CI
Rx Day	Duloxetine Alone 5	Duloxetine & Fluvoxamine 19	Duloxetine Alone 5	Duloxetine & Fluvoxamine 19	(D + F) / Fluvoxamine
N	2	2			
Tmax (h)	NC ± NC (NC) 4.00 – 5.97 [4.99]	NC ± NC (NC) 4.00 – 6.00 [5.00]	NC ± NC	790 ± 1.40	
Cmax (ng/mL)	116 ± 36.5 (31.5) 90.1 – 141.7 [115.9]	812 ± 270 (33.2) 621.5 – 1003.2 [812.4]	113 ± 1.38	687 ± 1.58	6.07
Clast (ng/mL)	84.7 ± 29.7 (35.1) 63.7 – 105.7 [84.7]	723 ± 321 (44.4) 496.4 – 950.2 [723.3]	82.1 ± 1.43	NC ± NC	
Cmin (ng/mL)	70.1 ± 19.7 (28.0) 56.2 – 84.0 [70.1]	659 ± 281 (42.7) 459.7 – 857.3 [658.5]	68.7 ± 1.33	628 ± 1.55	
Cavg (ng/mL)	91.5 ± 26.0 (28.4) 73.1 – 109.9 [91.5]	732 ± 254 (34.7) 552.3 – 911.7 [732.0]	89.6 ± 1.33	710 ± 1.43	
AUC_τ (h•ng /mL)	1080 ± 311 (28.7) 862 – 1300 [1080]	8690 ± 3010 (34.7) 6560 – 10800 [8690]	1060 ± 1.34	8430 ± 1.42	7.95
CL/F (L/h)	38.6 ± 11.1 (28.7) 30.7 – 46.4 [38.6]	4.90 ± 1.70 (34.7) 3.70 – 6.10 [4.90]	37.8 ± 1.34	4.75 ± 1.42	
RA		7.96 ± 0.495 (6.22) 7.61 – 8.31 [7.96]		7.95 ± 1.06	

Table 12 4-Hydroxy-Duloxetine Glucuronide Pharmacokinetic Metrics in the Presence and Absence of Fluvoxamine in CYP2D6 Poor Metabolizers – Smokers – Study HMDS

	Summary Statistics		Geometric Mean ± SD		Geometric Mean Ratio 90% CI
	Duloxetine Alone	Duloxetine & Fluvoxamine	Duloxetine Alone	Duloxetine & Fluvoxamine	(1) ÷ (2) Fluvoxamine
Rx Day	5	19	5	19	
N	2	2	2	2	
Tmax (h)	NC ± NC (NC) 5.97 - 6.00 [5.99]	NC ± NC (NC) 11.87 - 11.88 [11.88]	NC ± NC	NC ± NC	
Cmax (ng/mL)	232 ± 25.8 (11.1) 213.8 - 250.3 [232.05]	98.2 ± 47.4 (48.3) 64.69 - 131.70 [98.20]	231 + 1.12	92.3 ± 1.65	
Clast (ng/mL)	162 ± 4.88 (3.01) 158.9 - 165.8 [162.35]	98.2 ± 47.4 (48.3) 64.69 - 131.70 [98.20]	162+1.03	92.3 ± 1.65	
Cmin (ng/mL)	162 ± 4.88 (3.01) 158.9 - 165.8 [162.35]	77.6 ± 30.4 (39.2) 56.13 - 99.13 [77.63]	162 + 1.03	74.6 ± 1.50	
Cavg (ng/mL)	193 ± 3.79 (1.96) 190.74 - 196.1 [193.42]	83.5 ± 33.2 (39.7) 60.07 - 106.98 [83.52]	193 + 1.02	80.2 ± 1.50	
AUC_T (h•ng /mL)	2290 ± 38.0 (1.66) 2260 - 2310 [2290]	992 ± 394 (39.8) 713 - 1270 [992]	2290 + 1.02	952 ± 1.50	
CL/F (L/h)					
R_{Cmax}		0.41 ± 0.16 (38.2) 0.30 - 0.53 [0.41]			
R_{AUCinf}		0.43 ± 0.17 (38.3) 0.32 - 0.55 [0.43]			

Table 13 5-Hydroxy-6-Methoxy-Duloxetine Sulfate Pharmacokinetic Metrics in the Presence and Absence of Fluvoxamine in CYP2D6 Poor Metabolizers – Smokers – Study HMDS

	Summary Statistics		Geometric Mean ± SD		Geometric Mean Ratio (90% CI)
Rx Day	Duloxetine Alone 5	Duloxetine & Fluvoxamine 19	Duloxetine Alone 5	Duloxetine & Fluvoxamine 19	(19 / 5) Fluvoxamine
N	2	2	2	2	
Tmax (h)	NC ± NC (NC) 5.97 – 6.0 [5.99]	NC ± NC (NC) 11.9 – 11.9 [11.88]	NC ± NC	NC ± NC	
Cmax (ng/mL)	188 ± 18.7 (9.94) 175.2 – 201.7 [188.45]	77.7 ± 39.1 (50.3) 50.04 – 105.3 [77.67]	188 ± 1.10	72.6 ± 1.69	
Clast (ng/mL)	123 ± 20.7 (16.8) 108.5 – 137.8 [123.15]	77.7 ± 39.1 (50.3) 50.0 – 105.3 [77.67]	122 ± 1.18	72.6 ± 1.69	
Cmin (ng/mL)	111 ± 3.82 (3.43) 108.5 – 113.9 [111.20]	47.0 ± 16.4 (35.0) 35.3 – 58.6 [46.95]	111 ± 1.03	45.5 ± 1.43	
Cavg (ng/mL)	148 ± 2.47 (1.67) 146.0 – 149.5 [147.8]	58.5 ± 26.5 (45.3) 39.7 – 77.2 [58.5]	148 ± 1.02	55.4 ± 1.60	
AUCT (h•ng /mL)	1750 ± 24.0 (1.37) 1730 – 1760 [1750]	694 ± 315 45.4 472 - 917 694	1750 ± 1.01	658 ± 1.60	
CL/F (L/h)					
RCmax		0.40 ± 0.23 (57.6) 0.11 - 0.79 [0.33]			
RAUCinf		0.40 ± 0.21 (52.2) 0.12 - 0.73 [0.36]			

Table 14 Duloxetine Pharmacokinetic Metrics in the Presence and Absence of Fluvoxamine in CYP2D6 Poor Metabolizers - Females – Study HMDS

Rx Day	Summary Statistics: Duloxetine Alone 5	Summary Statistics: Duloxetine & Fluvoxamine 19	Geometric Mean ± SD: Duloxetine Alone 5	Geometric Mean ± SD: Duloxetine & Fluvoxamine 19	Geometric Mean Ratio 90% CI (19) / (5) Fluvoxamine
N	10	10	10	10	
Tmax (h)	NC ± NC (NC) 4.00 – 10.07 [6.00]	NC ± NC (NC) 0.00 – 11.83 [6.00]	NC ± NC	NC ± NC	
Cmax (ng/mL)	141 ± 82.2 (58.3) 54.9 – 307.1 [111.3]	751 ± 227 (30.2) 349.7 – 1185.4 [706.2]	122 ± 1.74	718 ± 1.38	5.88
Clast (ng/mL)	101 ± 66.6 (65.7) 32.8 – 231.0 [71.7]	641 ± 209 (32.6) 288.1 – 998.2 [603.8]	84.7 ± 1.87	608 ± 1.42	
Cmin (ng/mL)	94.8 ± 65.3 (69.0) 25.9 – 231.0 [68.1]	596 ± 206 (34.6) 283.5 – 998.2 [553.6]	77.9 ± 1.93	564 ± 1.42	
Cavg (ng/mL)	116 ± 70.6 (60.9) 41.9 – 263.8 [89.9]	674 ± 218 (32.3) 310.6 – 1114.7 [621.2]	99.7 ± 1.77	642 ± 1.40	
AUCτ (h•ng /mL)	1390 ± 849 (61.3) 503 – 3170 [1070]	8040 ± 2590 (32.3) 3730 – 13300 [7440]	1190 ± 1.77	7660 ± 1.40	6.43
CL/F (L/h)	38.6 ± 20.3 (52.5) 12.6 – 79.5 [37.8]	5.51 ± 2.08 (37.7) 3.01 – 10.7 [5.38]	33.7 ± 1.77	5.22 ± 1.40	
RA		7.16 ± 3.33 (46.5) 2.38 – 14.0 [6.96]		6.44 ± 1.66	

Table 15 4-Hydroxy-Duloxetine Glucuronide Pharmacokinetic Metrics in the Presence and Absence of Fluvoxamine in CYP2D6 Poor Metabolizers – Females – Study HMDS

	Summary Statistics		Geometric Mean ± SD		Geometric Mean Ratio 90% CI
	Duloxetine Alone	Duloxetine & Fluvoxamine	Duloxetine Alone	Duloxetine & Fluvoxamine	(9) / (5) Fluvoxamine
Rx Day	5	19	5	19	
N	10	10			
Tmax (h)	NC ± NC (NC) 5.97 – 12.00 [7.00]	NC ± NC (NC) 0.00 – 12.00 [9.00]	NC ± NC	NC ± NC	
Cmax (ng/mL)	212 ± 90.5 (42.8) 128.8 – 418.4 [194.0]	105 ± 86.8 (82.7) 25.9 – 321.5 [69.3]	197 ± 1.47	82.5 ± 2.02	
Clast (ng/mL)	170+101 59.3 69.5-354.5 154.8	103+87.8 85.4 21.2-321.5 67.4	149 + 1.67	79.0+2.12	
Cmin (ng/mL)	155 ± 82.9 (53.4) 69.5 – 354.5 [154.85]	81.8 ± 60.6 (74.0) 21.2 – 231.9 [60.3]	139 ± 1.62	66.9 ± 1.93	
Cavg (ng/mL)	184 ± 83.9 (45.6) 101.9 – 379.0 [180.09]	91.7 ± 72.6 (79.2) 23.5 – 274.4 [64.3]	170 ± 1.51	73.7 ± 1.97	
AUCτ (h•ng /mL)	2190 ± 1010 (45.9) 1210 – 4550 [2160]	1100 ± 873 (79.7) 280 – 3290 [768]	2020 ± 1.51	878 ± 1.97	
CL/F (L/h)					
RCmax		0.47 ± 0.2 (48.7) 0.16 - 0.86 [0.44]			
RAUCinf		0.48 ± 0.2 (44.4) 0.16 - 0.81 [0.49]			

Table 16 **5-Hydroxy-6-Methoxy-Duloxetine Sulfate Pharmacokinetic Metrics in the Presence and Absence of Fluvoxamine in CYP2D6 Poor Metabolizers – Females – Study HMDS**

	Summary Statistics		Geometric Mean ± SD		Geometric Mean Ratio 90% CI
	Duloxetine Alone	Duloxetine & Fluvoxamine	Duloxetine Alone	Duloxetine & Fluvoxamine	(1) : (2) Fluvoxamine
Rx Day	1	19	1	19	
N	10	10	10	10	
Tmax (h)	NC ± NC (NC) 0.0 - 12.00 [6.0]	NC ± NC (NC) 10.0 - 12.02 [11.85]	NC ± NC	NC ± NC	
Cmax (ng/mL)	176 ± 51.1 (29.0) 117.8 – 283.6 [158.45]	72.4 ± 54.6 (75.4) 21.18 – 202.50 [51.49]	170 ± 1.31	57.7 ± 2.02	
Clast (ng/mL)	126 ± 35.4 (28.0) 79.76 – 190.00 [115.65]	71.3 ± 54.5 (76.5) 19.48 – 202.50 [51.16]	122 ± 1.30	56.6 ± 2.04	
Cmin (ng/mL)	107 ± 31.0 (28.9) 77.76 – 177.80 [98.20]	46.0 ± 31.2 (67.9) 13.55 – 121.50 [37.71]	104 ± 1.30	38.3 ± 1.89	
Cavg (ng/mL)	141 ± 43.4 30.8 94.1 - 235.0 124.0	57.8 ± 41.7 72.2 17.07 - 157.77 42.84	136 ± 1.32	47.0 ± 1.96	
AUCT (h•ng /mL)	1680 ± 520 (31.0) 1130 – 2830 [1470]	690 ± 501 (72.6) 203 – 1890 [507]	1620 ± 1.32	560 ± 1.96	
CL/F (L/h)	25.5 ± 6.34 (24.8) 14.1 – 35.4 [27.2]	86.4 ± 54.8 (63.4) 21.1 – 197 [79.0]	24.7 ± 1.32	71.4 ± 1.96	
RCmax		0.57 ± 0.20 (34.7) 0.34 - 0.68 [0.68]			
RAUCinf		0.60 ± 0.18 (29.9) 0.39 - 0.72 [0.69]			

Table 17 Duloxetine Pharmacokinetic Metrics in the Presence and Absence of Fluvoxamine in CYP2D6 Poor Metabolizers - Males – Study HMDS

Tx Day	Summary Statistics: Duloxetine Alone 5	Summary Statistics: Duloxetine & Fluvoxamine 19	Geometric Mean ± SD: Duloxetine Alone 5	Geometric Mean ± SD: Duloxetine & Fluvoxamine 19	Geometric Mean Ratio 90% CI (1) / (2) Fluvoxamine
N	4	3			
Tmax (h)	NC ± NC (NC) 2.00 – 6.00 [5.00]	NC ± NC (NC) 6.00 – 8.05 [8.00]	NC ± NC	NC ± NC	
Cmax (ng/mL)	97.5 ± 49.8 (51.0) 62.2 – 169.1 [79.4]	479 ± 135 (28.1) 372.6 – 630.7 [435.0]	89.5 ± 1.59	468 ± 1.31	5.23
Clast (ng/mL)	55.0 ± 18.8 (34.3) 39.4 – 79.1 [50.7]	409 ± 153 (37.4) 300.5 – 584.1 [342.9]	52.6 ± 1.40	392 ± 1.42	
Cmin (ng/mL)	55.0 ± 18.8 (34.3) 39.4 – 79.1 [50.7]	399 ± 136 (34.0) 300.5 – 554.1 [342.9]	52.6 ± 1.40	385 ± 1.38	
Cavg (ng/mL)	75.3 ± 32.1 (42.6) 50.6 – 120.0 [65.2]	448 ± 133 (29.8) 344.1 – 598.2 [400.3]	70.7 ± 1.49	435 ± 1.33	
AUCT (h•ng /mL)	902 ± 386 (42.8) 604 – 1440 [783]	5360 ± 1610 (30.1) 4100 – 7180 [4800]	847 ± 1.49	5210 ± 1.33	6.15
CL/F (L/h)	49.9 ± 17.9 (35.8) 27.8 – 66.3 [52.8]	7.88 ± 2.12 (26.9) 5.57 – 9.75 [8.33]	47.2 ± 1.49	7.68 ± 1.33	
RA		5.66 ± 0.996 (17.6) 4.98 – 6.80 [5.19]		5.60 ± 1.18	

Table 18 4-Hydroxy-Duloxetine Glucuronide Pharmacokinetic Metrics in the Presence and Absence of Fluvoxamine in CYP2D6 Poor Metabolizers – Males – Study HMDS

Ro Day	Summary Statistics		Geometric Mean ± SD		Geometric Mean Ratio 90% CI
	Duloxetine Alone 3	Duloxetine & Fluvoxamine 19	Duloxetine Alone 3	Duloxetine & Fluvoxamine 19	(3) / (2) Fluvoxamine
N	4	3	4	3	
Tmax (h)	NC ± NC (NC) 0.00 – 6.00 [4.00]	NC ± NC (NC) 8.05 – 12.00 [10.00]	NC ± NC	NC ± NC	
Cmax (ng/mL)	155 ± 75.1 (48.5) 77.20 – 254.90 [144.00]	80.9 ± 14.9 (18.4) 68.9 – 97.6 [76.2]	142 ± 1.65	80.0 ± 1.20	
Clast (ng/mL)	110+57.8 52.8 54.4-188.5 97.8	77.3+12.9 16.7 65.0-90.7 76.2	98.9+1.69	76.6+1.18	
Cmin (ng/mL)	108 ± 58.8 (54.3) 54.40 – 188.50 [94.97]	71.4 ± 13.7 (19.2) 61.8 – 87.1 [65.2]	97.2 ± 1.71	70.5 ± 1.20	
Cavg (ng/mL)	134 ± 70.7 (52.6) 67.36 – 230.27 [119.96]	76.2 ± 13.7 (18.0) 65.6 – 91.6 [71.3]	121 ± 1.69	75.4 ± 1.19	
AUCT (h•ng /mL)	1610 ± 849 (52.7) 808 – 2760 [1440]	912 ± 160 (17.6) 787 – 1090 [856]	1450 ± 1.69	903 ± 1.19	
CL/F (L/h)					
RCmax		0.73 ± 0.3 (38.9) 0.43 - 0.99 [0.78]			
RAUCinf		0.82 ± 0.3 (38.11) 0.47 - 1.06 [0.92]			

