CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-192

APPROVABLE LETTER

NDA 22-192

Vanda Pharmaceuticals
Attention: Paolo Baroldi, M.D., PhD
Chief Medical Officer
9605 Medical Center Drive
Suite 300
Rockville, MD 20850

Dear Dr. Baroldi:

Please refer to your new drug application (NDA) dated and received September 27, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for iloperidone tablets.

We acknowledge receipt of your submissions dated:

November 27, 2007	December 14, 2007	January 28, 2008	February 20, 2008
March 17, 2008	April 2, 2008	April 18, 2008	April 25, 2008
May 1, 2008	May 16, 2008	June 13, 2008	June 20, 2008

This new drug application provides for the use of iloperidone for the treatment of schizophrenia.

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

Non-Approvable Deficiencies

There are two major deficiencies that are the basis for the non-approvable action.

Lack of Sufficient Effectiveness Data

We agree that study 3101 can be considered a positive study in support of the acute treatment of schizophrenia at a dose of 24 mg/day. We also note that this study had an active control group (ziprasidone 160 mg/day) and that iloperidone 24 mg/day had effectiveness similar to ziprasidone. We do not believe, however, that the other three controlled effectiveness studies in your program support the effectiveness of iloperidone.

The remaining three studies (3000, 3004, and 3005) included a mix of schizoaffective and schizophrenic patients. In our analyses, we have focused on the patients with schizophrenia. We consider schizoaffective disorder a distinct entity that would require a separate development program.

Study 3000: This study examined three fixed doses of iloperidone (4, 8, and 12 mg/day), haloperidol 15 mg/day, and placebo. The analysis plan for this study was to consider the entire randomized population (i.e., schizophrenic and schizoaffective) and to look first at the 8+12 mg/day group vs placebo. Only if this contrast was positive would it be permissible to look at the other groups vs placebo. Whether one looks at the results for the total population or, as we preferred, the schizophrenic subgroup (69% of total sample), the p-value for the 8+12 mg/day group vs placebo is not significant. Therefore, we consider this a negative study for iloperidone, although there is some evidence of an effect at 12 mg. It is important to note, however, that the active control arm in this trial, i.e., haloperidol 15 mg/day, was highly statistically significantly superior to placebo.

Study 3004: This study examined two dose ranges for iloperidone (4-8 mg/day and 10-16 mg/day), risperidone 4-8 mg/day, and placebo. The analysis plan for this study was to consider the entire randomized population (i.e., schizophrenic and schizoaffective) and to look first at the 10-16 mg/day group vs placebo. Only if this contrast were positive would it be permissible to look at the 4-8 mg/day group vs placebo. The initial contrast was significant (p=0.001), as was the 4-8 vs placebo contrast (p=0.012), but only for the entire randomized population. For the schizophrenic subgroup both iloperidone vs placebo contrasts are non-significant and we consider this a negative study for schizophrenia at the lower doses studied. It is important to note that the active control arm in this trial, i.e., risperidone 4 to 8 mg/day, was highly statistically significantly superior to placebo. Risperidone was also statistically significantly superior to iloperidone at both doses (p=0.006 vs iloperidone 4-8 mg/day and p=0.021 vs iloperidone 10-16 mg/day).

Study 3005: This study examined two dose ranges for iloperidone (12-16 mg/day and 20-24 mg/day), risperidone 6-8 mg/day, and placebo. The analysis plan for this study was to consider the entire population randomized (i.e., schizophrenic and schizoaffective) and to look first at the 12-16 mg/day group vs placebo. Only if this contrast were positive would it be permissible to look at the 20-24 mg/day group vs placebo. In fact, this initial contrast was not significant (p=0.09), so that the study could be considered a failed study. As noted, however, we made a decision, independent of the results of this study, to focus on the schizophrenic patients in this study (about 78% of the sample). If one takes this approach and looks first at 12-16 vs placebo, this contrast is significant (p=0.033). We feel this is an acceptable approach, even though it was not the protocol-specified approach. The next contrast, i.e., 20-24 vs placebo, is even more highly significant (p=0.005).

Although this might be considered a positive study in support of the effectiveness of iloperidone in the treatment of schizophrenia in a dose range of 20-24 mg/day and possibly at 12-16 mg/day, there are two additional findings that complicate this interpretation. First, there is some evidence that iloperidone is substantially inferior to existing alternative treatments, although we do not consider this entirely established. The agency has, in the recent past, taken the relative effectiveness of new psychiatric drugs compared to currently available drugs into consideration when making overall risk benefit decisions about new psychiatric drugs. The overall principle is

