CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 078789

Name: Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg (base), 75 mg (base) and 150 mg (base)

Sponsor: Mylan Pharmaceuticals, Inc.

Approval Date: June 1, 2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078789

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078789

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 078789

Mylan Pharmaceuticals, Inc.
Attention: S. Wayne Talton
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated Januray 15, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg (base), 75 mg (base), and 150 mg (base).

Reference is made to the tentative approval letter issued by this office on November 13, 2008, and to your amendments dated November 16, 2007; and March 18, April 2, April 7, April 29, May 5, and May 6, 2011.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg (base), 75 mg (base), and 150 mg (base), to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Effexor XR Capsules, 37.5 mg (base), 75 mg (base) and 150 mg (base), respectively, of Wyeth Pharmaceuticals, Inc. (Wyeth).

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA. The USP Test 2 method and FDA-recommended “interim” dissolution specifications are as follows:

Medium:	Water
Volume:	900 mL
USP Apparatus:	Type I (Basket)

Rotation (rpm): 100 rpm

The drug product should meet these "interim" specifications:

Time (Hours)	Percent Dissolved
2	(b) (4)
4	
8	
12	
24	

These "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data from the first three production size batches. These data should be submitted as a "Special Supplement – Changes Being Effected" if there are no revisions to be made to the "interim" specifications, or if the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The RLD upon which you have based your ANDA, Wyeth's Effexor XR Capsules, is subject to periods of patent protection. The following patents and their expiration dates are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

U.S. Patent Number	Expiration Date
5,916,923 (the '923 patent)	December 28, 2013*
6,274,171 (the '171 patent)	September 20, 2017*
6,310,101 (the '101 patent)	June 28, 2013
6,403,120 (the '120 patent)	September 20, 2017*
6,419,958 (the '958 patent)	September 20, 2017*
6,444,708 (the '708 patent)	December 28, 2013*

*with pediatric exclusivity added

With respect to the '923, '101, and '708 patents, as well as the '120 patent insofar as it pertains to U-451 (generalized anxiety disorder only), and the '958 patent insofar as it pertains to U-459 (generalized anxiety disorder only), your ANDA contains statements under section 505(j)(2)(A)(viii) of the Act that these are method of use patents that do not claim any indication for which you are seeking approval under your ANDA.

With respect to the '171, '120, and '958 patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each of these patents is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg (base), 75 mg (base), and 150 mg (base), under this ANDA. You notified the agency that Mylan complied with the requirements of section 505(j)(2)(B) of the Act, and litigation for infringement of the '171, '120, and '958 patents was brought against Mylan in the United States District Court for the Northern District of West Virginia [Wyeth Pharmaceuticals Inc. v. Mylan Pharmaceuticals Inc., Civil Action No. 07-CV-91]. You have notified the agency that on February 10, 2011, the court dismissed the litigation based on a License Agreement between Mylan and Wyeth.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and 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

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/U CM072392.pdf The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
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 L WEST

06/01/2011

Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078789

TENTATIVE APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-789

Mylan Pharmaceuticals Inc.
Attention: S. Wayne Talton
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated January 15, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg (base), 75 mg (base), and 150 mg (base).

Reference is also made to your amendments dated November 6, 2007; and February 15, May 21, June 2, June 23, July 8, August 1, August 19, and October 20, 2008.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the patent issues noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention. This letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The reference listed drug (RLD) upon which you have based your ANDA, Effexor XR Capsules, 37.5 mg, 75 mg, and 150 mg, of Wyeth Pharmaceuticals, Inc., is subject to multiple periods of patent protection and exclusivity. The following unexpired patents (with their expiration dates) are currently listed in the

agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

U.S. Patent Number	Expiration Date
5,916,923 (the '923 patent)	December 28, 2013*
6,274,171 (the '171 patent)	September 20, 2017*
6,310,101 (the '101 patent)	June 28, 2013
6,403,120 (the '120 patent)	September 20, 2017*
6,419,958 (the '958 patent)	September 20, 2017*
6,444,708 (the '708 patent)	December 28, 2013*

*pediatric exclusivity added

With respect to the '101, '923 and '708 patents, as well as the '120 patent insofar as it pertains to U-451 (generalized anxiety disorder), and the '958 patent insofar as it pertains to U-459 (generalized anxiety disorder), your ANDA contains statements under section 505(j)(2)(A)(viii) of the Act that these are method of use patents that do not claim any indication for which you are seeking approval under your ANDA.