Table 19 5-Hydroxy-6-Methoxy-Duloxetine Sulfate Pharmacokinetic Metrics in the Presence and Absence of Fluvoxamine in CYP2D6 Poor Metabolizers – Males – Study HMDS

	Summary Statistics		Geometric Mean ± SD		Geometric Mean Ratio 90% CI
	Duloxetine Alone	Duloxetine & Fluvoxamine	Duloxetine Alone	Duloxetine & Fluvoxamine	(+) / (-) Fluvoxamine
Rx Day	5	19	5	19	
N	4	3	4	3	
Tmax (h)	4.0 - 6.0 [5.0]	10.02 - 12.0 [12.0]			
Cmax (ng/mL)	138 ± 11.2 (8.10) 123.9 - 151.1 [137.9]	79.5 ± 32.6 (41.0) 42.21 - 102.70 [93.54]	137 ± 1.08	74.0 ± 1.63	
Clast (ng/mL)	101 ± 14.6 (14.4) 80.5 - 114.4 [104.9]	79.3 ± 32.4 (40.9) 42.2 - 102.1 [93.54]	100 ± 1.17	73.9 ± 1.63	
Cmin (ng/mL)	94.3 ± 12.9 (13.6) 79.4 - 107.0 [95.4]	58.5 ± 21.9 (37.5) 34.0 - 76.4 [65.01]	93.6 ± 1.15	55.3 ± 1.54	
Cavg (ng/mL)	115 ± 12.6 11.0 96.9-126.4 118.1	68.2 ± 26.1 38.2 38.2-84.9 81.5	114 ± 1.12	64.1 ± 1.57	
AUCT (h•ng /mL)	1380 ± 151 (10.9) 1160 - 1520 [1410]	816 ± 311 (38.1) 458 - 1010 [978]	1370 ± 1.12	768 ± 1.57	
CL/F (L/h)	29.4 ± 3.49 (11.9) 26.4 - 34.4 [28.3]	55.9 ± 27.2 (48.7) 39.5 - 87.4 [40.9]	29.2 ± 1.12	52.1 ± 1.57	
RCmax		0.45 ± 0.24 (54.4) 0.11 - 0.79 [0.34]			
RAUCinf		0.46 ± 0.23 (49.6) 0.12 - 0.73 [0.39]			

7.2.2.2 *Effect of Duloxetine on CYP1A2 – Study SBCR*

The average increase in theophylline AUC∞ is 20% with a range of -6% to approximately 60% using a duloxetine dose that will mimic exposures in Female CYP2D6 poor metabolizers.

Based on the results of study SBCR there may be a clinically significant inhibition of CYP1A2 by duloxetine under steady-state conditions, especially in female CYP2D6 poor metabolizers. The true extent of this interaction cannot be determined by the present study. In addition, the present study was designed and reported in such a way as to minimize the ability to detect or recognize the presence of any interaction even with a single dose of aminophylline.

This was a single-center, single-blind, randomized, two-way crossover study in 19 nonsmoking, healthy female subjects between the ages of 18 and 65 years who are CYP2D6 extensive metabolizers.

In this study Duloxetine 60 mg (3 x 20 mg) or placebo was administered BID for 4.5 days. Four hours after the last dose of duloxetine, aminophylline 250 mg in D5W was given over 30 minutes. The 250-mg dose of aminophylline (ethylenediamine salt) is equivalent to a 197.5-mg dose of theophylline.

This study is similar in design to study HMBF that was submitted in the original NDA was conducted in 10 healthy non-smoking adult males using similar dosages. That study failed to find an interaction in males, although the upper limit of the 90% CI on the geometric mean ratio for Cmax was 1.25. Consequently the original NDA review concluded that duloxetine did not significantly inhibit CYP1A2

For the present study the sponsor's conclusions are as follows: *"The pharmacokinetics of theophylline are not affected in the presence of duloxetine. Thus, duloxetine is unlikely to have a clinically significant effect on the metabolism of drugs that are substrates of CYP1A2 enzyme."*

This conclusion is open to discussion.

Results are shown in Table 20.

Appropriate aspects of the study design include the use of females, as females tend to have higher duloxetine exposures than males and the use of steady-state dosing of a higher than typical dose of duloxetine.

Unfortunately there are a number of aspects of the study design and analysis that inappropriately bias the results in favor of not finding an interaction.

Most importantly the sponsor exclusively uses CYP2D6 extensive metabolizers in this study. Since these subjects will have much lower concentrations than poor metabolizers, if an interaction is due to competitive inhibition by duloxetine itself this would significantly minimize the ability to detect an interaction, and any interaction may be more pronounced in poor metabolizers.

Secondly, the sponsor inappropriately bases their conclusion on the 90% CI of the differences in AUCt, which has an upper limit of 1.25. However, this is not the appropriate metric for a single dose of theophylline. When the appropriate metric of AUC∞ is used, the upper limit is 1.27 thus the criteria for bio-inequivalence are reached. Since, the interaction is more pronounced at lower theophylline concentrations, the use of AUCt instead of AUC∞ skews the data to not detect an interaction. In addition, since only a small percent of the AUC∞ is extrapolated, this difference in conclusions cannot be dismissed as due to extrapolation errors. When changes in individual subjects are examined the average increase in AUC∞ is 20% with a range of -6% to approximately 60%.

The sponsor bases their claim of no interaction on comparisons using all subjects, including the subject that did not complete both arms. The theophylline AUCinf data from this subject is in the absence of

duloxetine and is the 6th lowest. Consequently data from this subject will skew the findings in the direction of not finding an interaction.

On the other hand, the dose of aminophylline was administered 4 hours after dosing with duloxetine, although this will result in peak concentration of each drug occurring close to each other, i.e. 4.5 hours for theophylline and for duloxetine at around 5 – 6 hours, the shorter half-life of theophylline results in a greater ratio of duloxetine to theophylline the longer after dosing and thus more inhibition the longer after dosing. Consequently the extent of inhibition may be less when theophylline exposures are compared under steady-state conditions than would be predicted from this single dose experiment.

An appropriately designed study would examine the effect of steady-state dosing on theophylline kinetics in CYP2D6 poor metabolizers. In addition, it's difficult to predict the extent of the interaction in smokers whose CYP1A2 are induced and who would likely be receiving higher doses of theophylline.

Table 20 Theophylline Pharmacokinetic Metrics in the Absence and Presence of Duloxetine - Study SBCR

	Summary Statistics		Sponsor's Mean Geometric CV%				Geometric Mean Ratio (90% CI)		Arithmetic Ratio
			Sponsor		OCP				
	Aminophylline Alone	Aminophylline + Duloxetine	Amino Alone	Amino + Duloxetine	Amino Alone	Amino + Duloxetine	Sponsor	OCP	
N	19	18	19	18	18	18	19/18	—	18
Weight (kg)	74.8 ± 10.4 (13.9) 58.7 - 94.8 [76.7]	74.8 ± 10.4 (13.9) 58.7 - 94.8 [76.7]	74.2 (14.1)	74.2 (14.1)					
Duration (h)	0.51 ± 0.03 (5.66) 0.5 - 0.62 [0.50]	0.5 ± 0.0 (0.0) 0.5 - 0.5 [0.50]	0.51 (5.18)	0.50 (0.00)					
Rinf (mg/h)	491 ± 23.1 (4.70) 404.92 - 499.4 [499.40]	498 ± 5.21 1.05 483.3 - 499.4 [499.40]	490 (5.08)	498 (1.06)					
Cmax (µg/mL)	7.33 ± 1.91 (26.0) 4.74 - 12.3 [7.02]	7.87 ± 1.46 (18.6(5.91 - 11.1 [7.57]	**7.12 (24.6)**	**7.75 (18.2)**	7.02	7.65	1.09 (1.01, 1.18)	1.09	110.4 ± 20.0 (18.1) 81.6 - 151.9 [109.8]
tmax (h)	NC ± NC (NC) 0.47 - 2.00 [0.75]	NC ± NC (NC) 0.45 - 2.00 [0.50]	NC (NC)	NC (NC)					
AUC(0-tlast) (µg•h/mL)	86.6 ± 31.7 (36.6) 45.0 - 167 [79.6]	101 ± 32.5 (32.4) 52.0 - 190 [98.5]	**81.6 (36.5)**	**96.0 (31.7)**	78.35	92.95	1.19 (1.13, 1.25)		
AUC(0-24) (µg•h/mL)	67.9 ± 18.5 (27.3) 43.4 - 114 [65.9]	75.0 ± 16.9 (22.6) 51.8 - 115 [76.0]	65.6 (27.5)	73.2 (22.7)					
AUC(0-∞) (µg•h/mL)	88.1 ± 33 (37.5) 46.1 - 174 [80]	103 ± 35.4 (34.2) 54.4 - 206 [99.9]	82.8 (37.0)	98.4 (32.5)	79.46	95.29	1.20 (1.13, 1.27)	1.199	119.9 ± 16.9 (14.1) 94.2 - 158.3 [116.1]
AUCextrap (%)	1.5 ± 1.1 (74.2) 0.10 - 3.8 [1.04]	2.5 ± 2.3 (92.5) 0.14 - 7.6 [1.31]	1.02 (131)	1.58 (141)					
t1/2 (h)	NC ± NC (NC) 4.55 - 15.3 [10.3]	NC ± NC (NC) 5.49 - 19.8 [11.6]	10.0 (33.1)	11.6 (34.5)	9.78	11.55	1.18 (1.10, 1.27)		
CL (L/h)	2.53 ± 0.882 (34.9) 1.14 - 4.28 [2.47]	2.10 ± 0.647 (30.8) 0.959 - 3.63 [1.98]	2.38 (37.0)	2.01 (32.5)	2.49	2.07	0.83 (0.79, 0.88)		
Vss (L)	31.3 ± 7.9 (25.2) 22.1 - 56.4 [31.0]	32.0 ± 9.0 (28.2) 21.5 - 58.9 [28.5]	30.6 (22.8)	31.0 (25.5)	30.69	31.19	1.02 (0.97, 1.06)		
MRT (h)	13.4 ± 3.94 (29.4) 6.0 - 20.4 [13.6]	16.3 ± 5.3 (32.7) 7.2 - 26.7 [15.6]	12.8 (32.7)	15.4 (35.3)					

7.3 Special Population Studies

7.3.1 Breast Feeding and Lactating Women – Study SBCS

Study SBCS was also submitted and reviewed as labeling supplement N21-427 SLR-009 submitted January 23rd, 2006. OCP labeling recommendations for the sponsor were included in the review for SLR-009 and the reader is referred to that review for more details.

The sponsor's primary conclusion in that submission was as follows:

'The estimated daily infant dose of duloxetine from breast milk is approximately 7 µg (range 4 to 15 µg), or about 1/10,000 the total daily maternal dose (80 mg). The estimated daily infant dose based on body weight normalization is about 2 µg /kg/day, or approximately 0.14% of the maternal dose.'

Major comments from the reviewer included the following:

'The effect of changing breast milk composition during the typical course of breast feeding was not examined and this will have an effect on the partitioning into breast milk. However, the general conclusions are probably not affected.

The excretion of metabolites into human breast milk was not examined.

As duloxetine in breast milk is not enteric coated up to the entire dose an infant receives may be converted to naphthol in the acidic environment of the stomach, thus the safety we are concerned with is not duloxetine but naphthol. In spite of this the absolute amount appears to be quite low, although the amount delivered from metabolites is unknown.'

7.4 Pharmacodynamics

7.4.1 Thalamic Serotonin Receptor Binding – Study HMDZ

Results indicate that doses above 40 mg daily are unlikely to add additional clinical benefit.

Study HMDZ was an investigation of the dose and concentration response of duloxetine vs. binding to thalamic sertotonin transporters in 15 healthy adult males 20 – 29 years of age using Positron Emission Tomography (PET), by measuring displacement of [^{11}C]- DASB. The result support a dose of

The study was conducted in 2 parts.

Part A

In Part A 4 groups of 3 subjects were treated with a single oral dose of Duloxetine 5 mg, 20 mg, 40 mg, or 60 mg after breakfast as shown below:

Group 1: 5 mg single dose group (5 mg capsule × 1) n = 3
Group 2: 20 mg single dose group (20 mg capsule × 1) n = 3
Group 3: 40 mg single dose group (20 mg capsule × 2) n = 3
Group 4: 60 mg single dose group (20 mg capsule × 3) n = 3

Part B

In Part B (Group 5), 3 subjects were treated with duloxetine 60 mg po after breakfast once daily for 7 days as shown below:

Group 5: 60 mg multiple dose group (20 mg capsule × 3) n = 3

PK/PD Assessments

Timing of PK/PD assessments are shown for parts A and B are shown in Table 21 and Table 22 respectively.

Table 21 Flow Chart for Single Dose Duloxetine PK / PD Assessments in PET Study HMDZ Part A

Day	Day 1			Day 2			Day 3		
Time	*0*	*6*	*7.5*	*0*	*1*	*2.5*	*0*	*5*	*6.5*
Time post Dose	*0*	*6*	*7.5*	*24*	*25*	*26.5*	*48*	*53*	*54.5*
PET	–	All doses	–	–	60 mg only	–	–	60 mg only	–
Plasma Drug Conc	–	All doses	All doses	–	60 mg only	60 mg only	–	60 mg only	60 mg only

Table 22 Flow Chart for Multiple Dose Duloxetine PK / PD Assessments in PET Study HMDZ Part B

Day	Days 1-6	Day 7			Day 8	Day 9			Day 10		
Time	*-t*	*0*	*6*	*7.5*	*0*	*0*	*1*	*2.5*	*0*	*6*	*7.5*
Time post Dose	*-t*	*0*	*6*	*7.5*	*24*	*48*	*49*	*50.5*	*72*	*78*	*79.5*
PET	–	–	X	–	–	–	X		–	X	–
Plasma Drug Conc	–	–	X	X	–	–	X	X	–	X	X

Results:

Receptor Occupancy at 6 hours after a Single Dose

Figure 1 and Figure 2 show the dose and concentration effect profiles for thalamic serotonin transporter receptor occupancy 6 hours after a single dose. The apparent ED_{50} and EC_{50}'s are reported as 7.9 mg and 3.7 ng/ml respectively. The raw data for the dose and receptor occupancy is shown in Table 23.

According to the sponsor:

'The effective range of serotonin transporter occupancy that is expected to provide clinical effects has not been fully elucidated at this point, but serotonin transporter occupancy of approximately 80% has been reported in patients under treatment with SSRIs such as paroxetine or citalopram. For LY248686 (duloxetine) in this study, estimates based on the Part A dose/occupancy curve indicated that a dose of at least 40 mg would be required in order to achieve serotonin transporter occupancy in the estimated effective range of 80%.'

It should be noted that this is only an apparent receptor occupancy percentage the drug is needed to displace the PET ligand and the occupancy is determined by the ratio of the ratios of the concentrations of each of the binding substances to their respective Km's. Thus the occupancy at a particular concentration under clinical conditions in the absence of the PET ligand is likely to be higher at any concentration. In addition because of the potential for differences in uptake of drug across the blood brain barrier concentration effect relationships are likely to be different at different times post dose, and this needs to be considered in comparing occupancy rates across drugs.

Time Course of Receptor Occupancy Offset

The time course of offset of receptor occupancy as compared to changes in duloxetine plasma concentrations after single and multiple dosing are shown in Figure 3 and Figure 4 respectively, and the data are shown in Table 24 and

Table 25. It's readily apparent from these figures and tables that offset from the receptor is much slower than elimination from plasma.

Table 26 shows a comparison of duloxetine half-lives for receptor offset and for plasma.

