

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-992

APPROVABLE LETTER



NDA 21-992

Wyeth Pharmaceuticals, Inc.
Kenneth R. Bonk
Director II, Global Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101

Dear Mr. Bonk:

Please refer to your new drug application (NDA) dated and received December 22, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pristiq (desvenlafaxine succinate) extended release tablets.

We acknowledge receipt of your submissions dated February 1, 14, 16, 2006, March 7, 16 2006, April 21, 28, 2006, May 10, 17, 2006, June 7, 9, 26, 2006, July 3, 13, 31, 2006, August 31, 2006, September 5, 14, 22, 26, 2006, October 10, 12, 26, 2006, November 1, 2006, and December 8, 2006.

Your July 31, 2006 submission constituted an extension on the regulatory due date.

This new drug application provides for the use of Desvenlafaxine Succinate tablets for the treatment of Major Depressive Disorder (MDD) in the adult population.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies and respond to our request listed below:

Chemistry, Manufacturing, and Controls

- 1) Your drug product manufacturing facility located in Guayama, PR (CFN #1819470) was found unacceptable during a recent cGMP inspection. A satisfactory inspection of this site will be required before this application may be approved.
- 2) The Comparability Protocol (CP) for "implementation of PAT and real time release via a CBE-30 supplement" is inadequate. We acknowledge the receipt on December 12, 2006, of your December 8, 2006, amendment intended to address this deficiency. The information concerning the CP in this amendment was not reviewed for this action. You may refer to the portion of the amendment regarding the CP in your response to this deficiency.

3)
us

- 4) The design space for HPMC should be revised to include a particle size specification.
- 5) The established name does not match the labeled strength. Revise all labeling using either of the following example formats:

a) Pristiq
desvenlafaxine
Extended Release Tablets

b) Pristiq
desvenlafaxine
Extended Release Tablets

Dissolution Method and Specification

We ask that you agree to the following final dissolution method and specification for all strengths:

Method:

| | |
|--------------|---------------------------|
| Apparatus: | USP Apparatus 1 (baskets) |
| Speed: | 100 rpm |
| Medium: | 900 mL 0.9% NaCl in water |
| Temperature: | 37°C ± 0.5°C |

Specification:

| Time | Criteria (% LC Released) |
|----------|---|
| 2 hours |  |
| 4 hours | |
| 8 hours | |
| 12 hours | |
| 24 hours | |
| | NLT |

Office of Surveillance and Epidemiology

Regarding RiskMAP Evaluation Activities:

- Provide the details of how you plan to evaluate the impact of your modified packaging and other risk management strategies on overdose toxicity and suicide
- Submit a full protocol that includes a more detailed description of your survey methodology, that includes (but is not limited to):
 - The numbers of patients and prescribers who will be surveyed
 - An explanation of methods to be used to determine the sample
 - A clear definition of the selection criteria
 - An explanation of the controls to be used to minimize bias
 - An explanation of the controls to be used to compensate for the limitations associated with their methodology
- Submission of the survey instrument (questionnaire and moderator's guide).

Regarding the Modified Packaging Plan:

- Provide details on how this packaging has been implemented for venlafaxine and how it will be implemented for desvenlafaxine, including:
 - Whose responsibility it is for ensuring that high risk patients are dispensed only the small pack
 - What the pharmacists' role is to be in dispensing the small pack, and how they are to be informed about its purpose
 - How the proposed packaging configuration is different than a physician writing a prescription for a small quantity, especially since the proposed packaging does not convey any messages to the pharmacist.

Regarding the Proposed Education Plan:

- The focus of the educational plan should be to educate health care providers not only in identifying high risk patients, but also in when and how to write prescriptions appropriately for high risk patients.
 - The health care provider target population for your education and outreach should be all psychiatrists and other physicians and healthcare providers who are currently prescribing venlafaxine.
 - The education plan should also target pharmacists specifically with regard to the importance and purpose of the 15-day unit-of-use pack.
 - Provide clear and measurable objectives for the Clinician Resource Program, the Patient Resource Program, the Pharmacists Resource Program, and the Small Pack/Unit-of-Use Program. For example, for the Clinical Resource Program, the following objectives could be used:
 - Eighty percent of prescribers will be able to identify the three main methods to evaluate patients at times of higher risks for suicidality.
 - Seventy-five percent of prescribers will be able to identify the three main methods to manage patients at times of higher risks for suicidality.
- In addition, for the "Patient Resource Program," one objective could be:
- Ninety percent of patients will be able to recognize at least five early symptoms of depression and what to do whenever those arise.
- Identify and describe the barriers to the treatment of major depressive disorder that these four programs intend to address.
 - Describe the major findings of the RxFMEA project and the CareMAP project, and describe how these findings led to the development of the four programs proposed and listed on page 46 of your submission.
 - Provide a description of the Clinician Resource Program, the Patient Resource Program, the Pharmacists Resource Program, and the Small Pack/Unit-of-Use Program, including a description of their plan for implementation.
 - Provide a description of the "practical materials and tools, developed to distribute to clinicians and patients," and describe the implementation plan for these materials, in particular, how these will be used by the clinicians and patients.