that markedly inferior performance on the treatment of an acute schizophrenia episode presents a risk to patients. In the two previous instances where we have taken an action unfavorable to the new drug based on this type of analysis, the difference between the test drug and the standard treatment was significant at $p<0.05$. It is, therefore, worth noting that the contrast for risperidone vs iloperidone 12-16 mg/day is highly statistically significant in favor of risperidone ($p=0.005$). This indicates that, although iloperidone 12 to 16 mg/day was superior to placebo in this trial, this dose range is clearly inferior to a standard dose of an active control agent. We believe this shows that iloperidone doses lower than 20 mg/day do not have a useful effect in the treatment of schizophrenia and could not be recommended for that use. Moreover, risperidone in this trial was considerably superior to the iloperidone 20-24 mg/day arm, although not at conventional levels of statistical significance ($p=0.093$) and we believe this represents a substantial concern. Second, in study 3005, the effect in both iloperidone groups is driven entirely by the non-U.S. population, with almost no effect in U.S. patients. We realize that cross-national differences in effect are not rare, but as study 3005 is one of only two studies supporting the 20-24 mg dose, this observation further weakens the degree of support it provides. We therefore have serious questions about the effectiveness of iloperidone relative to other available antipsychotic agents, and indeed about whether effectiveness is sufficiently established. We therefore ask that you design and conduct one additional trial to demonstrate the effectiveness of iloperidone in the treatment of schizophrenia. This trial should be placebo-controlled and should also include as an active control arm a robustly effective antipsychotic agent, e.g., olanzapine or risperidone. We would be happy to discuss the design of such an additional trial with you.

I should add that our concern with establishing a reasonable level of effectiveness is strengthened by the finding of a clear QT prolonging effect of iloperidone that would relegate the drug to what is, in effect, second line status. I note further that although the hypotensive effect of the drug is mitigated by the proposed daily titration, the need for this makes iloperidone a difficult drug to use.

Lack of Sufficient Safety Data in a Relevant Dose Range

At the doses for which you have some evidence of effectiveness and at least one study suggesting an effect similar to other antipsychotic agents (20 to 24 mg/day), you have not accumulated sufficient safety data. For this dose range of 20 to 24 mg/day, you have safety data for only 508 patients, with only 64 treated for at least 6 months and only 22 for at least 1 year. These exposures are far below the minimum requirements for relevant doses according to ICH standards for a chronically used drug. Thus, we ask that you obtain additional exposures within this iloperidone dose range of 20-24 mg/day. You would need at least 1000 additional patients exposed, and the chronic use would need to meet the minimum standard of at least 300 for 6 months and at least 100 for 1 year. We would be happy to discuss with you study designs to accumulate these additional data.

Other Issues That Need to be Addressed

Although not reasons for this not approvable action, you will also need to address the following items:

Clinical

It has come to our attention that there have been allegations of research misconduct by a clinical investigator named Dr. John Gilliam. We note that Dr. Gilliam participated in the iloperidone development program. It will be necessary, therefore, to assess whether or not findings from Dr. Gilliam's site(s) had an important impact on the outcome of your development program for your above referenced NDA. As such, we are asking that you provide the following information:

1. Determine whether Dr. Gilliam was an investigator in any of your pivotal efficacy studies. These would be the studies that are described in the labeling for the above referenced product as the basis for its claimed efficacy.

2. If so, reanalyze the data for these studies, excluding the subjects from his study site(s) from the efficacy analysis with regard to all efficacy endpoints mentioned in labeling, and compare those results to the original analysis.

3. Also assess the safety data from Dr. Gilliam's research sites to determine if it is consistent with the safety data coming from other sites and consistent with what is currently in approved labeling. The safety assessment should include all studies in which Dr. Gilliam was an investigator (not limited to pivotal efficacy studies). If there are notable safety differences between Dr. Gilliam's data and what is described in the proposed labeling (e.g. in Adverse Events), please characterize those differences.

4. Please submit the requested information identifying each of the relevant studies, including study name/protocol number and date of submission.

Clinical Pharmacology

1. Study CIL0522A0103, conducted in subjects with normal, mildly and moderately impaired hepatic function, was inconclusive because the exposure for mild subjects was greater than for moderately impaired subjects. We ask that you repeat the study in a moderately impaired group, comparing them to normals in the same study. The genotyping for the extensive metabolizers used in this study should be submitted to the Office of Clinical Pharmacology.

2. You should conduct a study investigating the possible in vitro interaction of iloperidone and P-Gp as discussed in a prior communication.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
   a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   b. Present tabulations of the new safety data combined with the original NDA data.

c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
d. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.
8. When you have obtained the additional clinical data that are needed to support this application, we would be happy to meet with you to discuss the resubmission of the safety data for this program. There were a number of technical deficiencies in the application that would need to be addressed.

Within 10 days after the date of this letter, you are required to amend the applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

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

If you have any questions, contact Kimberly Updegraff, M.S., Regulatory Project Manager, at (301) 796-2201.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Robert Temple
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