Figure 1 **Percent (%) Serotonin Transporter Receptor Occupancy 6 hours after a Single Dose vs. Dose – Study HMDZ**

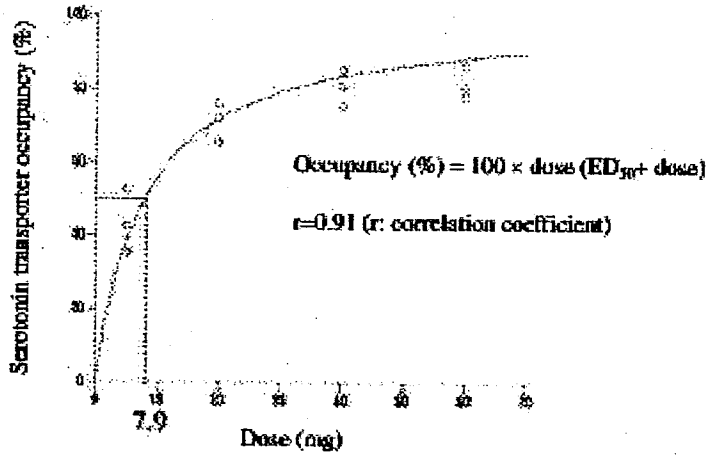

Figure 11.4–1 **Relationship between dose and serotonin transporter occupancy**

Figure 2 **Percent (%) Serotonin Transporter Receptor Occupancy 6 hours after a Single Dose vs. Duloxetine Plasma Concentration – Study HMDZ**

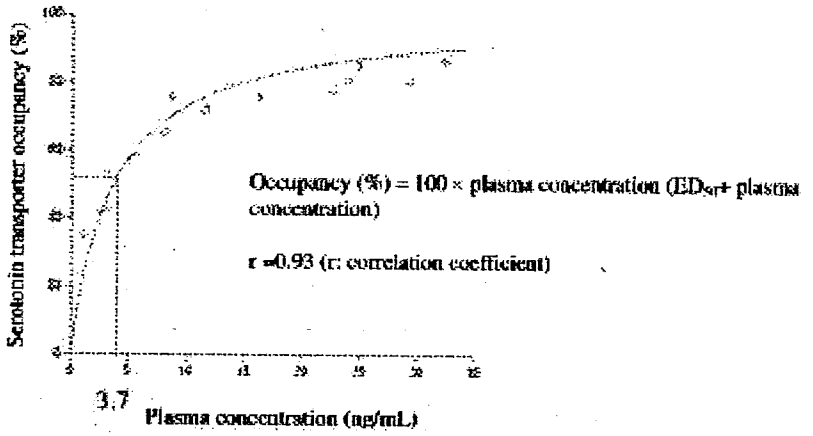

Figure 11.4–2 Relationship between plasma concentration and serotonin transporter occupancy

Table 23 **Data of Percent (%) Serotonin Transporter Receptor Occupancy 6 hours after a Single Dose vs. Dose – Study HMDZ**

Table 11.4-1 Serotonin transporter occupancy in single-dose administration (%)

Dose (mg)	Subject No.	Occupancy (%)	
		6 h after administration	Mean ± SD estimated from approximation curve
5	G1-1		43.6 ± 8.8
	G1-2		38.8
	G1-3		
20	G2-1		71.3 ± 5.3
	G2-2		71.7
	G2-3		
40	G3-1		80.6 ± 4.8
	G3-3		83.5
	G3-4		
60	G4-1		81.8 ± 4.3
	G4-3		88.4
	G4-4		

b(4)

Figure 3 **Percent (%) Serotonin Transporter Receptor Occupancy and Duloxetine Plasma Concentration vs. Time after a Single Dose – Study HMDZ**

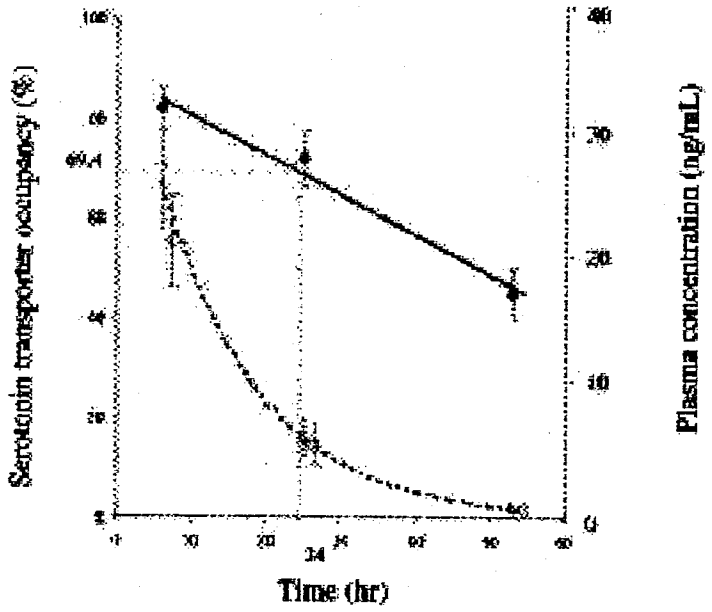

Figure 11.4-3 Time-course changes in plasma concentration (○), and serotonin transporter occupancy (●) in single-dose administration of LY248686 at 60 mg

Figure 4 **Percent (%) Serotonin Transporter Receptor Occupancy and Duloxetine Plasma Concentration vs. Time after a Repeat Daily Doses of 60 mg – Study HMDZ**

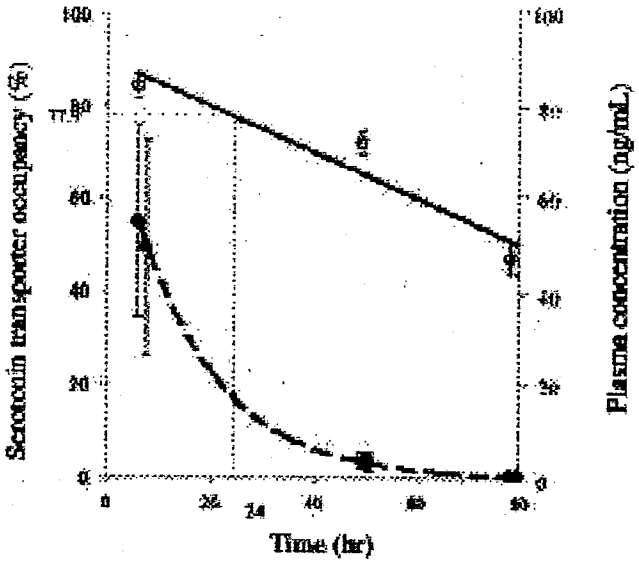

Figure 11.4-4 Time-course changes in plasma concentration (●), and serotonin transporter occupancy (○) after 7-day repeated-dose administration of LY248686 at 60 mg

Table 24 Percent (%) Serotonin Transporter Receptor Occupancy vs. Time after a Single Dose of Duloxetine – Study HMDZ

Table 11.4-2 Time-course changes in serotonin transporter occupancy (%) in single-dose administration (60 mg)

Time after administration (hr) \ Subject No.	G4-1	G4-3	G4-4	Mean ± SD
6				81.8 ± 4.3
25				71.9 ± 5.7
53				44.9 ± 5.3

b(4)

Table 25 Percent (%) Serotonin Transporter Receptor Occupancy and Duloxetine Plasma Concentration vs. Time after 7 Repeat Daily Doses of 60 mg – Study HMDZ

Table 11.4-4 Serotonin transporter occupancy (%) in 7-day repeated-dose administration (60 mg)

Time after administration (hr) \ Subject No.	G5-1	G5-2	G5-3	Mean ± SD
6				84.3 ± 2.8
49				71.9 ± 2.6
78				47.1 ± 3.7

b(4)

Table 26 Comparison of Duloxetine Thalamic Serotonin Receptor Occupancy and Plasma Half-lives after Multiple Dosing – Study HMDZ

Table 11.4-5 Half-lives of serotonin transporter occupancy and plasma concentration in 7-day repeated-dose administration

Subjects	Half-life (hr)	
	Occupancy	Plasma concentration
G5-1		
G5-2		
G5-3		
Mean ± SD	90.3 ± 5.0	10.8 ± 0.4

b(4)

7.4.2 PK/PD of Efficacy and Safety in GAD

The protocols for the GAD efficacy studies included in this submission were searched for any additional pharmacokinetic information that may have been collected.

There were no occurrences of the term pharmacokinetic in the following protocols.

F1J-MC-HMBR Duloxetine Hydrochloride 60 mg or 120 mg Once Daily Compared with Placebo in Patients with Generalized Anxiety Disorder

F1J-MC-HMDT Duloxetine Hydrochloride Once Daily Compared with Placebo in the Treatment of Generalized Anxiety Disorder

F1J-MC-HMDU A Comparison of Duloxetine Hydrochloride, Venlafaxine Extended Release, and Placebo in the Treatment of Generalized Anxiety Disorder

7.5 Biopharmaceutic Issues

7.5.1 Bioequivalence Study for Manufacturing Site Change – Study HMCE

Study HMCE was an open-label, randomized, single-dose, two-period, crossover study to test the bioequivalence of 60 mg duloxetine hydrochloride capsules (20% w/w) manufactured at Lilly del Caribe, Inc., Carolina, Puerto Rico (test) to 60-mg capsules manufactured at Eli Lilly and Company, Indianapolis, Indiana facility (reference), in 24 healthy male and female smoking and non-smoking East Asian (Chinese) and West Asian, CYP2D6 extensive metabolizers under fasting conditions. According to the sponsor each manufacturing site used the identical unit formula and essentially the same manufacturing process.

The capsules manufactured at the two sites are bioequivalent as indicated by the data in Table 27, and a biowaiver for the lower strengths is appropriate.

The effects of gender smoking and ethnicity may be found in the appropriate sections of this review but typically the numbers of women and non-Chinese are too small to draw any firm conclusions.

Table 27 Bioequivalence of Duloxetine 60 mg Capsules Manufactured at Lilly del Caribe (test) to Capsules Manufactured at Lilly Indianapolis, Indiana (reference) – Study HMCE

Metric	Summary Statistics		Geometric Means		Geometric Mean Ratio (90% CI)[a]
Rx	Ref	Test	Ref	Test	
N	24	24	24	24	
Wt (kg)	70.6 ± 10.3 (14.5) 53.6 - 89.3 [70.55]	70.6 ± 10.3 (14.5) 53.6 - 89.3 [70.55]			
Tmax (hrs)	6.3 ± 1.0 (15.2) 4 - 8 [6]	6.3 ± 1.4 (21.7) 4 - 8 [6]			0.00 (-4.00, 2.00) p = 0.844
Cmax (ng/ml)	39.3 ± 23.1 (58.9) 9.8 - 106 [34.05]	40.0 ± 25.2 (63.1) 12.7 - 119 [32.1]	32.6	32.9	1.01 (0.94, 1.09)
AUCt (ng/ml x hr^{-1})	664.8 ± 484.9 (72.9) 156 - 2170 [497]	654.0 ± 504.2 (77.1) 202 - 2310 [522.5]	521	511	0.98 (0.90, 1.06)
AUCinf (ng/ml x hr^{-1})	714.1 ± 534.4 (74.8) 161 - 2290 [515]	678.0 ± 529.8 (78.2) 214 - 2480 [535.5]	555	531	0.96 (0.86, 1.06)
AUCextrap (%)	5.4 ± 7.3 (136.1) 1.13 - 38.3 [3.8]	3.6 ± 2.0 (56.6) 1.08 - 8.99 [3.1]			
CL/F (L/hr)	124.2 ± 77.8 (62.7) 26.2 - 372 [116.5]	123.1 ± 62.5 (50.7) 24.2 - 281 [112]			
Vz (L)	1939.4 ± 1016.6 (52.4) 609 - 4830 [1655]	1858.8 ± 902.8 (48.6) 562 - 4370 [1740]			
t½ (hrs)	12.7 ± 9.2 (72.5) 6.7 - 54.8 [10.45]	11.0 ± 2.1 (19.5) 6.55 - 17.8 [10.7]			

a Tmax values are Median of Differences (Min, Max)
b p-value for Wilcoxon Signed Rank Test

7.5.2 BE Study for Capsule Composition – Study HMEB

Study HMEB was a randomized, unblended, single dose, 2-way crossover, bioequivalence study under fed conditions of duloxetine 20 mg capsules encapsulated with gelatin or Hydroxy-Methyl-Propyl-Cellulose capsules in 16 healthy male presumably Japanese volunteers between 20 and 50 years of age.

Although not stated, since this study was conducted in Japan by Shinogi Pharmaceuticals the manufacturing sites and or formulations may be different than in the US.

Table 28 Bioequivalence of of Duloxetine 20 mg HPMC Capsules (test) to Gelatin Capsules (reference) - Study HMEB

Metrics	Gelatin Capsule	HPMC Capsule	Geometric Mean Ratio (90% CI)
N	16	15	
Tmax (hr)	5.7 ± 1.0 (17.5) 4.0 - 8.0	5.9 ± 0.7 (11.9) 5.0 - 7.0	
Cmax (ng/ml)	12.5 ± 4.5 (36.0) 4.0 - 19.2	13.3 ± 6.1 (45.9) 0.0 - 22.4	1.093 (1.001, 1.194)
AUC0-48 (ng/ml x hr^{-1})	185.8 ± 76.1 (41.0) 48.0 - 341.4	192.0 ± 90.2 (47.0) 0.0 - 327.9	1.074 (0.969, 1.190)
AUCinf (ng/ml x hr^{-1})	198.0 ± 81.1 (41.0) 54.5 - 357.4	205.7 ± 98.0 (47.6) 0.0 - 357.7	1.073 (0.971, 1.184)
MRT (hr)	18.34 ± 2.90 (15.8) 13.37 - 25.20	18.85 ± 4.02 (21.3) 13.01 - 29.36	1.012 (0.975, 1.051)
t½β (hr)	10.99 ± 2.22 (20.2) 6.87 - 14.20	11.19 ± 2.72 (24.3) 6.99 - 16.30	1.015 (0.952, 1.082)
t½λz (hr)	10.56 ± 2.01 (19.0) 7.42 - 15.14	10.67 ± 2.67 (25.0) 7.02 - 17.20	0.988 (0.955, 1.023)

8 SIGNATURES

Ronald E. Kavanagh, BS Pharm, Pharm.D., Ph.D., OCP/DCP-1 **Date**

Raman Baweja, Ph.D., Team Leader, OCP/DCP-1 **Date**

CC:

DFS	NDA 21-427 SES-011
HFD-120	(BenderW, KhinN, LaughrenT, OliverT)
HFD-860	(BawejaB, KavanaghR, MehtaM)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ron Kavanagh
12/6/2006 11:47:52 AM
BIOPHARMACEUTICS

Raman Baweja
12/6/2006 03:52:11 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-427 / S-011

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-427

NAME OF APPLICANT / NDA HOLDER
Eli Lilly and Company

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Cymbalta™

ACTIVE INGREDIENT(S)	STRENGTH(S)
Duloxetine Hydrochloride	20mg, 30mg, 60mg

DOSAGE FORM
Capsules, Delayed Release, Oral (20mg, 30mg, 60mg)

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,023,269	6/11/1991	6/11/2008

d. Name of Patent Owner	Address *(of Patent Owner)*	
Eli Lilly and Company	P. O. Box 6288	
	City/State: Indianapolis, IN	
	ZIP Code: 46206-6288	FAX Number *(if available)*: 317-276-3861
	Telephone Number: 317-276-2958	E-Mail Address *(if available)*: patents@lilly.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
☞ General Patent Counsel, Eli Lilly and Company	P. O. Box 6288	
	City/State: Indianapolis, IN	
	ZIP Code: 46206-6288	FAX Number *(if available)*: 317-276-3861
	Telephone Number: 317-276-2958	E-Mail Address *(if available)*: patents@lilly.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? X Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes X No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	X Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	X No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	X No
2.6	Does the patent claim only an intermediate?	☐ Yes	X No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	X Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	X No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	X Yes	☐ No

4.2	Patent Claim Number *(as listed in the patent)* 20	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement	X Yes ☐ No
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Cymbalta is a selective serotonin and norepinephrine reuptake inhibitor for oral administration. Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.	

4.2	Patent Claim Number *(as listed in the patent)* 21	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement	X Yes ☐ No
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Cymbalta is a selective serotonin and norepinephrine reuptake inhibitor for oral administration. Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.	