With respect to the '171, '120, and '958 patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg (base), 75 mg (base), and 150 mg (base), under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action was brought against Mylan for infringement of one or more of these patents that were the subjects of the paragraph IV certifications. This action must have been brought against Mylan prior to the expiration of 45 days from the date the notice you provided under section 505 (j)(2)(B)(i) was received by the NDA/patent holder(s). You notified the agency that Mylan complied with the requirements of section 505(j)(2)(B) of the Act, and litigation for infringement of the '171, '120, and '958 patents was brought against Mylan in the United States District Court for the Northern District of West Virginia [Wyeth Pharmaceuticals Inc. v. Mylan Pharmaceuticals Inc., Civil Action No. 07-CV-91].

Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii)[1]

   b. the date the court decides[2] that the '171, '120, and '958 patents are invalid or not infringed (see sections 505(j)(5)(B)(iii)(I), (II), and (III) of the Act), or

   c. the '171, '120, and '958 patents have expired, and

2. The agency is assured there is no new information that would affect whether final approval should be granted.

With respect to the exclusivities listed for the RLD, Mylan is not seeking approval, at this time, for the indications covered by the I-538 and I-537 exclusivities (short-term and long-term treatment, respectively, of panic disorder), and is not seeking approval of its ANDA prior to the expiration on December 14, 2010, of the I-561 exclusivity (long-term treatment of social anxiety disorder).

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED.

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[1] Because information on the '171, '120, and '958 patents was submitted to FDA before August 18, 2003, this reference to section 505(j)(5)(B)(iii) is to that section of the Act as in effect prior to December 8, 2003, when the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) was enacted. See MMA § 1101(c)(3).

[2] This decision may be either a decision of the district court or the court of appeals, whichever court is the first to decide that the patent is invalid or not infringed.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book."

For further information on the status of this application, or prior to submitting additional amendments, please contact Thomas Hinchliffe, Project Manager, at 240-276-8536.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
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 L. West
11/13/2008 01:07:20 PM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078789

LABELING

VNLAER:R1mc

VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES

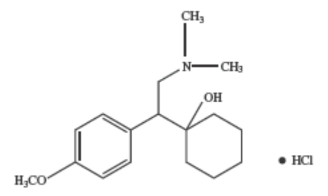
37.5 mg, 75 mg and 150 mg

℞ only

Suicidality and Antidepressant Drugs:

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of venlafaxine hydrochloride extended-release or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and 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. Venlafaxine hydrochloride extended-release is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

DESCRIPTION: Venlafaxine hydrochloride extended-release capsules for oral administration contain venlafaxine hydrochloride, a structurally novel antidepressant. It is designated as 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol hydrochloride or (±)-1-[α- [(dimethyl-amino)methyl]-*p*-methoxybenzyl] cyclohexanol hydrochloride and has the molecular formula of $C_{17}H_{27}NO_2$ HCl. Its molecular weight is 313.9. The structural formula is shown below.



Venlafaxine Hydrochloride

Venlafaxine hydrochloride, USP is a white crystalline powder. It is very soluble in water, freely soluble in ethanol and chloroform. It has a solubility of 572 mg/mL in water (adjusted to ionic strength of 0.2 M with sodium chloride). Its octanol: water (0.2 M sodium chloride) partition coefficient is 0.43.

Venlafaxine hydrochloride extended-release capsules are for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent. Capsules contain venlafaxine hydrochloride equivalent to 37.5 mg, 75 mg or 150 mg of venlafaxine. Inactive ingredients consist of ethylcellulose, hypromellose, polyethylene glycol, sugar spheres and talc. In addition, each of the empty gelatin capsules contain the following: gelatin, sodium lauryl sulfate, titanium dioxide and the following colorant agents:

37.5 mg – FD&C Blue No. 1 and FD&C Red No. 3
75 mg – D&C Red No. 28 and FD&C Blue No. 1
150 mg – D&C Red No. 28, D&C Yellow No. 10 and FD&C Red No. 40

The imprinting ink contains the following: black iron oxide, D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, propylene glycol and shellac glaze.