General Comments:

- You should report to the Agency the status of any efforts and data relating to your risk management plan. This information should be submitted every six months for the first three years and could be included in every other Quarterly Periodic report submitted to the Agency, beginning with the second Quarterly report.

Post Marketing Commitments

1. Long-Term Efficacy Studies

Although your NDA for Desvenlafaxine Succinate documents the effectiveness as a treatment major depressive disorder over an interval of _____, it fails to provide information about the duration and conditions of treatment with Desvenlafaxine that are necessary to sustain its antidepressant effects over the full duration (presumed to be 6 months to a year) of an acute depressive episode. However, because it is widely assumed that continued treatment of symptomatically remitted patients reduces their risk of relapse, the proposed labeling for desvenlafaxine succinate recommends

_____ These labeling recommendations notwithstanding, the conditions of extended use that maximally decrease the risk of relapse are unknown. In fact, we are aware that you have conducted a randomized withdrawal study to address longer-term efficacy for this drug. Accordingly, we ask for your commitment to submit, either in response to this approvable action, or subsequent to approval as a Postmarketing commitment, the results of this study to evaluate desvenlafaxine's ability to reduce the risk of relapse in acutely remitted patients. If the results of this trial are to be submitted post-approval, we ask that you commit to submitting these results no later than 6 months after the date of approval of this NDA.

2. Pediatric Studies

We request that you commit to conducting studies to assess the safety and effectiveness of desvenlafaxine succinate as a treatment for Major Depressive 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.

We request that you commit to conducting and submitting the results of these studies no later than _____ years after the date of approval of this NDA.

3. Exploration of Dose Response for Effectiveness

Your studies with desvenlafaxine succinate as a treatment for Major Depressive Disorder have not established the dose response of the drug for effectiveness. In these studies there was no difference in effectiveness over the dose range studied, 100 to 400 mg/day. We therefore, ask that you conduct additional studies to explore lower doses than those studied. This is particularly important given the finding of dose-relatedness for a number of adverse events. In fact, we are aware of your ongoing studies in Major Depressive Disorder that involve a lower dose of 50 mg/day. Accordingly, we ask for your commitment to submit, either in response to this approvable action, or subsequent to approval as a Postmarketing commitment, the results of these studies to evaluate the lower end of the dose-response curve for this drug. If the results of these trials are to be submitted post-approval, we ask that you commit to submitting these results no later than 6 months after the date of approval of this NDA.

4. Pharmacology/Toxicology

Your combined fertility and embryo-fetal toxicity study in rats did not adequately assess desvenlafaxine's potential for embryo-fetal toxicity, including teratogenicity, due to decreased number of fetuses available for analysis at the high dose of 300 mg/kg. This appeared to result from effects of desvenlafaxine on fertility and pre-implantation loss and would not be factors if dosing were only done during the period of organogenesis. Consequently, we ask that you commit to conducting a standard embryo-fetal toxicity study in rats; this may be done after drug approval.

Labeling

Please submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling text for the package insert.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Proprietary Name and Container Label

The Division of Medication Errors and Technical Support (DMETS) find the proprietary name "Pristiq" acceptable. However, our approval of the proprietary name is tentative based upon the final date of NDA approval. We remind you that this proprietary name will need to be re-evaluated approximately three months (90 days) prior to the expected approval of this application.

Additionally, we have the following recommendations pertaining to the carton and container label:

1. The container and carton labeling were submitted in black and white. The container labels and carton labeling recommendations may not be accurate and complete as font, coloring, contrast and sharpness can play an important role, and may reveal safety issues undetectable at this time. Submit the full quality color version of the container and carton labeling for review and comment.
2. Ensure the font size of the letters comprising the established name is at least half as large as the letters comprising the proprietary name. We refer you to 21 CFR 201.10(g)(2) for guidance.
3. Decrease the prominence of the net quantity. In the current presentation with bolded font, the net quantity is more prominent than the product strength.
4. Revise the presentation so that the strengths are differentiated by color, boxing, or some other means. With the current presentation, the different strengths are presented identically.

5.



6. Decrease the prominence of the sponsor's name, as it appears almost as prominent as the proprietary name.

Foreign Regulatory Update/Labeling

We require a review of the status of all Desvenlafaxine succinate actions taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. If Desvenlafaxine succinate has been approved by any non-US regulatory bodies, we ask that you provide us any approved labeling for Desvenlafaxine succinate along with English translations when needed.

Request for Safety Update and World Literature Update

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:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - 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. Prior to an approval action, we require an updated report on the world's archival literature pertaining to the safety of Desvenlafaxine Succinate. Please provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries. This report should include only literature not covered in your previous submissions. We will need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of Desvenlafaxine Succinate. The report should also detail how the literature

search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

Promotional Material

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 Products and two copies of both the promotional materials and the package insert 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

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. 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 the application is approved.

If you have any questions, call Renmeet Grewal, Regulatory Project Manager, at (301) 796-1080.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center of 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/

Russell Katz
1/22/2007 12:40:33 PM
Signed for Dr. Robert Temple