4.2 Patent Claim Number *(as listed in the patent)* 22	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement X Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Cymbalta is a selective serotonin and norepinephrine reuptake inhibitor for oral administration. Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.
4.2 Patent Claim Number *(as listed in the patent)* 23	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement X Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Cymbalta is a selective serotonin and norepinephrine reuptake inhibitor for oral administration. Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.
4.2 Patent Claim Number *(as listed in the patent)* 24	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement X Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Cymbalta is a selective serotonin and norepinephrine reuptake inhibitor for oral administration. Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.
4.2 Patent Claim Number *(as listed in the patent)* 25	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement X Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Cymbalta is a selective serotonin and norepinephrine reuptake inhibitor for oral administration. Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.
4.2 Patent Claim Number *(as listed in the patent)* 26	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement X Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Cymbalta is a selective serotonin and norepinephrine reuptake inhibitor for oral administration. Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.
4.2 Patent Claim Number *(as listed in the patent)* 27	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement X Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Cymbalta is a selective serotonin and norepinephrine reuptake inhibitor for oral administration. Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.
4.2 Patent Claim Number *(as listed in the patent)* 28	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement X Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Cymbalta is indicated for the treatment of major depressive disorder (MDD)

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement
29	X Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Cymbalta is indicated for the treatment of major depressive disorder (MDD)

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement
30	X Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Cymbalta is indicated for the treatment of major depressive disorder (MDD)

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement
31	X Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Cymbalta is indicated for the treatment of major depressive disorder (MDD)

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement
32	X Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Cymbalta is indicated for the treatment of Generalized Anxiety Disorder (GAD)

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement
33	X Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Cymbalta is indicated for the treatment of Generalized Anxiety Disorder (GAD)

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement
34	X Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Cymbalta is indicated for the treatment of Generalized Anxiety Disorder (GAD)

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement
35	X Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Cymbalta is indicated for the treatment of Generalized Anxiety Disorder (GAD)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	X NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Arvie J. Anderson	
Address P. O. Box 6288	City/State Indianapolis, IN
ZIP Code 46206-6288	Telephone Number 317-277-7217
FAX Number *(if available)* 317-276-3861	E-Mail Address *(if available)* patents@lilly.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

ITEM 14: CLAIMED EXCLUSIVITY

Eli Lilly and Company (Lilly) claims a three-year period of exclusivity for the use of Cymbalta in the treatment of generalized anxiety disorder as provided in 21 C.F.R. § 314.108(b)(5) and 21 U.S.C. §§ 355(c)(3)(E)(iv) and 355(j)(5)(F)(iv). The present supplemental application contains reports of new clinical investigations (other than bioavailability studies) that were conducted or sponsored by Lilly, and that are essential to the approval of this supplemental application, as follows:

1. "New Clinical Investigation": To the best of Lilly's knowledge and belief, each of the clinical investigations included in this supplemental application meets the definition of a "new clinical investigation" set forth in 21 C.F.R. § 314.108(a);
2. "Essential to Approval": Lilly has thoroughly searched the scientific literature for all published studies and publicly available reports of clinical investigations relevant to the approval being requested in this supplement. No such studies or publicly available reports were identified. Therefore the clinical investigations contained in this application are essential to approval as defined in 21 C.F.R. § 314.108(a).
3. "Conducted or Sponsored By Lilly": Lilly was the sponsor named in the Form FDA-1571 for an investigational new drug application, IND No. 37,071, under which the new clinical investigation(s) that are essential to the approval of its application were conducted.

EXCLUSIVITY SUMMARY

NDA # 21-427 SUPPL # SE1-011 HFD # 120

Trade Name Cymbalta

Generic Name duloxetine hydrochloride

Applicant Name Eli Lilly

Approval Date, If Known See DFS for signature page

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505b1

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 ☒ 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 ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?
YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?
YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 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# 21-733 Diabetic Periphal Neuropathic Pain

NDA# 21-427 Cymbalta

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. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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 ☒ 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 ☒ 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 ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

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:

- HMBR-a placebo controlled, 9 week, adult, fixed dose (60, 120 mg or pbo) study.
- HMDT- a flexible dose (60-120 mg, or pbo), placebo controlled, 10 week study.
- HMDU- a flexible dose placebo- and active-controlled, 10 week study (duloxetine: 60 to 120 mg , venlafaxine ER: 75-225 mg or pbo).

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 ☐	NO ☒
Investigation #2	YES ☐	NO ☒

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 ☒
Investigation #2	YES ☐	NO ☒

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"):

same as 2C

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 # 38,838	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 38,838	YES ☐	! 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 ☐	! NO ☐
Explain:	! Explain:
	!
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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 ☐

If yes, explain:

==========

Name of person completing form: Felecia Curtis
Title: RPM
Date: 2/12/07

Name of Office/Division Director signing form: Thomas Laughren, MD
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-427 **Supplement Type (e.g. SE5):** 1 **Supplement Number:** 011

Stamp Date: April 27, 2006 **Action Date:** February 27, 2007

HFD____ **Trade and generic names/dosage form:** Cymbalta (duloxetine hydrochloride) Capsules

Applicant: Eli Lilly & Company **Therapeutic Class:** Anti-anxiety

Indication(s) previously approved: Major Depressive Disorder/ Diabetic Peripheral Neuropathy

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Generalized Anxiety Disorder

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

XNo: Please check all that apply: X **Partial Waiver** X **Deferred** ____ **Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	**kg**____	**mo.**____	**yr.** 0	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.** 7	**Tanner Stage**____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:** Difficult to accurately diagnosis and treat children in this age range

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr.__7___ Tanner Stage_____
Max_____ kg_____mo._____ yr.__17___ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **X Adult studies ready for approval**
- ☐ **Formulation needed**

Other: Efficacy for this indication not yet established in the adult population.

Date studies are due (mm/dd/yy): 6/30/08

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

LT Felecia Curtis, RN, Regulatory Project Manager

cc: NDA 21-427
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

DEBARMENT CERTIFICATION

sNDA Application No.: 21-427

Drug Name: Cymbalta (duloxetine hydrochloride)

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Gregory T. Brophy, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: _____

Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs

Date: April 18, 2006

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

...pleted form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
ELI LILLY AND CO Michelle Folz Lilly Corporate Center Indianapolis IN 46285 US	21-427
2. TELEPHONE NUMBER 317-433-2787	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? [X] YES [ ] NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: [X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION [ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
3. PRODUCT NAME Duloxetine hydrochloride (Cymbalta)	6. USER FEE I.D. NUMBER PD3006509

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE ...LICABLE EXCLUSION.

...ARGE VOLUME PARENTERAL DRUG PRODUCT ...ROVED UNDER SECTION 505 OF THE FEDERAL FOOD, ...UG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act	[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Gregory T. Brophy, Ph.D.	Director, U.S. Regl Aff	4-19-06

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$383,700.00

Form FDA 3397 (12/03)

IBE_PRMT_CLOSE_G) (Print Cover sheet)

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: February 23, 2007

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for Cymbalta for Generalized Anxiety Disorder (GAD) (short-term efficacy only)

TO: File NDA 21-427/S-011
[Note: This overview should be filed with the 4-26-06 original submission of this supplemental NDA.]

1.0 BACKGROUND

Cymbalta (duloxetine) is an SNRI that is approved for the treatment of both MDD and diabetic peripheral neuropathic pain. This supplement seeks a claim for the short-term treatment of GAD, in a dose range of 60 to 120 mg/day. The studies supporting this claim were conducted under IND 38,838, and a pre-supplemental NDA meeting was held with the sponsor on 8-17-05.

2.0 CHEMISTRY

There were no CMC issues that required a review.

3.0 PHARMACOLOGY

There were no pharmacology/toxicology issues that required a review.

4.0 BIOPHARMACEUTICS

The results of 7 clinical pharmacology studies were submitted as part of this supplement. Several labeling changes have been made based on these studies.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

There were 3 double-blind, randomized, parallel-group, placebo-controlled, short-term (9 to 10 weeks) efficacy and safety trials in this program. These studies evaluated Cymbalta in adult outpatients with GAD in a dose range of 60 to 120 mg/day. The primary endpoint was change from baseline to endpoint in HAM-A total score. One of these studies was fixed dose in design (HMBR) and the other two were flexible dose (HMDT and HMDU). HMBR evaluated doses of 60 and 120 mg/day, and was positive for both doses on the HAM-A, with no indication of any advantage of the higher dose over the lower dose. The 2 flexible dose studies evaluated the dose range of 60 to 120 mg/day, and again, both were positive on the HAM-A. The Sheehan Disability Scale (SDS) was the designated key secondary endpoint for all 3 studies, and was also positive for all 3 studies, including both doses in HMBR.

5.1.2 Comment on Other Important Clinical Issues Regarding the Efficacy Data

Evidence Bearing on the Question of Dose/Response for Efficacy

As noted, the results of the only fixed dose study (HMBR) did not suggest any advantage of the 120 mg/day dose over the 60 mg/day dose. I agree with Drs. Khin and Glass that labeling will need to be clear that there was no demonstrated advantage of the higher dose.

Secondary Efficacy Variables

As noted, the SDS was the designated key secondary endpoint for these studies, and was positive for all 3. Thus, this finding can be included in labeling.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis primarily of age, gender, and race. There was no indication of any difference in effectiveness based on these subgroups.

Size of Treatment Effect

The effect sizes observed in these trials were similar to those seen in other positive GAD trials.

Duration of Treatment

The sponsor presented no data pertinent to longer-term efficacy for GAD in this supplement. There is, however, a randomized withdrawal study for this indication underway (HMDV). We will request that they submit the results of this study as a phase 4 commitment.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of short-term efficacy of Cymbalta in the treatment of GAD.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review and Overview of Findings

The safety data for this supplement were derived from a total of n=668 patients with GAD exposed to Cymbalta across the 3 clinical trials comprising this program. The observed common adverse events profile was consistent with that seen in other programs with this drug. There was the expected slight increase in heart rate and blood pressure. One surprising finding was a weak signal for QTc increase (+4.5 msec for drug vs -1.3 msec for placebo). This finding was inconsistent with negative findings in clinical trials for the other 2 indications studied (MDD and DNP) and negative findings in a thorough QT study.

5.2.2 Safety Findings from Other Sources

Based on consults from OSE based on AERS reports, we have added language to labeling regarding reports of serious skin reactions and reports of hallucinations. We have also added language regarding hyperglycemia, and made several other changes to labeling based on new findings.

5.2.3 Conclusions Regarding Safety of Cymbalta in the Treatment of GAD

The common adverse event profile for Cymbalta in GAD is quite similar to that seen for Cymbalta in the other approved indications, and can be adequately characterized in labeling.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling, and have asked the sponsor to make a number of changes, and in some cases, provide new information. We have incorporated new language pertinent to 3 CBE supplements. We reached agreement with the sponsor on final labeling on 2-22-07.

6.0 WORLD LITERATURE

The sponsor provided literature references that were reviewed by Dr. Glass. These provided no new information that would change conclusions about the approvability of this application.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Cymbalta is not approved anywhere at this time for the treatment of GAD.

8.0 DSI INSPECTIONS

Inspections were conducted at 3 sites, and data from all 3 were deemed to be acceptable.

10.0 LABELING AND APPROVAL LETTER

10.1 Labeling

As noted, we reached agreement with the sponsor on final labeling on 2-22-07.

10.2 Foreign Labeling

To my knowledge, Cymbalta is not approved anywhere at this time for the treatment of MDD.

10.3 Approval Letter

The approval letter includes final agreed upon labeling and requests for phase 4 commitments.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Lilly has submitted sufficient data to support the conclusion that Cymbalta is effective and acceptably safe in the treatment of GAD. We have reached agreement on final labeling, and we will issue an approval letter.

cc:
Orig NDA 21-427/S-011
HFD-130
HFD-130/TLaughren/MMathis/NKhin/RGlass/FCurtis

DOC: Cymbalta_GAD_Laughren_AP_Memo.doc

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
2/23/2007 01:08:09 PM
MEDICAL OFFICER

ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # 21-427	BLA STN# NDA Supplement # S-011	If NDA, Efficacy Supplement Type SE-1	
Proprietary Name: Cymbalta Established Name: Duloxetine hydrochloride Dosage Form: 20, 30, 40 & 60 mg		Applicant: Eli Lilly and Company	
RPM: Felecia Curtis		Division: DPP	Phone # 796-0877

NDAs: NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) NDAs and 505(b)(2) NDA supplements: Not applicable (N/A) Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	2/26/07
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☒ No
• OC clearance for approval *(file communication in* Administrative Documents *section) N/A*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ FDA Press Release ☒ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**No**," continue with question (3).*	☐ Yes ☐ No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	☐ Yes ☐ No
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**No**," continue with question (5).*	☐ Yes ☐ No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced	☐ Yes ☐ No

within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	See Action Package Ni Khin 1/30/07
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	2/2/07
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	1/24/07
• Original applicant-proposed labeling	4/27/06
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	2/2/07
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	1/24/07
• Original applicant-proposed labeling	4/27/07
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	None Applicable
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	N/A
• Most recent applicant-proposed labeling	
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings) N/A*	☐ DMETS ☐ DSRCS ☐ DDMAC ☐ SEALD ☐ Other reviews ☐ Memos of Mtgs

Page 6

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	See Tab Q RPM 9/14/06
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included See Tab P & DFS
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	Not applicable
❖ Pediatric Page (all actions)	☒ Included See Tab J
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☐ None See Tab D
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	2/8/07 See Tab D
• Incoming submission documenting commitment	2/9/07 See Tab D
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	See DFS and See Tab E
❖ Internal memoranda, telecons, email, etc.	See DFS and See Tab E
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	N/A
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 8/17/05
• EOP2 meeting *(indicate date)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	☒ No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	See Tab N
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☒ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☒ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	2/4/07
• ☒ Review & FONSI *(indicate date of review)*	2/4/07
• ☒ Review & Environmental Impact Statement *(indicate date of each review)*	2/4/07
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☒ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 11/27/06 ☒ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	N/A ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**N/A**
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc **See tab K & DFS 1/11/07**
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	☐ None requested **See Tab L**
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	2/7/07
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	yes
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☒ None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☒ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	August 22, 2006
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	**N/A**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested **INCLUDED**
• Clinical Studies	See Tab L
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☐ None 1/11/07 See Tab K
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 12/6/06 See tab M

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.

(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.

(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).

(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.

(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).

(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.

(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Felicia Curtis
2/16/2007 12:42:11 PM

www.lilly.com

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

February 23, 2007

Response to Proposed Labeling

Division of Psychiatry Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-427 sNDA S-011, CYMBALTA® (LY248686, duloxetine hydrochloride) for Generalized Anxiety Disorder

Dear Dr. Laughren,

As requested in an email from Ms. Felecia Curtis on February 22, 2007, this letter acknowledges our acceptance of the proposed GAD labeling included in that email. Also, as requested, included in this submission are two copies of the agreed upon labeling: 1 clean copy and 1 copy that highlights the two changes the FDA made and Lilly agreed to. Desk copies of these labels have also been sent to Ms. Curtis, as she requested.

The electronic submission is approximately 1 MB in size. The electronic medium has been checked and verified to be free of know viruses. The virus checking software was Symantec AntiVirus Corporate Edition program 10.0.2.2002, scan engine 71.1.0.11 using Virus Definition File Version 2/22/2007 rev.33.

Please don't hesitate to contact me if there are any questions regarding this submission. I can be reached at my work phone (317-651-5642), cell phone (317-529-2569) or via email at sakai_ann_robbins@lilly.com. If I am not available, please call Dr. Gregory Brophy, Director, U.S. Regulatory Affairs, at (317) 277- 3799.

Sincerely,

Eli Lilly and Company

Ann R. Sakai, Ph.D.
Associate Director
U.S. Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
ELI LILLY AND COMPANY	2/23/07
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(317) 276-2000	(317) 276-1652
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* Eli Lilly Corporate Center Indianapolis, IN 46285	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 21-427

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	CODE NAME *(If any)*
Duloxetine Hydrochloride	Cymbalta	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsules	20, 30, 40 and 60 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Generalized Anxiety Disorder

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Response to FDAs proposed labeling of Feb 22, 2007

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Response to Proposed Labeling

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Ann R Sakai	Ann R. Sakai, Ph.D., Associate Director U.S. Regulatory Affairs	2/23/07

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Lilly Corporate Center , Indianapolis, IN 46285	(317) 651-5642

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Attachment for Form FDA 356h

Cymbalta capsules are manufactured by Eli Lilly and Company at the following facilities:

Facility Location	Facility Function	Registration No.
Eli Lilly and Company Lilly Technology Center Indianapolis, Indiana 46285	Manufacturing, packaging, and control (release and stability testing)	1819470
Lilly del Caribe, Inc. Puerto Rico Industrial Park 12.6 KM 65th Infantry Road Carolina, Puerto Rico 00985	Manufacturing, packaging, and control (release and stability testing)	2619243

Site is ready for inspection, and the contact is Ms. Rafiqah Williams (phone: 317-277-7036)

Curtis, Felecia

From: Curtis, Felecia
Sent: Thursday, February 08, 2007 9:32 AM
To: 'Ann Robbins Sakai'
Cc: Curtis, Felecia
Subject: NDA 21-427 S-011 Postmarketing Commitment Request

NDA 21-427/S-011

Hi Ann,

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cymbalta. We request a prompt written response in order to continue our evaluation of your NDA.