CLINICAL PHARMACOLOGY: Pharmacodynamics: The mechanism of the antidepressant action of venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic cholinergic, H_1-histaminergic, or α_1-adrenergic receptors *in vitro*. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

Pharmacokinetics: Steady-state concentrations of venlafaxine and ODV in plasma are attained within 3 days of oral multiple dose therapy. Venlafaxine and ODV exhibited linear kinetics over the dose range of 75 to 450 mg/day. Mean ± SD steady-state plasma clearance of venlafaxine and ODV is 1.3 ± 0.6 and 0.4 ± 0.2 L/h/kg, respectively; apparent elimination half-life is 5 ± 2 and 11 ± 2 hours, respectively; and apparent (steady-state) volume of distribution is 7.5 ± 3.7 and 5.7 ± 1.8 L/kg, respectively. Venlafaxine and ODV are minimally bound at therapeutic concentrations to plasma proteins (27% and 30%, respectively).

Absorption: Venlafaxine is well absorbed and extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the only major active metabolite. On the basis of mass balance studies, at least 92% of a single oral dose of venlafaxine is absorbed. The absolute bioavailability of venlafaxine is about 45%.

Administration of venlafaxine hydrochloride extended-release (150 mg q24 hours) generally resulted in lower C_{max} (150 ng/mL for venlafaxine and 260 ng/mL for ODV) and later T_{max} (5.5 hours for venlafaxine and 9 hours for ODV) than for immediate-release venlafaxine tablets (C_{max}'s for immediate-release 75 mg q12 hours were 225 ng/mL for venlafaxine and 290 ng/mL for ODV; T_{max}'s were 2 hours for venlafaxine and 3 hours for ODV). When equal daily doses of venlafaxine were administered as either an immediate-release tablet or the extended-release capsule, the exposure to both venlafaxine and ODV was similar for the two treatments, and the fluctuation in plasma concentrations was slightly lower with the venlafaxine hydrochloride extended-release capsule. Venlafaxine hydrochloride extended-release, therefore, provides a slower rate of absorption, but the same extent of absorption compared with the immediate-release tablet.

Food did not affect the bioavailability of venlafaxine or its active metabolite, ODV. Time of administration (AM vs PM) did not affect the pharmacokinetics of venlafaxine and ODV from the 75 mg venlafaxine hydrochloride extended-release capsule.

Metabolism and Excretion: Following absorption, venlafaxine undergoes extensive presystemic metabolism in the liver, primarily to ODV, but also to N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine, and other minor metabolites. *In vitro* studies indicate that the formation of ODV is catalyzed by CYP2D6; this has been confirmed in a clinical study showing that patients with low CYP2D6 levels ("poor metabolizers") had increased levels of venlafaxine and reduced levels of ODV compared to people with normal CYP2D6 ("extensive metabolizers"). The differences between the CYP2D6 poor and extensive metabolizers, however, are not expected to be clinically important because the sum of venlafaxine and ODV is similar in the two groups and venlafaxine and ODV are pharmacologically approximately equiactive and equipotent.

Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is thus the primary route of excretion.

Special Populations: *Age and Gender:* A population pharmacokinetic analysis of 404 venlafaxine-treated patients from two studies involving both b.i.d. and t.i.d. regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered by age or gender differences. Dosage adjustment based on the age or gender of a patient is generally not necessary (see DOSAGE AND ADMINISTRATION).

Extensive/Poor Metabolizers: Plasma concentrations of venlafaxine were higher in CYP2D6 poor metabolizers than extensive metabolizers. Because the total exposure (AUC) of venlafaxine and ODV was similar in poor and extensive metabolizer groups, however, there is no need for different venlafaxine dosing regimens for these two groups.

Liver Disease: In nine subjects with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV was significantly altered after oral administration of venlafaxine. Venlafaxine elimination half-life was prolonged by about 30%, and clearance decreased by about 50% in cirrhotic subjects compared to normal subjects. ODV elimination half-life was prolonged by about 60%, and clearance decreased by about 30% in cirrhotic subjects compared to normal subjects. A large degree of intersubject variability was noted. Three patients with more severe cirrhosis had a more substantial decrease in venlafaxine clearance (about 90%) compared to normal subjects.

