

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-992**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-992

**NDA APPROVAL**

Wyeth Pharmaceuticals, Inc.  
Attention: Kenneth Bonk  
Director II, Global Regulatory Affairs  
P.O. Box 8299  
Philadelphia, PA 19101-9822

Dear Mr. Bonk:

Please refer to your new drug application (NDA) dated and received on December 22, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pristiq (desvenlafaxine succinate) 50mg, and 100mg extended release tablets.

We acknowledge receipt of your submissions dated:

April 4, 2007	December 14, 2007	February 14, 2008
May 11, 2007	December 19, 2007	February 15, 2008
June 1, 2007	December 20, 2007	February 20, 2008
June 27, 2007	January 14, 2008	February 21, 2008
August 23, 2007	February 4, 2008	February 22, 2008
August 29, 2007	February 11, 2008	

The August 29, 2007 submission constituted a complete response to our January 22, 2007 action letter.

This new drug application provides for the use of Pristiq (desvenlafaxine succinate) tablets for the treatment of major depressive disorder.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, please submit the 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 to the enclosed labeling (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the

National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-992."

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the submitted carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*.

Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 21-992.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **PEDIATRIC RESEARCH EQUITY ACT (PREA)**

All applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are waiving the pediatric study requirement for ages 0-6 years because the necessary studies are impossible or highly impracticable because there are not enough patients in that age group with the disease to study. We are deferring submission of your pediatric studies for ages 7-17 years because the drug is ready for approval for use in adults and the pediatric studies have not been completed.

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.

### **POSTMARKETING COMMITMENTS**

We remind you of your following postmarketing study commitments agreed upon in your submission dated February 19, 2008. These commitments are listed below.

#### 1. Deferred Pediatric Studies Under PREA

You have agreed to conduct 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 years) and adolescents (ages 12 to 17 years) will be equally represented in the samples, and there will be a reasonable distribution of both sexes in these age strata. You have agreed to submit the results of these studies no later than 4.5 years after the date of approval for this NDA.

**Final Report Submission:** 4.5 years from the date of approval

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. Exploration of Dose Response for Effectiveness

Your NDA for desvenlafaxine succinate (DVS) demonstrates the effectiveness of doses as low as 50 mg as a treatment for Major Depressive Disorder (MDD), however, the available data for effectiveness for this drug in MDD suggests a flat dose response curve for efficacy between 50 and 400 mg/day. On the other hand, there is a clear dose response for adverse events as the dose increases from 50 to 400 mg/day. Therefore, there is a need to better understand the lower end of the dose response curve to determine if efficacy might be achieved at doses even lower than 50 mg/day. You have agreed to conduct and submit the results of a randomized controlled study including placebo and DVS doses of 10, 25, and 50 mg/day as a Postmarketing commitment. This study will assess efficacy in this dose range and will also include a validated and reliable outcome measure to assess for sexual dysfunction. You have agreed to submit the results of this trial no later than 3 years after the date of the approval for this NDA.

**Final Report Submission:** 3 years from the date of approval

3. Long-Term Efficacy Studies

Although your NDA for desvenlafaxine succinate demonstrates effectiveness of recommended doses (50-100 mg/day) as a treatment for Major Depressive Disorder over an interval of 8 weeks, it does not provide information about the duration and conditions of treatment with desvenlafaxine that are necessary to sustain its antidepressant effects over the full duration (likely 6 months to a year or longer) of an acute major depressive episode at these same recommended doses. While it is widely assumed that continued treatment of symptomatically remitted patients reduces their risk of relapse, [REDACTED] we have no evidence that desvenlafaxine at these lower doses has efficacy after 8 weeks. Once you have established the lower end of the dose-response curve for efficacy, you have agreed to conduct and submit the results of a randomized withdrawal study to address longer-term efficacy for your drug at appropriate doses. If the lower dose study establishes that 50 mg/day is the lowest effective dose, this study will evaluate doses of 50 and 100 mg/day. You have agreed to submit the results of this trial no later than 3 years after the date of initiation, or approximately 5.5 years from the date of approval for this NDA..

**Final Report Submission:** 5.5 years from the date of approval

4. Sexual Dysfunction

While it is clear that desvenlafaxine has a qualitatively negative effect on sexual function from the adverse events collected during your earlier trials, we do not have quantified sexual dysfunction data. You have agreed to assess sexual dysfunction in your planned lower dose study. If the lower dose study establishes that 50 mg/day is the lowest effective dose, you have

agreed to conduct another acute, randomized controlled trial with placebo, 50, and 100 mg/day, and employ a validated and reliable outcome measure to assess for sexual dysfunction. This study could be conducted in parallel with the longer-term efficacy trial, and the results could be submitted approximately 5.5 years from the date of approval for this NDA.

**Final Report Submission:** 5.5 years from the date of approval

5. 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, you have agreed to conduct a standard embryo-fetal toxicity study in rats, and submit the results no later than 3 years after the date of the approval for this NDA.

**Final Report Submission:** 3 years from the date of approval

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "Postmarketing Study Commitment Protocol", "Postmarketing Study Commitment Final Report", or "Postmarketing Study Commitment Correspondence."

**DISSOLUTION METHOD AND SPECIFICATION**

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	<div style="border: 1px solid black; width: 100px; height: 100px;"></div>
4 hours	
8 hours	
12 hours	
24 hours	

**EXPIRY DATE**

An expiration of 24 months has been granted.

### **ADVISORY COMMITTEE**

NDA 21-992 was not referred to an advisory committee for review because there are several previously approved agents in the antidepressant class of drugs, evaluation of the safety data did not reveal particular safety issues that were unexpected for this class, and the design and results of the efficacy trials did not pose particular concerns.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) 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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see [www.fda.gov/cder/ddmac](http://www.fda.gov/cder/ddmac).

### **LETTERS TO HEALTH CARE PROFESSIONALS**

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

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

### **REPORTING REQUIREMENTS**

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

### **MEDWATCH-TO-MANUFACTURER PROGRAM**

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The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at [www.fda.gov/medwatch/report/mmp.htm](http://www.fda.gov/medwatch/report/mmp.htm).

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

Sincerely,

*{See appended electronic signature page}*

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

Enclosure: Label & Medguide

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Robert Temple  
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