Since GAD is a chronic illness, we would require your commitment in conducting a maintenance study. If there is an ongoing GAD maintenance study (protocol # and title) would you be willing to have this as a Postmarketing commitment (PMC) under the acute GAD supplement.

Please provide the protocol number, title, description and complete the target dates for the study report submission.

Protocol Title

Study #

DESCRIPTION

Protocol Submission:	Within _____ months of the date of this letter
Study Start:	Within _____ months of the date of this letter
Final Report Submission:	Within _____ months of the date of this letter

If you have any questions, please email Felecia Curtis, Regulatory Project Manager.

Sincerely,

Felecia Curtis, RN, LT, USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
U.S. Food and Drug Administration
10903 New Hampshire Ave Bldg 22 RM 4399 Silver Spring, MD 20993-0002
301-796-0877 felecia.curtis@fda.hhs.gov

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/s/

Felicia Curtis
2/12/2007 01:20:49 PM

Response to Request for a Postmarketing Commitment
NDA 21-427, S-011
Cymbalta for the treatment of Generalized Anxiety Disorder
February 9, 2007

On 08 February 2007, Ann Sakai, Lilly U.S. Regulatory, received the following request via email from Felecia Curtis, FDA Regulatory Health Project Manager.

FDA REQUEST

"We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cymbalta. We request a prompt written response in order to continue our evaluation of your NDA.

Since GAD is a chronic illness, we would require your commitment in conducting a maintenance study. If there is an ongoing GAD maintenance study (protocol # and title) would you be willing to have this as a Postmarketing commitment (PMC) under the acute GAD supplement

Please provide the protocol number, title, description and complete the target dates for the study report submission.

Protocol Title
Study #
DESCRIPTION

Protocol Submission:	*Within* _____	*months of the date of this letter*
Study Start:	*Within* _____	*months of the date of this letter*
Final Report Submission:	*Within* _____	*months of the date of this letter*

LILLY RESPONSE:
Lilly will accept this as a Postmarketing commitment under the acute GAD supplement.

Protocol Title: Duloxetine 60 to 120 mg Once Daily Compared with Placebo in the Prevention of Relapse in Generalized Anxiety Disorder

Study #: F1J-MC-HMDV (Study HMDV)

Description: Protocol F1J-MC-HMDV is a randomized, double-blind, placebo-controlled relapse prevention study to demonstrate maintenance of efficacy, with a 6-month open-label, flexible dose acute therapy phase and a 6-month double-blind continuation therapy phase.

Protocol Submission: The protocol was submitted to GAD IND 69,749 on 30 November 2004, Serial No. 014. Please note that Protocol Amendment A was the initial protocol submitted to the IND.

Study Start: The date of the first patient visit (FPV) for Study HMDV was 06 January 2005.

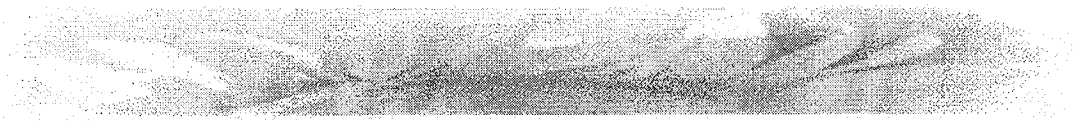
Final Report Submission: A clinical study report for Study HMDV will be available within 6 months of the date of this letter.

Curtis, Felecia

To: Ann Robbins Sakai
Cc: Curtis, Felecia
Subject: NDA 21-427 S-011

Hi Ann,

Do you have a follow up email or submission on the wording for orthostasis & syncope; effects on BP and hyponatremia/SIADH. The agreed upon language on these topics has not been incorporated into this version of labeling. Please include these in the revised proposed labeling document (both clean and mark up copy).



Thanks,

Felecia Curtis, RN, LT, USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
U.S. Food and Drug Administration
10903 New Hampshire Ave Bldg 22 RM 4399 Silver Spring, MD 20993-0002
301-796-0877 felecia.curtis@fda.hhs.gov

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/s/

Felicia Curtis
1/23/2007 01:32:28 PM
CSO

Curtis, Felecia

From: Curtis, Felecia
Sent: Friday, January 19, 2007 1:18 PM
To: 'Ann Robbins Sakai'
Cc: Curtis, Felecia
Subject: RE: Duloxetine GAD sNDA 21-427 s-011

Hi Ann,

Please provide a new proposed labeling (both clean and mark-up, word version) which incorporates all of the changes proposed in:

SE1-011 (GAD)

SLR-006

SLR-009

SLR-013

In addition, please submit last approved labeling (with no CBEs). Please submit the following requested information by COB Monday.

Thanks,
Felecia Curtis
301-796-0877
felecia.curtis@fda.hhs.gov

From: Ann Robbins Sakai [mailto:SAKAI_ANN_ROBBINS@LILLY.COM]
Sent: Wednesday, January 17, 2007 10:52 AM
To: Curtis, Felecia
Cc: David, Paul A
Subject: RE: Duloxetine GAD sNDA 21-427 s-011

Thank you, Felecia. I will look for your email by Friday.
Ann

Ann R. Sakai, PhD.
Regulatory Advisor
Desk Phone: 317-651-5642
Cell Phone: 317-529-2569
Fax: 317-276-1652
email: sakai_ann_robbins@lilly.com

"Curtis, Felecia" <Felecia.Curtis@fda.hhs.gov> To Ann Robbins Sakai <SAKAI_ANN_ROBBINS@LILLY.COM>

01/17/2007 10:40 AM

cc "David, Paul A" <paul.david@fda.hhs.gov>
Subject RE: Duloxetine GAD sNDA 21-427 s-011

I will be emailing you by end of this week.

Thanks,
Felecia Curtis
301-796-0877
felecia.curtis@fda.hhs.gov

From: Ann Robbins Sakai [mailto:SAKAI_ANN_ROBBINS@LILLY.COM]
Sent: Wednesday, January 17, 2007 10:35 AM
To: Curtis, Felecia
Cc: David, Paul A
Subject: Re: Duloxetine GAD sNDA 21-427 s-011

Dear Felecia,
As per my email last week below, can you please provide me with a status report on the duloxetine sNDA for Generalized Anxiety disorder? We are now 6 weeks away from the action date and we have heard virtually nothing on the progress of this NDA review. I am very aware of how busy both you and the Division are, but if there is any of the information requested below that you could share with me, I would really appreciate it.
Sincerely,
Ann

Ann R. Sakai, PhD.
Regulatory Advisor
Desk Phone: 317-651-5642
Cell Phone: 317-529-2569
Fax: 317-276-1652
email: sakai_ann_robbins@lilly.com

Ann Robbins Sakai/AM/LLY

01/12/2007 04:10 PM

To "Curtis, Felecia" <Felecia.Curtis@fda.hhs.gov>
cc
Subject Duloxetine GAD sNDA 21-427 s-011 Link

Dear Felicia,
Happy New Year. I hope you had an enjoyable holiday break.

Given that we are now 1.5 months away from the PDUFA action date for this duloxetine GAD sNDA referenced above, is there any update you can provide me on where the Division stands with their review? I would appreciate any information you could share regarding status of reviews, timing of receipt of any additional questions the Division may have and timing of labeling negotiations.
Thank you in advance,
Ann

Ann R. Sakai, PhD.
Regulatory Advisor
Desk Phone: 317-651-5642
Cell Phone: 317-529-2569
Fax: 317-276-1652
email: sakai_ann_robbins@lilly.com

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/s/

Felicia Curtis
1/19/2007 01:49:26 PM
CSO

Curtis, Felecia

To: Ann Robbins Sakai

Cc: Curtis, Felecia

Subject: RE: URGENT CLARIFICATION NEEDED Re: NDA 21-427/SE1-011

You are correct. What we would need is submission IND, serial numbers and dates for all protocols, amendments and SAP pertaining to the studies HMBR, HMDT and HMDU for NDA 21-427.

Thanks,
Felecia Curtis
301-796-0877
felecia.curtis@fda.hhs.gov

From: Ann Robbins Sakai [mailto:SAKAI_ANN_ROBBINS@LILLY.COM]
Sent: Wednesday, November 29, 2006 10:57 AM
To: Curtis, Felecia
Subject: URGENT CLARIFICATION NEEDED Re: NDA 21-427/SE1-011

Dear Felecia
I received both of your emails yesterday requesting information for the GAD sNDA-011. Can you please clarify that the email directly below (sent at 5:09 pm) is what you were referring to in the last bullet point of the email further below, sent at 5:02 pm (I highlighted it in red)? That last bullet point request from the 5:02 email would included thousands of submissions so I am assuming what you want is below. Can you please clarify. Also, please confirm that the 'three particular studies" you refer to below are indeed the 3 pivotal GAD studies (HMBR, HMDT, and HMDU). We urgently need to receive your clarification in order to comply with your short response time of Dec 1. Thank you,
Ann

Email sent 5:09 pm
Hi Ann,

Please provide submission IND and serial numbers and submission dates **for all protocols, amendments, and SAPs pertaining to three particular studies for NDA 21-427.**

Ann R. Sakai, PhD.
Regulatory Advisor
Desk Phone: 317-651-5642
Cell Phone: 317-529-2569
Fax: 317-276-1652
email: sakai_ann_robbins@lilly.com

"Curtis, Felecia" <Felecia.Curtis@fda.hhs.gov> To Ann Robbins Sakai <SAKAI_ANN_ROBBINS@LILLY.COM>

11/28/2006 05:02 PM

CC "Curtis, Felecia" <Felecia.Curtis@fda.hhs.gov>

Subject NDA 21-427/S E1-011

Eli Lilly and Company
Attention: Ann Sakai, Ph. D.
Senior Regulatory Research Scientist, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Sakai:

Please refer to your April 27, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cymbalta.

We are reviewing the Clinical and Statistical section of your submission and have the following comments and information requests. We request by December 1, 2006 a prompt written response in order to continue our evaluation of your NDA.

In the protocols and study reports of the pivotal studies (HMBR, HMDT, and HMDU), the screening procedures state that "a complete psychiatric assessment" included a list of assessment instruments such as the Mini-International Neuropsychiatric Interview (MINI), the CGI and other psychological assessment tests for anxiety and depression. Please clarify how the diagnosis of generalized anxiety disorder was made for each of the pivotal studies (HMBR, HMDT, and HMDU).

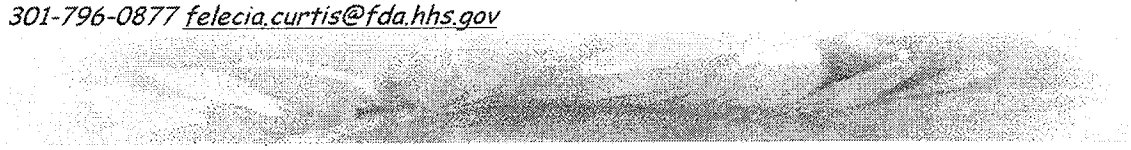
- What was the training level/background of the person who administered the MINI and the CGI?
- Did the screening process include a clinical psychiatric evaluation conducted by a psychiatrist?
- What criteria were most important in making the diagnosis of GAD, and how were excluded diagnoses (i.e. other anxiety disorders and other psychiatric diagnoses) determined?

Statistical Comments

- Please provide serial numbers and dates of the correspondence related to NDA 21427.

If you have any questions, call Felecia Curtis, RN, RPM, at 301-796-0877.

Felecia Curtis, RN, LT, USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
U.S. Food and Drug Administration
10903 New Hampshire Ave Bldg 22 RM 4399 Silver Spring, MD 20993-0002
301-796-0877 felecia.curtis@fda.hhs.gov



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/s/

Felicia Curtis
11/29/2006 12:41:27 PM
CSO

Curtis, Felecia

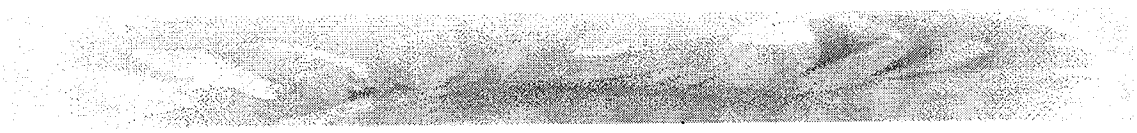
To: Ann Robbins Sakai
Cc: Curtis, Felecia
Subject: NDA 21-427

Hi Ann,

Please provide submission IND and serial numbers and submission dates **for all protocols, amendments, and SAPs pertaining to three particular studies for NDA 21-427.**

Thanks,

Felecia Curtis, RN, LT, USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
U.S. Food and Drug Administration
10903 New Hampshire Ave Bldg 22 RM 4399 Silver Spring, MD 20993-0002
301-796-0877 felecia.curtis@fda.hhs.gov



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/s/

Felicia Curtis
11/28/2006 05:16:06 PM
CSO

Curtis, Felecia

To: Ann Robbins Sakai
Cc: Curtis, Felecia
Subject: NDA 21-427/SE1-011

Eli Lilly and Company
Attention: Ann Sakai, Ph. D.
Senior Regulatory Research Scientist, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Sakai:

Please refer to your April 27, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cymbalta.

We are reviewing the Clinical and Statistical section of your submission and have the following comments and information requests. We request by December 1, 2006 a prompt written response in order to continue our evaluation of your NDA.

In the protocols and study reports of the pivotal studies (HMBR, HMDT, and HMDU), the screening procedures state that "a complete psychiatric assessment" included a list of assessment instruments such as the Mini-International Neuropsychiatric Interview (MINI), the CGI and other psychological assessment tests for anxiety and depression. Please clarify how the diagnosis of generalized anxiety disorder was made for each of the pivotal studies (HMBR, HMDT, and HMDU).

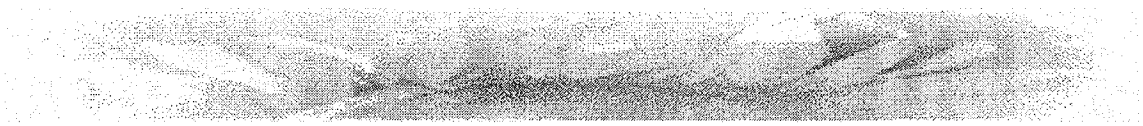
- What was the training level/background of the person who administered the MINI and the CGI?
- Did the screening process include a clinical psychiatric evaluation conducted by a psychiatrist?
- What criteria were most important in making the diagnosis of GAD, and how were excluded diagnoses (i.e. other anxiety disorders and other psychiatric diagnoses) determined?

Statistical Comments

- Please provide serial numbers and dates of the correspondence related to NDA 21427.

If you have any questions, call Felecia Curtis, RN, RPM, at 301-796-0877.

Felecia Curtis, RN, LT, USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
U.S. Food and Drug Administration
10903 New Hampshire Ave Bldg 22 RM 4399 Silver Spring, MD 20993-0002
301-796-0877 felecia.curtis@fda.hhs.gov



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/s/

Felicia Curtis
11/28/2006 05:09:21 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-427/SE-1

INFORMATION REQUEST LETTER

Eli Lilly and Company
Attention: Ann Sakai, Ph. D.
Senior Regulatory Research Scientist, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Sakai:

Please refer to your April 27, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cymbalta.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request by December 1, 2006 a prompt written response in order to continue our evaluation of your NDA.

In the protocols and study reports of the pivotal studies (HMBR, HMDT, and HMDU), the screening procedures state that "a complete psychiatric assessment" included a list of assessment instruments such as the Mini-International Neuropsychiatric Interview (MINI), the CGI and other psychological assessment tests for anxiety and depression. Please clarify how the diagnosis of generalized anxiety disorder was made for each of the pivotal studies (HMBR, HMDT, and HMDU).

- What was the training level/background of the person who administered the MINI and the CGI?
- Did the screening process include a clinical psychiatric evaluation conducted by a psychiatrist?
- What criteria were most important in making the diagnosis of GAD, and how were excluded diagnoses (i.e. other anxiety disorders and other psychiatric diagnoses) determined?

If you have any questions, call Felecia Curtis, RN, RPM, at 301-796-0877.