In a second study, venlafaxine was administered orally and intravenously in normal (n = 21) subjects, and in Child-Pugh A (n = 8) and Child-Pugh B (n = 11) subjects (mildly and moderately impaired, respectively). Venlafaxine oral bioavailability was increased 2- to 3-fold, oral elimination half-life was approximately twice as long and oral clearance was reduced by more than half, compared to normal subjects. In hepatically impaired subjects, ODV oral elimination half-life was prolonged by about 40%, while oral clearance for ODV was similar to that for normal subjects. A large degree of intersubject variability was noted.

Dosage adjustment is necessary in these hepatically impaired patients (see DOSAGE AND ADMINISTRATION).

Renal Disease: In a renal impairment study, venlafaxine elimination half-life after oral administration was prolonged by about 50% and clearance was reduced by about 24% in renally impaired patients (GFR = 10 to 70 mL/min), compared to normal subjects. In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance was reduced by about 57% compared to normal subjects. Similarly, ODV elimination half-life was prolonged by about 40% although clearance was unchanged in patients with renal impairment (GFR = 10 to 70 mL/min) compared to normal subjects. In dialysis patients, ODV elimination half-life was prolonged by about 142% and clearance was reduced by about 56% compared to normal subjects. A large degree of intersubject variability was noted. Dosage adjustment is necessary in these patients (see DOSAGE AND ADMINISTRATION).

Clinical Trials: *Major Depressive Disorder:* The efficacy of venlafaxine hydrochloride extended-release capsules as a treatment for major depressive disorder was established in two placebo-controlled, short-term, flexible-dose studies in adult outpatients meeting DSM-III-R or DSM-IV criteria for major depressive disorder.

A 12-week study utilizing venlafaxine hydrochloride extended-release doses in a range 75 to 150 mg/day (mean dose for completers was 136 mg/day) and an 8-week study utilizing venlafaxine hydrochloride extended-release doses in a range 75 to 225 mg/day (mean dose for completers was 177 mg/day) both demonstrated superiority of venlafaxine hydrochloride extended-release over placebo on the HAM-D total score, HAM-D Depressed Mood Item, the MADRS total score, the Clinical Global Impressions (CGI) Severity of Illness item, and the CGI Global Improvement item. In both studies, venlafaxine hydrochloride extended-release was also significantly better than placebo for certain factors of the HAM-D, including the anxiety/somatization factor, the cognitive disturbance factor, and the retardation factor, as well as for the psychic anxiety score.

A 4-week study of inpatients meeting DSM-III-R criteria for major depressive disorder with melancholia utilizing venlafaxine hydrochloride tablets (the immediate-release form of venlafaxine) in a range of 150 to 375 mg/day (t.i.d. schedule) demonstrated superiority of venlafaxine hydrochloride tablets over placebo. The mean dose in completers was 350 mg/day.

Examination of gender subsets of the population studied did not reveal any differential responsiveness on the basis of gender.

In one longer-term study, adult outpatients meeting DSM-IV criteria for major depressive disorder who had responded during an 8-week open trial on venlafaxine hydrochloride extended-release capsules (75 mg, 150 mg, or 225 mg, qAM) were randomized to continuation of their same venlafaxine hydrochloride extended-release dose or to placebo, for up to 26 weeks of observation for relapse. Response during the open phase was defined as a CGI Severity of Illness item score of ≤ 3 and a HAM-D-21 total score of ≤ 10 at the day 56 evaluation. Relapse during the double-blind phase was defined as follows: (1) a reappearance of major depressive disorder as defined by DSM-IV criteria and a CGI Severity of Illness item score of ≥ 4 (moderately ill), (2) two consecutive CGI Severity of Illness item scores of ≥ 4, or (3) a final CGI Severity of Illness item score of ≥ 4 for any patient who withdrew from the study for any reason. Patients receiving continued venlafaxine hydrochloride extended-release treatment experienced significantly lower relapse rates over the subsequent 26 weeks compared with those receiving placebo.