Sincerely,

LT Felecia Curtis

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/s/

Felicia Curtis
11/28/2006 05:04:06 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM *(Name, Office/Division, and PhoneNumber of Requestor)*:
OPS, Staff (HFD-354) Attn: Bai Nguyen (301-796-1531) WO21 RM3523	Teshara G. Bouie, ONDQA, Division of Post-Marketing Assessment, 301-796-1649

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10/17/2006		21-427	SE1-011	April 27, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Cymbalta			December 17, 2006

NAME OF FIRM: Lilly

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This efficacy supplement is located in the EDR at:
\\Cdsesub1\n21427\S_011\2006-04-27

Please evaluate. This supplement is due February 27, 2007.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Teshara G. Bouie	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Teshara Bouie
10/17/2006 11:05:58 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-427 Supplement # 011 Efficacy Supplement Type SE- 1

Proprietary Name: Cymbalta
Established Name: Duloxetine Hydrochloride

Strengths: 20 mg, 30 mg, 40 mg, & 60 mg capsules

Applicant: Eli Lilly & Co
Agent for Applicant (if applicable): N/A

Date of Application: 4/27/06
Date of Receipt: 4/27/06
Date clock started after UN:
Date of Filing Meeting: 6/8/06
Filing Date: 6/26/06
Action Goal Date (optional): User Fee Goal Date: 2/27/07

Indication(s) requested: Generalized Anxiety Disorder

Type of Original NDA:	(b)(1) ☐	(b)(2) ☐
AND (if applicable)		
Type of Supplement:	(b)(1) ☒	(b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 6
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☒ NO ☐
  If yes, explain: 3 year

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐ NO ☒

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☒ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☒

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. N/A YES ☒
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

   Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, 3 Years NO ☐
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: (see 356H form)

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) (NONE) NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) Aug,17, 2005 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☐ NO ☒

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☐ NO ☒

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ NO ☒

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☐ NO ☒

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☒

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☐ NO ☐
  If no, did applicant submit a complete environmental assessment? **N/A** YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? **N/A** YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? N/A YES ☐ NO ☐

- If a parenteral product, consulted to Microbiology Team? N/A YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 8, 2006

NDA #: 21-427 SE-011

DRUG NAMES: Cymbalta

APPLICANT: Eli Lilly & Company b(4)

BACKGROUND: Cymbalta® (duloxetine hydrocholoride) has been approved for the major depressive disorder (MDD), and neuropathic pain associated with diabetic peripheral neuropathy (DPNP). Duloxetine is also being developed as a treatment for _____. The sponsor submitted this NDA for another indication, Generalized Anxiety Disorder.

ATTENDEES:
Thomas Laughren, Roberta Glass, Chen Yeh-Fong, Ray Baweja, Ron Kavanagh, Susan Player, Felecia Curtis

ASSIGNED REVIEWERS (including those not present at filing meeting):

Discipline/Organization	Reviewer
Medical:	Roberta Glass
Secondary Medical:	
Statistical:	George Kordzakhia
Secondary Statistical:	Chen Yeh-fong
Pharmacology:	Linda Fossom
Statistical Pharmacology:	
Chemistry:	Janice Brown
Environmental Assessment (if needed):	
Biopharmaceutical:	Ron Kavanagh
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Connie Lewin
Regulatory Project Management:	Felecia Curtis
Other Consults:	
OPS:	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A	☒	FILE	☐	REFUSE TO FILE	☐	
STATISTICS	N/A	☐	FILE	☒	REFUSE TO FILE	☐	
BIOPHARMACEUTICS			FILE	☒	REFUSE TO FILE	☐	
• Biopharm. study site audits(s) needed? YES						☐	NO ☒
PHARMACOLOGY/TOX	N/A	☐	FILE	☒	REFUSE TO FILE	☐	
• GLP audit needed?					YES	☐	NO ☐
CHEMISTRY			FILE	☒	REFUSE TO FILE	☐	
• Establishment(s) ready for inspection?				N/A	YES	☐	NO ☐
• Sterile product?					YES	☐	NO ☐
If yes, was microbiology consulted for validation of sterilization?					YES	☐	NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

LT Felecia Curtis, RN, Regulatory Project Manager

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/s/

Felicia Curtis
9/14/2006 03:53:07 PM
CSO

Felicia Curtis
9/14/2006 04:08:03 PM
CSO

Curtis, Felecia

To: Ann Robbins Sakai

Subject: PT IR for NDA 21-427 SE-011

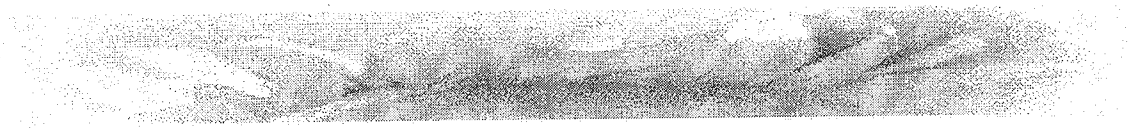
Hello Ann,

The Pharmacologist really just wants to know whether you have submitted any new non-clinical studies that haven't been previously submitted to this NDA either in the original submission or in the response to the first Approvable letter (where the issue of qualifying impurities was addressed); no non-clinical studies were submitted (or needed) in the response to the second Approvable letter.

We don't mean to suggest that any additional non-clinical studies would be expected for this change in indication, but just want to verify whether or not any new studies were submitted in the current efficacy supplement.

Thanks,

Felecia Curtis, RN, LT, USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
U.S. Food and Drug Administration
10903 New Hampshire Ave Bldg 22 RM 4399 Silver Spring, MD 20993-0002
301-796-0877 felecia.curtis@fda.hhs.gov



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/s/

Felicia Curtis
9/13/2006 02:52:31 PM
CSO

Curtis, Felecia

To: Ann Robbins Sakai

Subject: Pharmacology/Toxicology IR NDA 21-427 SE1-011

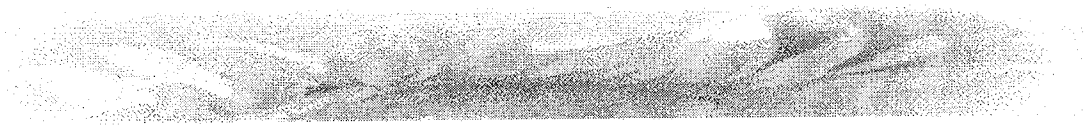
Hello Ann,

The Pharmacology/Toxicology reviewer requests the following information:

Regarding your supplement (NDA 21-427, SE1, N-001, letter-dated 4/27/06) for use of Cymbalta for treatment of Generalized Anxiety Disorder, it appears that you have not submitted any new non-clinical (pharmacology or toxicology) data that was not submitted in the original submission of this NDA. If you have submitted any new non-clinical data, please provide us with a list of the study reports.

Thanks,

Felecia Curtis, RN, LT, USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
U.S. Food and Drug Administration
10903 New Hampshire Ave Bldg 22 RM 4399 Silver Spring, MD 20993-0002
301-796-0877 felecia.curtis@fda.hhs.gov



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/s/

Felicia Curtis
9/11/2006 01:58:01 PM
CSO

www.lilly.com

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

August 22, 2006

120 Day Safety Update

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-427 sNDA S-011, CYMBALTA® (LY248686, duloxetine hydrochloride) for Generalized Anxiety Disorder

Dear Dr. Laughren,

Enclosed please find the 120 day Safety Update for the Generalized Anxiety Disorder sNDA referenced above. The enclosed "Note to Reviewer" provides further information on this submission.

The electronic medium has been checked and verified to be free of know viruses. The size of the submission is approximately 261 Mb. The virus checking software was Symantec AntiVirus Corporate Edition program 8.1.0.825, scan engine 4.2.0.7 using Virus Definition File Version 8/17/2006 rev. 32.

Please don't hesitate to contact me if there are any questions regarding this submission. All correspondence on this matter should be directed to my attention via my work phone (317-651-5642), cell phone (317-529-2569) or via email at sakai_ann_robbins@lilly.com If I am not available, please call Dr. Gregory Brophy, Director, U.S. Regulatory Affairs, at (317) 277- 3799.

Sincerely,

Eli Lilly and Company

Ann R Sakai

Ann R. Sakai, Ph.D.
Associate Director
U.S. Regulatory Affairs

Note to Reviewers
sNDA 21-427, Supplement 011, Cymbalta (Duloxetine Hydrochloride)
for treatment of Generalized Anxiety Disorder (GAD)
120-day Safety Update

The content of this submission is as follows:

- Safety Update for completed and ongoing duloxetine studies
- Revised dataset and revised specific tables for the duloxetine suicidality report

Safety Update:
Since our GAD sNDA submission on 26 April 2006, completed studies of duloxetine have not yielded data for more than 25% new subjects compared with the original submission. Therefore, we did not include an amended integrated analysis of safety in the 120-day safety update, but have included additional safety information from completed and on-going duloxetine studies between the cut off date of the original sNDA submission (09 December 2005) and the cut-off date for this 120 day safety update (26 April 2006).

Completed studies - There was only one completed clinical study since the submission of the GAD sNDA by the 26 April 2006 cut off data for this Safety Update. This is study F1J-US-HMDR, entitled "A Comparison of Duloxetine Dosing Strategies in the Treatment of Patients with Major Depression". A summary of the safety data from this study, as well as the final clinical study report, is included in this submission.

Ongoing studies - We have included an update on safety information obtained from the 28 on-going duloxetine studies (any indication) between the 09 December 2006 cut off for the initial GAD sNDA and 26 April 2006 cut off for this safety update. Information on any death reported to Lilly by 25 July 2006 is also included.

Since our original sNDA submission, we have made no change to the overall conclusions regarding the safety of duloxetine in the treatment of patients with GAD.

Revisions to suicidality dataset and report tables
During the course of conducting additional analyses using the overall duloxetine exposures integrated safety base, Lilly discovered an error in the construct of the dataset used for the suicidality analyses included in the original GAD sNDA. As a consequence of the dataset construct error, a total of 10 events, all from patients enrolled in MDD studies, were inappropriately included in the analyses as treatment-related suicidality events. Three events were in patients in the placebo-controlled study database and 7 events were in patients in the open label study database. A revised dataset and revised tables that present results from the reanalysis are provided in this safety update. Based on these updated analyses, none of the conclusions from the Suicidality Report included in the original GAD sNDA have changed.

If you have any questions regarding this submission, please contact Dr. Ann Sakai, Associate Director, U.S. Regulatory Affairs by phone (317-651-5642), cell phone (317-529-2569), email (sakai_ann_robbins@lilly.com) or fax (317-276-1652). In her absence, please call Dr. Gregory Brophy, Director, U.S. Regulatory Affairs, at (317) 277- 3799.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
OFFICE OF NEW DRUG QUALITY ASSESSMENT

POST-MARKETING EVALUATION
CMC ASSESSMENT FORM

APPLICANT:	NDA NUMBER:	DOC TYPE:	SEQ NUMBER:	SUBMISSION TYPE:
LILLY	021427	SE1	011	ORIGINAL

PROPRIETARY NAME:	ESTABLISHED NAME:
CYMBALTA(DULOXETINE HCL)20,30,40,60MG	DULOXETINE HCL

DOSAGE FORM:	STRENGTH/POTENCY:	PHARMACOLOGICAL CATEGORY:
CAP	20 MG, 30 MG, 40 MG, 60	

LETTER DATE:	STAMP DATE:	PDUFA GOAL DATE:	SUBMISSION (CHECK ONE)
4/27/2006	4/27/2006	2/27/2007	FIRM: PA FINAL: PA

DIVISION IV	OND Division:	MANAGED BY:	PAL: Janice Brown
BRANCH: VII		OND	MEDIA SUBMISSION: Electronic

SUPPLEMENT PROVIDES FOR: A new indication

BUNDLED: No

CHANGE CATEGORY: the use of Cymbalta in the treatment of Generalized Anxiety Disorder.

LABELING INVOLVED:	PAT:	COMPARABILITY PROTOCOL:	PHASE 4 COMMITMENT:
Yes - Both PI & Label	No	No	

REVIEW PATH: 3 - Moderate Risk - Minimal Review

CONSULTS:

JUSTIFICATION/COMMENTS: 7/14/2006 – BROWNJA

1. Issue a Environmental Assessment consult requesting whether the total use of duloxetine is still below the maximum total amount estimated in the original Environmental Assessment filed with NDA 21-427. This information needed for this consult is located in the EDR for NDA 21427, SE1-S-011.

2. PAL requested an inspection on 14-Jul-2006, of Eli Lilly and Company, Indianapolis, Indiana 46285 (Reg. No.: 1819470) and Lilly del Caribe, Inc., Carolina, Puerto Rico 00985 (Reg. No.: 2619243).

3. Review changes in labeling if required.

4. Recommended reviewer: Janice Brown.

PAL ACTION:

BRANCH CHIEF: James Vidra

REVIEWER:

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/s/

Janice Brown
8/7/2006 03:02:52 PM
CHEMIST

Jim Vidra
8/7/2006 03:16:49 PM
CHEMIST

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: November 9, 2006

TO: LT Felecia Curtis, RN, Regulatory Health Project Manager
Roberta Glass, M.D., Clinical Reviewer
Division of Psychiatry Products, HFD-130

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Sherbet Samuels, R.N., M.P.H.

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-427/SE1-011

APPLICANT: Eli Lilly & Company

DRUG: Cymbalta (Duloxetine Hydrocholoride)

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of General Anxiety Disorder

CONSULTATION REQUEST DATE: July 10, 2006

DIVISION ACTION GOAL DATE: December 1, 2006

PDUFA DATE: February 27, 2007

I. BACKGROUND:

Cymbalta is approved for the treatment of Major Depressive Disorder. The sponsor submitted a supplemental New Drug Application (NDA # 21-427/SE-011) for the use of Cymbalta in the treatment of Generalized Anxiety Disorder (GAD). Dr. William Carter and Dr. Robert Horne's sites were selected for inspection due to significant primary

efficacy results for study HMDT. The preliminary statistical analysis indicated that the results from these two sites would impact the p-values for study HMDT. Dr. Richard Brown's site was selected for inspection due to large enrollment for study HMBR. The goals of the inspections were to assess adherence to FDA regulatory requirements; specifically, investigator oversight, protocol compliance, accuracy of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare. The following protocols were audited: HMDT entitled "Duloxetine Hydrochloride Once Daily Compared with Placebo in the Treatment of Generalized Anxiety Disorder" and HMBR entitled "Duloxetine Hydrochloride 60 mg or 120 mg Once Daily Compared with Placebo in Patients with Generalized Anxiety Disorder".

Summary Report of U.S. Inspections

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol	Insp. Date	EIR Received Date	Final Classification
Dr. William Carter/104	Belmont, MA	HMDT	Sept. 11 - 19, 2006	10/10/06	NAI
Dr. Robert Horne/113	Las Vegas, NV	HMDT	Aug. 31 –Sep. 12, 2006	10/04/06	VAI
Dr. Richard Brown/901	Cincinnati, OH	HMBR	Sept. 6 - 11, 2006	11/1/06	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations from regulations. Data unreliable.

A. Protocol #HMDT

1. William Carter, M.D./104
   McLean Hospital
   115 Mill Street, Oakes Building
   Belmont, MA 02478

a. What was inspected: Dr. Carter enrolled 13 subjects. The inspection encompassed an audit of all subjects' records. Primary endpoint efficacy data were verified for all subjects.

b. Limitations of inspection: none

c. General observations/commentary: One discrepancy was noted on the HAMA total score for subject 1403 at visit 7. The data listings report a HAMA total score of 7 while the source documents indicate a HAMA total score of 6. Other than the discrepancy, the inspection found no significant regulatory deviations.

d. Data from this site are acceptable.

2. Robert Horne, M.D. /113
2915 West Charleston, Suite 4
Las Vegas, NV 89030

a. What was inspected: Dr. Horne enrolled 14 subjects. The inspection encompassed an audit of 14 subjects' records. Primary endpoint efficacy data were verified for 14 subjects.

b. Limitations of inspection: none

c. General observations/commentary: The inspection found instances of inadequate record keeping. Specifically:

a) The protocol inclusion criteria specified that female study subjects of childbearing potential must "test negative for pregnancy at the time of enrollment". The records for subject 2301 indicate that a pregnancy test was performed. However, there is no documentation of the test results.

b) The protocol specified that a comprehensive physical examination be performed at Visit 1. The records for subjects 2301 and 2302 indicate that a physical examination was performed. However, there is no documentation of the physical examination results.

d. Data from this site are acceptable.

B. Protocol # HMBR

1. Richard Brown, M.D. /901
Hartford Research Group, Inc.
3120 Burnet Ave, Ste 103
Cincinnati, OH 45242

What was inspected: Dr. Brown enrolled 29 subjects. The inspection encompassed an audit of 24 subjects' records. Primary endpoint efficacy data were verified for 24 subjects.

b. Limitations of inspection: none

c. General observations/commentary: The inspection found the following four discrepancies regarding the HAMA total score:

- The data listings report a HAMA total score of 12 at visit 4 for subject 9109 while the source documents and CRF indicate a HAMA total score of 13.