In a second longer-term trial, adult outpatients meeting DSM-III-R criteria for major depressive disorder, recurrent type, who had responded (HAM-D-21 total score ≤ 12 at the day 56 evaluation) and continued to be improved [defined as the following criteria being met for days 56 through 180: (1) no HAM-D-21 total score ≥ 20; (2) no more than 2 HAM-D-21 total scores > 10, and (3) no single CGI Severity of Illness item score ≥ 4 (moderately ill)] during an initial 26 weeks of treatment on venlafaxine hydrochloride tablets (100 to 200 mg/day, on a b.i.d. schedule) were randomized to continuation of their same venlafaxine hydrochloride tablet dose or to placebo. The follow-up period to observe patients for relapse, defined as a CGI Severity of Illness item score ≥ 4, was for up to 52 weeks. Patients receiving continued venlafaxine hydrochloride tablets treatment experienced significantly lower relapse rates over the subsequent 52 weeks compared with those receiving placebo.

Social Anxiety Disorder (Social Phobia): The efficacy of venlafaxine hydrochloride extended-release capsules as a treatment for Social Anxiety Disorder (also known as Social Phobia) was established in four double-blind, parallel group, 12-week, multicenter, placebo-controlled, flexible-dose studies and one double-blind, parallel group, 6-month, placebo-controlled, fixed/flexible-dose study in adult outpatients meeting DSM-IV criteria for Social Anxiety Disorder. Patients received doses in a range of 75 to 225 mg/day. Efficacy was assessed with the Liebowitz Social Anxiety Scale (LSAS). In these five trials, venlafaxine hydrochloride extended-release was significantly more effective than placebo on change from baseline to endpoint on the LSAS total score. There was no evidence for any greater effectiveness of the 150 to 225 mg/day group compared to the 75 mg/day group in the 6-month study.

Examination of subsets of the population studied did not reveal any differential responsiveness on the basis of gender. There was insufficient information to determine the effect of age or race on outcome in these studies.

INDICATIONS AND USAGE: Major Depressive Disorder: Venlafaxine hydrochloride extended-release capsules are indicated for the treatment of major depressive disorder.

The efficacy of venlafaxine hydrochloride extended-release capsules in the treatment of major depressive disorder was established in 8- and 12-week controlled trials of adult outpatients whose diagnoses corresponded most closely to the DSM-III-R or DSM-IV category of major depressive disorder (see CLINICAL PHAMACOLOGY: Clinical Trials).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed mood or the loss of interest or pleasure in nearly all activities, representing a change from previous functioning, and includes the presence of at least five of the following nine symptoms during the same 2-week period: depressed mood, markedly diminished interest or pleasure 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, a suicide attempt or suicidal ideation.

The efficacy of venlafaxine hydrochloride tablets (the immediate-release form of venlafaxine) in the treatment of major depressive disorder in adult inpatients meeting diagnostic criteria for major depressive disorder with melancholia was established in a 4-week controlled trial (see CLINICAL PHAMACOLOGY: Clinical Trials). The safety and efficacy of venlafaxine hydrochloride extended-release capsules in hospitalized depressed patients have not been adequately studied.

The efficacy of venlafaxine hydrochloride extended-release capsules in maintaining a response in major depressive disorder for up to 26 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial. The efficacy of venlafaxine hydrochloride tablets in maintaining a response in patients with recurrent major depressive disorder who had responded and continued to be improved during an initial 26 weeks of treatment and were then followed for a period of up to 52 weeks was demonstrated in a second placebo-controlled trial (see CLINICAL PHAMACOLOGY: Clinical Trials). Nevertheless, the physician who elects to use venlafaxine hydrochloride tablets/venlafaxine hydrochloride extended-release capsules for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Social Anxiety Disorder: Venlafaxine hydrochloride extended-release capsules are indicated for the treatment of Social Anxiety Disorder, also known as Social Phobia, as defined in DSM-IV (300.23).

Social Anxiety Disorder (DSM-IV) is characterized by a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is a marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

The efficacy of venlafaxine hydrochloride extended-release capsules in the treatment of Social Anxiety Disorder was established in four 12-week and one 6-month placebo-controlled trials in adult outpatients with Social Anxiety Disorder (DSM-IV) (see CLINICAL PHAMACOLOGY: Clinical Trials).