- The data listings report a HAMA total score of 13 at visit 5 for subject 9111 while the source documents and CRF indicate a HAMA total score of 23.
- The data listings report a HAMA total score of 9 at visit 8 for subject 9115 while the source documents and CRF indicate a HAMA total score of 8.
- The data listings report a HAMA total score of 11 at visit 5 for subject 9120 while the source documents and CRF indicate a HAMA total score of 10.

Other than the discrepancies, no significant deviations from FDA regulations were observed.

d. The review division should evaluate the adverse impact, if any, of the above 4 data discrepancies on overall data acceptability.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As noted above, inspection of Dr. Horne found instances of inadequate record keeping. Inspection of Drs. Carter and Brown revealed that these investigators appear to have conducted the studies noted in accordance with FDA regulations. Except for the discrepancies noted above, data from these three clinical investigators are acceptable in support of NDA 21-427/SE1-011.

{See appended electronic signature page}

Sherbet Samuels, R.N., M.P.H.

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Sherbert Samuels
11/24/2006 08:47:43 AM
CSO

Constance Lewin
11/27/2006 11:35:40 AM
MEDICAL OFFICER

DSI CONSULT: Request for Clinical Inspections

Date: July 10, 2006

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46
Leslie K. Ball, M.D., Branch Chief, GCP2, HFD-47

Through: Joseph Salewski, Acting Director
Division of Scientific Investigations, HFD-45

Thomas Laughren, M.D., Division Director,
Division of Psychiatry, HFD-130
(only for foreign inspection requests)

From: LT Felecia Curtis, RN, Regulatory Health Project Manager
Division of Psychiatry Products

Subject: **Request for Clinical Site Inspections**
Application: NDA 21-427/Supplement No: SE-011
Sponsor: Eli Lilly & Company
Drug: Cymbalta (Duloxetine Hydrocholoride)

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. DSI may choose two out of four clinical sites listed for protocol HMBR.

This NDA provides data for the following: new indication. This drug is not a New Molecular Entity (NME).

Site # (Name,Address, Phone number)	Protocol #	Number of Subjects	Indication
Site 104 William Carter, MD McClean Hospital 115 Mill Street, Oakes Building Belmont, MA 02478	HMDT	Refer to EDR	Generalized anxiety disorder (GAD)
Site 113 Robert Horne, MD 2915 West Charleston, Suite 4 Las Vegas, NV 89030	HMDT	Refer to EDR	GAD

Page 2-Request for Clinical Inspections

Site # (Name,Address, Phone number)	Protocol #	Number of Subjects	Indication
Site 109 Finland: Dr. Jukka Penttinen Salon Psykiatripalvelu Helsingintie 1, 3.krs Salo 24100 Phone: 358-40-7492974 Fax: 358-2-2337802	HMBR	(n=32)	GAD
Site 105 Finland:Dr. Riitta Jokinen Lansi-Soumen Erikoislaakaripalvelut Oy Sibeliusenkatu 3 A, 5.krs Turku 20100 Phone: 3582250443 Fax: 35822504797	HMBR	(n=28)	GAD
Site 202 France:Dr. Odile Bourgeois-Adragna Cabinet Du Dr O. Bourgeois-Adragna Place de L'Hopital 49 Avenue De Gameville Saint Orens 31650 Phone: 0562243388 Fax: 0561002764	HMBR	(n=30)	GAD
Site 901 United States:Dr. Richard Brown Hartford Research Group, Inc. Cincinnati, OH 45242 Phone: 513-792-5042 Fax: 513-792-5041	HMBR	(n=29)	GAD

Domestic Inspections:

We have requested inspections because (please check all that apply):

____ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
__X__ Significant primary efficacy results (preliminary statistical analysis indicated that results from Sites 113 and 104 would impact the p-values for study HMDT)

Page 3-Request for Clinical Inspections

___ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
___ Other (specify)

International Inspections:

We have requested inspections because (please check all that apply):
__X__ There are insufficient domestic data
___ Only foreign data are submitted to support an application
___ Domestic and foreign data show conflicting results pertinent to decision-making
___ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
___ Other (specify):

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **December 1, 2006**. Our Division Action Goal date is January 26, 2007. The PDUFA due date for this application is February 27, 2007.

Should you require any additional information, please contact LT Felecia Curtis, RN, RPM.

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/s/

Thomas Laughren
7/11/2006 01:57:04 PM

DSI CONSULT: Request for Clinical Inspections

Date: June 8, 2006

To: Constance Lewin, M.D.
Division of Scientific Investigations, HFD-48

cc: Thomas Laughren, M.D.
Division Director, Division of Psychiatry, HFD-130

From: LT Felecia Curtis, RN, Regulatory Health Project Manager,
Division Director, Division of Psychiatry, HFD-130

Subject: **Request for Clinical Site Inspections**
NDA 21-427 Supplement No: SE1-011
Sponsor: Eli Lilly and Company
Drug: Cymbalta (Duloxetine hydrochloride) Capsules

Protocol/Site Identification:

Lilly has submitted 3 positive random, double-blind, placebo-controlled, and multicenter centers to support of their proposed indication of generalized anxiety disorder. The studies are as follows: F1J-MC-HMBR, F1J-MC-HMDT, and F1J-MC-HMDU.

This is an entirely electronic submission in eCTD format and may be found in our EDR using the following path: \\CDSESUB1\N21427\S_011\2006-04-27 . To find the investigator lists:
-Go to clinstat folder TOC and click on each study report
-The study report TOC has a line that states "investigator investigation" you can click on
-When you click on that page, it has a hyperlink to Appendix 16.1.4 that lists all investigators, names, address, and phone. HMDR study report, the list starts on p. 1245, HMDT study report, the list starts on p. 1071 and HMDU study report, the list starts on p. 1340.

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by December 1, 2006. We intend to issue an action letter on this application by February 27, 2007.

Should you require any additional information, please contact LT Felecia Curtis, RN, RPM.

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/s/

Thomas Laughren
6/27/2006 09:55:55 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-427/SE1-011

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

Please refer to your April 27, 2006 new drug application (NDA) 21-427/SE1-011 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cymbalta (duloxetine hydrochloride) capsules and 20 mg 30 mg, 40 mg and 60 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on June 8, 2006 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call LT Felecia Curtis, RN, Regulatory Project Manager, at (301) 796-0877.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren
6/16/2006 12:48:18 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

INFORMATION REQUEST LETTER

NDA 21-427/SE1-011

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

Please refer to your April 27, 2006 new drug application (NDA) 21-427/SE1-011 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cymbalta (duloxetine hydrochloride) capsules and 20 mg 30 mg, 40 mg and 60 mg.

Based on our preliminary review of the Clinical and Clinical Pharmacology sections of your submission we have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

The Clinical reviewer requests the following information:

Please provide the result(s), if any, of a literature searc h on the safety and efficacy of duloxentine hydrochloride in patients with General Anxiety Disorder. Please also describe your approach taken to this literature review.

The Clinical Pharmacology reviewer had difficulty distinguishing among the 132 clinical study reports submitted with regard to whether this was new or re-submitted information. Although we appreciate the completeness of the submission, we note that this problem of sorting through the massive amount of information to identify the new information is an obstacle to efficient review and, if not fixed, ultimately will result in a delay in our final action.

The *Tabular Listing of All Clinical Studies* from the CLINSTAT Table of Contents and the *Tabular Listing of All Clinical Pharmacology Studies* from the HPBIO Table of Contents combined, lists one hundred and thirty two clinical study reports that were included in the submission. To facilitate our review please provide for each of the aforementioned tabular listings a table in the same order as the tabular listing that includes:

1) Study Number
2) Study Title
3) Whether the study report was previously submitted, or if this is the first submission.
4) If previously submitted, the submission that it was submitted in.
5) Whether there are any changes from previous submissions.
6) If a first submission whether this is a completed study report or a report of and ongoing study.
7) Whether any pharmacokinetic sampling was performed in the study.

In addition for each of the tabular listings please provide two additional tables, one listing study numbers and titles for previously submitted study reports, and one table for new study reports included in the present submission. For new study reports please indicate whether this is a complete study report or a report of an ongoing study.

If you have any questions, call Felecia Curtis, RN, RPM, at 301-796-0877.

Sincerely,

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren
6/12/2006 12:23:21 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-427/S-011

PRIOR APPROVAL SUPPLEMENT

Eli Lilly and Company
Attention: Dr. Ann R. Sakai, Ph.D.
Associate Director, Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Sakai:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product	NDA Number	Supplement Number
Cymbalta® (duloxetine hydrochloride) tablets	21-427	S-011

Date of Supplement: April 27, 2006

Date of Receipt: April 27, 2006

This supplemental application proposes the use of Cymbalta in the treatment of Generalized Anxiety Disorder.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 26, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 27, 2007.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact Ms. Felecia Curtis, Regulatory Project Manager, at (301) 796-0877.

Sincerely,

{See appended electronic signature page}

Paul David, R.Ph.
Chief, Project Management Staff
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Paul David
5/24/2006 10:06:31 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*: HFD-710/Stat			FROM: HFD-130/Division of Psychiatry Products	
DATE May 8, 2006	IND NO.	NDA NO. 21-427	TYPE OF DOCUMENT Efficacy NDA supplement	DATE OF DOCUMENT April 27, 2006
NAME OF DRUG Cymbalta (duloxetine HCL) 20 mg, 30 mg, 40 mg, and 60 mg capsules	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG GAD	DESIRED COMPLETION DATE Filing deadline 6/26/06; PDUFA deadline 2/27/07
NAME OF FIRM: Eli Lilly & Company				

REASON FOR REQUEST

COMMENTS/SPECIAL INSTRUCTIONS:

The Division has received a new efficacy supplement for Cymbalta in the treatment of GAD. This is a totally electronic submission. The EDR link to the electronic portion of the sNDA is as follows:

\\CDSESUB1\N21427\S_011\2006-04-27

The filing meeting June 8, 2006. Please review the submission and provide comments.
Thanks!

SIGNATURE OF REQUESTER Richardae Taylor Araojo, Pharm.D. Regulatory Project Manager 301-594-5793 Richardae.araojo@fda.gov	METHOD OF DELIVERY (Check one) MAIL X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Susan Player
5/8/2006 04:58:10 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**			
TO *(Division/Office)*: HFD- 860/Biopharm			FROM: HFD-130, Division of Psychiatry Products	
DATE May 8, 2006	IND NO.	NDA NO. 21247/S-011	TYPE OF DOCUMENT NDA supplement	DATE OF DOCUMENT April 27, 2006
NAME OF DRUG Cymbalta (duloxetine HCL) 20 mg, 30 mg, 40 mg, and 60 mg capsules	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG GAD	DESIRED COMPLETION DATE Filing Deadline June 26, 2006; PDUFA deadline February 27, 2007
Eli Lilly and Company				

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	☐ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

COMMENTS/SPECIAL INSTRUCTIONS:

This is an efficacy NDA supplement that has included human pharmacology and bioequivalence data. Please review and provide comments, if needed. The supplement can be accessed in the EDR via the following link: \\CDSESUB1\N21427\S_011\2006-04-27

Thanks!

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Susan E. Player, MS Regulatory Project Manager 301-796-1074 susan.player@fda.hhs.gov	X MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Susan Player
5/8/2006 04:41:57 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-427

Eli Lilly & Company
Attention: Barbara Arning, MD
Manager, US Regulatory Affairs
Eli Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Arning:

Please refer to the meeting between representatives of your firm and the FDA on August 17, 2005.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Richardae C. Taylor, Pharm.D., Regulatory Health Project Manger, at (301) 594-5793.

Sincerely,
{See appended electronic signature page}

Thomas Laughren, M.D.
Acting Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES
NDA 21-427 / IND 69,749

Date:	August 17, 2005
Location:	Conference Room E; WOC2
Time:	10:00 – 11:30 AM
Firm:	Eli Lilly and Company
Type:	Face to Face
Meeting:	Type B Pre-sNDA
Drug:	Cymbalta (duloxetine HCL) Capsules
Indication:	Generalized Anxiety Disorder (GAD)
Meeting Chair:	Thomas Laughren, M.D., Acting Division Director, DPP
Meeting Recorder:	Richardae Taylor, Pharm.D., Regulatory Project Manager

Participants:

FDA:

Dr. Thomas Laughren	Acting Division Director, DPP
Dr. Paul Andreason	Acting Deputy Division Director, DPP
Dr. Roberta Glass	Clinical Reviewer
Dr. Peiling Yang	Biometrics Team Leader
Dr. Jialu Zhang	Biometrics Reviewer
Dr. Ronald Kavanagh	OCPB Reviewer
Dr. Richardae Taylor	Regulatory Project Manager

Eli Lilly and Company

Gregory Brophy, Ph.D.	Director U.S. Regulatory Affairs
Barbara Arning, M.D.	Manager U.S. Regulatory Affairs
Janelle Erickson, Ph.D.	Research Scientist Statistics
Mike Detke, M.D., Ph.D.	Medical Director
Jim Russell, M.D.	Medical Advisor
Joe Wernicke, M.D.	Medical Advisor, Global Product Safety
Mary Pat Knadler, Ph. D.	Head Drug Disposition
Evelyn Lobo, Ph.D.	Research Scientist Pharmacokinetics

Meeting Objective

Discuss planned pre-sNDA submission for duloxetine for the indication of GAD.

Background

Duloxetine is currently approved for Major Depressive Disorder (MDD) (NDA 21-427) and neuropathic pain associated with diabetic peripheral neuropathy (NDA 21-733). There are a total of 5 clinical trials in the GAD program, including 3 that are expected to be completed at the time of submission:

-HMBR: 9 week; Double-blind; fixed doses of 60 and 120 mg vs. placebo;
-HMDT & HMDU: 10 week; Double-blind; flexible-dose (60 to 120 mg) vs. placebo;
-Studies HMDV (a long-term trial) and HMDW are ongoing
-All patients in these trials will meet DSM-IV criteria for GAD; the primary endpoint for all trials is change from baseline in HAMA total score

-Lilly intends to submit a NDA supplement if 2 short-term trials are positive to support a GAD claim in early 2006.

Questions

Efficacy

Lilly believes that results from at least two positive studies of duloxetine in the treatment of generalized anxiety disorder (GAD) would be sufficient for the submission of duloxetine as a treatment for GAD. If Studies F1J-MC-HMDT and F1J-MC-HMBR are positive studies, and the data from the third study (Study F1J-MC-HMDU) are not available by the data cut-off date, Lilly will submit these two studies only in the sNDA. These two studies would then comprise the Summary of Clinical Efficacy. Results from Study HMDU (the full clinical study report including both efficacy and safety results) would then be submitted in the 4-month safety update.

1. Does the FDA agree with the proposal described above?

Comment: We indicated that two positive short-term trials would be sufficient to support a short-term claim. Further, we noted that we would not agree to review effectiveness data from a third short-term trial submitted at the 4-month safety update. If Lilly wanted to have information from a third positive study included in labeling, they would need to submit such information in a supplement following an initial approval. In addition, we alerted the sponsor that we plan to meet with the PDAC in the near future to discuss the issue of whether or not long-term efficacy data should be required as part of an initial filing of an NDA for a chronic illness, such as GAD. Although it is unlikely that a requirement for long-term effectiveness data at the time of filing would be applied to this supplement, we cannot completely rule out the possibility until we meet with the PDAC.

A gatekeeper strategy (Westfall and Krishen 2001) will be employed for sequentially testing the secondary hypotheses to be eligible for possible inclusion in the label. If the primary hypothesis is statistically significant at the 0.05 two-sided level, the first secondary hypothesis will be tested. If this comparison is statistically significant at the 0.05 two-sided level, subsequent secondary hypotheses will be tested in sequence until the first null hypothesis in the sequence fails to be rejected. Lilly seeks confirmation regarding inclusion of gatekeeper outcome measures in the label, where such variables have been incorporated into the *a priori* stated gatekeeper objectives. All three duloxetine GAD protocols included the following gatekeeper objectives: the Visual Analog Scale (VAS) for Pain – Severity of Overall Pain (Studies HMBR and HMDT) and the Sheehan Disability Scale Global Functioning Score (Studies HMBR, HMDT, and HMDU). Please refer to Appendix 2 for the Targeted Product Profile (TPP).

2. Does FDA agree that replicated findings on gatekeeper measures may be included in the Patient Outcomes section of the label?