Although the effectiveness of venlafaxine hydrochloride extended-release capsules has been demonstrated in a 6-month clinical trial in patients with Social Anxiety Disorder, the physician who elects to use venlafaxine hydrochloride extended-release capsules for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS: Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation.

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

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. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of nine antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated
	Increases Compared to Placebo
< 18	14 additional cases
18 to 24	5 additional cases
	Decreases Compared to Placebo
25 to 64	1 fewer case
≥ 65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and 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.

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: Discontinuation of Treatment with Venlafaxine Hydrochloride Extended-Release, for a description of the risks of discontinuation of venlafaxine hydrochloride extended-release).

Families and caregivers of 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 venlafaxine hydrochloride extended-release should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

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 venlafaxine hydrochloride extended-release is not approved for use in treating bipolar depression.

Potential for Interaction with Monoamine Oxidase Inhibitors: Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on venlafaxine, or who have recently had venlafaxine therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. In patients receiving antidepressants with pharmacological properties similar to venlafaxine in combination with an MAOI, there have also been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor, these reactions have included 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. Some cases presented with features resembling neuroleptic malignant syndrome. Severe hyperthermia and seizures, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI. The effects of combined use of venlafaxine and MAOIs have not been evaluated in humans or animals. Therefore, because venlafaxine is an inhibitor of both norepinephrine and serotonin reuptake, it is recommended that venlafaxine hydrochloride extended-release capsules 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 venlafaxine, at least 7 days should be allowed after stopping venlafaxine before starting an MAOI.

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions: The development of a potentially life threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including venlafaxine hydrochloride extended-release-treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. 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) (see PRECAUTIONS: Drug Interactions). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of venlafaxine hydrochloride extended-release with MAOIs intended to treat depression is contraindicated (see CONTRAINDICATIONS and WARNINGS: Potential for Interaction with Monoamine Oxidase Inhibitors).

If concomitant treatment of venlafaxine hydrochloride extended-release 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 venlafaxine hydrochloride extended-release with serotonin precursors (such as tryptophan) is not recommended (see PRECAUTIONS: Drug Interactions).

Treatment with venlafaxine hydrochloride extended-release and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Sustained Hypertension: Venlafaxine hydrochloride extended-release treatment is associated with sustained hypertension (defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥ 90 mm Hg and ≥ 10 mm Hg above baseline for three consecutive on-therapy visits (see Table 2)).

An analysis for patients in venlafaxine hydrochloride (immediate-release) studies meeting criteria for sustained hypertension revealed a dose dependent increase in the incidence of sustained hypertension for venlafaxine hydrochloride (immediate-release) (see Table 3).

An insufficient number of patients received mean doses of venlafaxine hydrochloride extended-release over 300 mg/day to fully evaluate the incidence of sustained increases in blood pressure at these higher doses.

Table 2: Number (%) of Sustained Elevations in SDBP in Venlafaxine Hydrochloride Extended-Release Premarketing Studies by Indication

MDD (75 to 375 mg/day)	Social Anxiety Disorder (75 to 225 mg/day)
19/705 (3)	5/771 (0.6)

MDD = major depressive disorder

Table 3: Incidence (%) of Sustained Elevations in SDBP in Venlafaxine Hydrochloride Immediate-Release Studies

Venlafaxine Hydrochloride mg/day	Incidence
< 100	3%
> 100 to ≤ 200	5%
> 200 to ≤ 300	7%
> 300	13%

In premarketing major depressive disorder studies, 0.7% (5/705) of the venlafaxine hydrochloride extended-release-treated patients discontinued treatment because of elevated blood pressure. Among these patients, most of the blood pressure increases were in a modest range (12 to 16 mm Hg, SDBP). In premarketing Social Anxiety Disorder studies up to 6 months, 0.6% (5/771) of the venlafaxine hydrochloride extended-release-treated patients discontinued treatment because of elevated blood pressure. In these patients, the blood pressure increases were modest (1 to 24 mm Hg, SDBP).