Comment: We indicated that the proposed gatekeeper strategy was acceptable, however, only for the SDS endpoint, and replication would be required to get this information into labeling. We noted that we do not consider pain or more than one quality of life scale as acceptable secondary endpoints. If Lilly wants an analgesic claim, this would require an independent development program. On the other hand, if they are targeting the pain and other physical symptoms that are

part of GAD, we indicated that we considered this a pseudospecific claim, since these symptoms would be expected to improve with effective treatment along with other aspects of this syndrome. Lilly accepted our views on this, and asked if they can modify the SAP to identify the SDS as the key secondary endpoint; we noted this is acceptable.

We also discussed additional issues regarding the statistical analysis plan (SAP):

- First, they confirmed that none of these trials has been unblinded as yet, but datalock is planned for study BR late in September, 2005. They agreed to submit a final SAP for this protocol to the IND prior to datalock, and similarly for the other studies.
- We then asked for clarification of the primary analysis model, since this was not clear from the outline submitted. We had a concern about the inclusion of the interaction term in the primary analysis model; they will reconsider this in light of our comments.
- We inquired about the plan to utilize type 2 sum of squares in the primary analysis. They clarified that this would be the plan only if the interaction term was to be included in the primary model; if not, they will use type 3 sum of squares, which we indicated is our preference.
- They clarified that ANCOVA will be used for both the primary and key secondary endpoints.
- We asked for clarification regarding how they will handle missing item scores, and they noted that they plan to drop data for any visits at which there are missing items. We suggested that use a less severe approach, e.g., dropping only if 20% of items are missing; in that event, the mean of the remaining scores would be used to impute the missing scores. They will consider this proposal, and also will include sensitivity analysis to explore the consequences of different approaches to dealing with missing items. They did note that, thus far, they have not seen any missing items for the primary assessment, so this may not be an important issue.
- We also asked for clarification of sequence for the testing of 2 doses in HMBR (the sponsor will test 120, then 60, for the primary--HAMA, and then only 60 for the first key secondary--Sheehan score). We asked the sponsor to provide a rationale for looking first at 60 mg for the key secondary.
- Finally, we asked that, when they submit the supplement, they submit both the complete raw efficacy datasets and also the SAS programs for their analyses of the efficacy data, so that we can try to replicate their findings. In addition, we requested the SAS programs that produce the derived variables from the raw variables.

Safety

Section 5.2.1 provides further detail on special safety considerations for duloxetine therapy to be included in the Summary of Clinical Safety. Topics that have a historical association with the serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI) or selective serotonin reuptake inhibitor (SSRI) classes, with duloxetine therapy or with the GAD disease state, or that are considered potentially clinically relevant for duloxetine, will be chosen for further examination.

3. ***Does the FDA agree with the special safety considerations proposed (Section 5.2.1)?***
   Comment: We indicated that the safety topics they had identified for special consideration (i.e., hepatic, suicidality, and cardiovascular) were acceptable.

Case report forms (CRFs) for completed studies (studies that have a completed clinical study report at the time of the data cut-off date) for GAD for individual patients will be provided for deaths, discontinuations due to adverse events, hepatic events, and serious adverse events (SAEs). For all other indications, CRFs will be provided for deaths and SAEs. CRFs for discontinuations due to adverse events for all other indications and CRFs for ongoing studies will be available upon request (Section 5.2.3).
In addition, a table listing all patients who experienced death or SAEs, discontinued because of an adverse event, or experienced a significant or notable treatment-emergent adverse event (TEAE) during clinical trials will be provided (see example provided in Appendix 3). A table listing patients experiencing these events in clinical pharmacology studies will be provided separately (in Module 2.7.2 and Module 2.7.4). Any deaths that may occur up to 30 days prior to the submission date will be included in the Summary of Clinical Safety.

4. ***Does the FDA agree with the proposal described above?***
   Comment: We indicated that this plan is acceptable, however, we asked if they will be unblinding patients with serious liver toxicity in ongoing studies, and if so, we want CRFs for these patients as well. They agreed to provide CRFs for any such patients. They also agreed to combine in one place in the application all of the line listings for deaths and SAEs (i.e., for the clinical trials, the clinical pharmacology trials, and Japanese studies). We also discussed the feasibility of providing an algorithm for generating individual patient's safety summaries for any patient, and it appears they do not have this capability.

Lilly proposes to provide narratives for patient cases meeting specific criteria (outlined in Section 5.2.2).

5. ***Does the FDA agree with the narratives criteria proposed (Section 5.2.2)?***
   Comment: We indicated that this plan is acceptable.

Lilly is currently addressing a request from the FDA Division of Neuropharmacological Drug Products (DNDP) (24 December 2004) regarding suicide-related events in adult patients. The cut-off date for this request was 01 October 2004. For this sNDA submission, Lilly proposes to analyze suicide-related events in the following manner:

- The suicide-related analysis for the GAD submission will have a cut-off date that is consistent with the cut-off date for the additional safety analyses for the submission.
- The analysis will be performed using an all placebo-controlled studies integrated safety database and the overall integrated duloxetine exposures database and will also be conducted by indication on all studies that are locked as of that date, including the GAD trials.
- Lilly will use the same methodology as requested by the DNDP (in correspondence dated 24 December 2004 and 12 May 2005) with the exception of

the data format used for categorization. For all potential events that have not been categorized in previous analyses, categorization will be done using "raw" data rather than pre-categorization narratives. Post categorization, narratives will be written for patients with categories of interest.

6. Does the FDA agree with the plan for the assessment of suicidality?

Comment: This is probably fine, but we asked for clarification of what Lilly means by "not categorized in previous analyses." They confirmed that this refers to new cases beyond the cutoff date for the adult suicidality analysis.

The clinical pharmacology safety database will include information from subjects in all single- and multiple-dose clinical pharmacology studies (not including Japan studies; refer to Appendix 4). In addition, Item 6 will contain reports for 13 additional clinical pharmacology studies completed since NDA 21-421 (refer to Appendix 1).

7. Does the FDA agree that the proposed biopharmaceutical package (Appendix 4) is sufficient to support the GAD indication?

Comment: We asked for, and the sponsor confirmed that no new strengths will be proposed in the submission.

We asked for clarification on the different study lists, i.e., the overall TOC has some clinical pharmacology studies not included in appendix 4. Lilly explained that the TOC includes studies already submitted previously and cross references will be provided for those studies, while appendix 4 includes only studies for which full study reports will be submitted in this supplement. We asked that study synopses be provided for these studies in addition to the cross reference citation.

We stated that whether the package is sufficient is a matter of review. However we had no recommendations for any biopharmaceutic or clinical pharmacology studies in addition to those proposed by the sponsor.

Cross-Referencing Strategy b(4)

Duloxetine has been approved for the treatment of major depressive disorder (MDD) under NDA 21-427 and for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPNP) under NDA 21-733. Duloxetine is [redacted]

[redacted] This supplement will include updates to appropriate items since the submission of the original NDA 21-427; however, certain items will be cross-referenced (as described in Section 3.1).

8. Does the FDA agree with Lilly's plan to cross-reference NDA 21-427 (as described in Section 3.1)?

Comment: We indicated that this cross-referencing plan is acceptable, however we asked if they could provide an integrated section of synopses for all studies for which safety data are included in the supplement, and they agreed to provide this. They did confirm that important safety information from all studies would be

included in the ISS, so that we do not have to go searching through full study reports for important safety information.

Databases/Reports
The primary placebo-controlled integrated safety database will include only patients from completed GAD studies.
The secondary placebo-controlled integrated safety database will include information from all placebo-controlled duloxetine clinical studies conducted by Lilly regardless of indication, except for the placebo-controlled GAD studies.
The long-term duloxetine exposures integrated safety database will include information from patients who participated in duloxetine clinical trials with a design duration of at least 6 months.
The overall duloxetine exposures integrated safety database will include information from patients who took at least one dose of duloxetine in GAD, MDD, DPNP, LUTD, and fibromyalgia clinical studies (see Appendix 1).

9. Does the FDA agree that Lilly's plan for integrating safety data as described above is acceptable (Section 4.3)?

Comment: We indicated that this plan is acceptable.

Section 5.4.2 presents a description of the format for the electronic datasets for EVENTS and HISTORY. Appendix 5 presents an example of the electronic datasets.

10. Does the FDA agree that the proposed structure, format, and content of the electronic datasets are acceptable?

Comment: We indicated that this plan is acceptable.

Administrative
Lilly proposes to provide financial disclosure information for GAD studies that are included in the submission only.

11. Does the FDA agree that it is acceptable to submit financial disclosure information for only these studies?

Comment: We indicated that this plan is acceptable.

b(4)

As with the original submission of NDA 21-427, and as described by the Pediatric Research Equity Act of 2003, Lilly requests a deferral of pediatric studies. Lilly believes that a deferral of pediatric studies is warranted until after the approval of the adult indication. Lilly is currently [redacted]. The final clinical study report will be submitted in 2008.

12. Does the FDA agree that a pediatric deferral is appropriate until after approval of the adult indication?

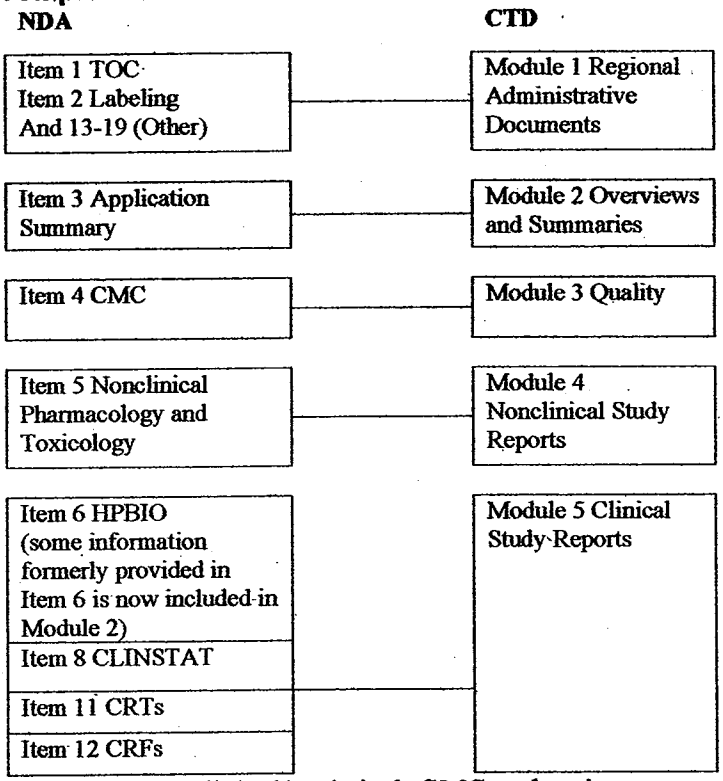
Comment: We indicated that this plan is acceptable.

Other
Lilly proposes to submit the GAD sNDA in a hybrid format of the Common Technical Document (CTD) and eNDA, as described on page 13 of the draft guidance *Submitting*

Marketing Applications According to the International Conference on Harmonization (ICH)-CTD Format – General Considerations (FDA 2001). The sNDA will be submitted electronically using Item Folders from the sNDA/NDA format, but some CTD formatting will be used. The content of each Item is described in Table 2.1 and in Section 5.4.4 of this briefing document.

Since the content of the former Integrated Summary of Safety and Integrated Summary of Efficacy (ISS/ISE) is available in CTD format, Lilly proposes to utilize the methods described in the guidance *M4: Common Technical Document for the Registration of Pharmaceuticals for Human Use* and clarified in *M4: The CTD – Efficacy* and *M4: The CTD – Safety* for this information. Modules 2.5 Clinical Overview, 2.7 Clinical Summary, and 5.0 Clinical Study Reports will therefore contain information formerly provided in the ISS/ISE.

Table 2.1. Comparison of CTD Format to Traditional NDA



Abbreviations: CLINSTAT = clinical/statistical; CMC = chemistry, manufacturing and control; CRFs = case report forms; CRTs = case report tabulations; CTD = common technical document; HPBIO = human pharmacology and bioavailability/bioequivalence; NDA = new drug application; TOC = table of contents.

13. Is the FDA in agreement with the plan to submit a hybrid format of the CTD/eNDA electronic version (Section 5.4.4)?

Comment: FDA Response emailed on 8/12/05- Yes, this is acceptable. We note that you will be submitting an eNDA with its typical file/folder structure, but the table of contents will be in the CTD format. Please be aware that the ISS and ISE are misnomers. They are, in fact, integrated ANALYSES of efficacy and safety, and as such, should typically be located in section 5.3.5.3. Occasionally, the ISS and ISE are short enough that they can be considered true summaries and can also

be referenced in section 2.7 (please do not submit the same information twice), but remember that the total size of the entire module 2 for ALL summaries is limited to 50-400 pages. Often, including the ISS/ISE in module 2 would exceed the recommended page limit.

Appendix 1 includes the proposed table of contents for the sNDA.

14. Does the FDA agree that the proposed table of contents in Appendix 1 is sufficient?

Comment: We indicated that the proposed table of contents is acceptable.

As described in Appendix 2, the Targeted Product Profile (TPP) is a nonbinding instrument designed to facilitate discussions with the FDA. To that end, Lilly has included a proposed indication statement for GAD and the clinical study descriptions of Study HMBR, Study HMDT, and Study HMDU. Lilly would appreciate receiving the FDA's comments on the indication and study descriptions.

15. Does the FDA agree that Study HMBR, Study HMDT, and Study HMDU, provided that the outcomes of at least two of these studies are positive, would support the indication described in the label language within the TPP (Appendix 2)?

Comment: As noted in the response to question 1, we indicated that two positive short-term trials would be sufficient to support a short-term claim. Further, we noted that we would not agree to review effectiveness data from a third short-term trial submitted at the 4-month safety update. If they wanted to have information from a third positive study included in labeling, they would need to submit such information in a supplement following an initial approval. We also noted that we could not comment on specific labeling language at this point, since this was a matter of review once the NDA is submitted. But we did suggest that the SDS would likely be the only secondary endpoint that could be mentioned in labeling.

Lilly plans to write synopses for studies which have not previously been submitted and are ongoing at the time of the data cut-off date for this sNDA.

16. Does the FDA agree that these criteria for writing the synopses are acceptable?

Comment: As noted earlier, we would like an integrated section including synopses for all studies for which they are including safety data in the supplement.

Lilly is conducting a 12-month relapse-prevention study that may be submitted after registration as support of a long-term efficacy claim. Study HMDV is comprised of approximately 22 to 26 weeks of acute, open-label treatment followed by 26 to 30 weeks of double-blind treatment. This study is designed to examine the long-term efficacy of duloxetine in preventing relapse of GAD symptoms. In Study HMDV, patients who have met response criteria at the end of open-label acute therapy phase are randomly assigned to receive placebo or to continue treatment with duloxetine in a 1:1 ratio. The primary efficacy analysis is the comparison of duloxetine with placebo in time-to-relapse using the log-rank test based on all randomized patients. An additional secondary *a priori*

planned time-to-relapse analysis will be assessed based upon a subset population. To qualify for the subset population, randomly assigned patients must have met response criteria in the acute, open-label treatment phase continuously for at least 6 weeks (see Section 4.1.1.4).

17. Does the FDA agree that data from Study HMDV may be submitted after registration and provides support for a long-term efficacy claim?

Comment: As noted in the response to question 1, we alerted the sponsor that we plan to meet with the PDAC in the near future to discuss the issue of whether or not long-term efficacy data should be required as part of an initial filing of an NDA for a chronic illness, such as GAD.

18. Does the FDA agree that a log-rank analysis of "time-to-relapse" using the relapse criteria defined in Section 4.1.1.4 is acceptable as the primary efficacy analysis for a long-term efficacy claim?

Comment: We indicated that a log-rank analysis is acceptable; however, we noted that it is our general preference that the only patients randomized should be those who meet criteria for being in a responder for at least some minimum period of time. We expect to finalize our policy on the minimum duration of responder status after the upcoming PDAC meeting.

19. Does the FDA agree that the subset population would provide further support of a long-term efficacy claim?

Comment: We indicated that we intended to seek advice from the PDAC on what would be an acceptable design for a long-term efficacy trial, and that one of the specific issues of interest is how long the stabilization period should be before randomizing patients. We noted that the committee's advice on this matter would likely affect our final policy on this matter, and that we fully expected that the final requirement will be for a much longer stabilization period than has been considered acceptable to date, e.g., it would likely be 3 to 4 months. We also noted that we would also ask the committee at what point in development for programs that were currently underway would long-term data be required at the time of approval.

We agreed that we would likely be willing to compromise on some reasonable subset for analysis for their long-term study that is very far along. We also agreed to discuss a possibly more liberal approach to defining "responder status," i.e., to include patients who have some excursions in their scores during the run-in but can still be considered reasonably stable.

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Thomas Laughren
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Richardae Taylor
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