Sustained increases of SDBP could have adverse consequences. Cases of elevated blood pressure requiring immediate treatment have been reported in post-marketing experience. Preexisting hypertension should be controlled before treatment with venlafaxine. It is recommended that patients receiving venlafaxine hydrochloride extended-release have regular monitoring of blood pressure. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered.

Elevations in Systolic and Diastolic Blood Pressure: In placebo-controlled premarketing studies, there were changes in mean blood pressure (see Table 4 for mean changes in supine systolic and supine diastolic blood pressure). Across most indications, a dose related increase in supine systolic and diastolic blood pressure was evident in venlafaxine hydrochloride extended-release-treated patients.

Table 4: Final On-Therapy Mean Changes from Baseline in Supine Systolic and Diastolic Blood Pressure (mm Hg) Results by Indication, Study Duration, and Dose in Placebo-Controlled Trials

	Venlafaxine Hydrochloride Extended-release mg/day				Placebo	
	≤ 75		> 75			
	SSBP[1]	SDBP[2]	SSBP	SDBP	SSBP	SDBP
Major Depressive Disorder						
8 to 12 weeks	-0.28	0.37	2.93	3.56	-1.08	-0.10
Social Anxiety Disorder						
12 weeks	-0.29	-1.26	1.18	1.34	-1.96	-1.22
6 months	-0.98	-0.49	2.51	1.96	-1.84	-0.65

[1] Supine Systolic Blood Pressure
[2] Supine Diastolic Blood Pressure

Across all clinical trials in MDD and Social Anxiety Disorder, 1.4% of patients in the venlafaxine hydrochloride extended-release-treated groups experienced a ≥ 15 mm Hg increase in supine diastolic blood pressure with blood pressure ≥ 105 mm Hg compared to 0.9% of patients in the placebo groups. Similarly, 1% of patients in the venlafaxine hydrochloride extended-release-treated groups experienced a ≥ 20 mm Hg increase in supine systolic blood pressure with blood pressure ≥ 180 mm Hg compared to 0.3% of patients in the placebo groups.

Mydriasis: Mydriasis has been reported in association with venlafaxine; therefore patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored (see PRECAUTIONS: Information for Patients).

PRECAUTIONS: General: *Discontinuation of Treatment with Venlafaxine Hydrochloride Extended-Release:* Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, to include retrospective surveys of trials in major depressive disorder and Social Anxiety Disorder. Abrupt discontinuation or dose reduction of venlafaxine at various doses has been found to be associated with the appearance of new symptoms, the frequency of which increased with increased dose level and with longer duration of treatment. Reported symptoms include agitation, anorexia, anxiety, confusion, impaired coordination and balance, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, flu-like symptoms, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tremor, vertigo, and vomiting.

During marketing of venlafaxine hydrochloride extended-release, other SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), and SSRIs (Selective Serotonin 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. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with venlafaxine hydrochloride extended-release. 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).

Insomnia and Nervousness: Treatment-emergent insomnia and nervousness were more commonly reported for patients treated with venlafaxine hydrochloride extended-release capsules than with placebo in pooled analyses of short-term major depressive disorder and Social Anxiety Disorder studies, as shown in Table 5.

Table 5: Incidence of Insomnia and Nervousness in Placebo-Controlled Major Depressive Disorder and Social Anxiety Disorder Trials

	Major Depressive Disorder		Social Anxiety Disorder	
Symptom	Venlafaxine HCl ER n = 357	Placebo n = 285	Venlafaxine HCl ER n = 819	Placebo n = 695
Insomnia	17%	11%	24%	8%
Nervousness	10%	5%	10%	5%

Insomnia and nervousness each led to drug discontinuation in 0.9% of the patients treated with venlafaxine hydrochloride extended-release in major depressive disorder studies.

In Social Anxiety Disorder trials, insomnia and nervousness led to drug discontinuation in 2% and 1%, respectively, of the patients treated with venlafaxine hydrochloride extended-release up to 12 weeks and 2% and 3%, respectively, of the patients treated with venlafaxine hydrochloride extended-release up to 6 months.

Changes in Weight: *Adult Patients:* A loss of 5% or more of body weight occurred in 7% of venlafaxine hydrochloride extended-release-treated and 2% of placebo-treated patients in the short-term placebo-controlled major depressive disorder trials. The discontinuation rate for weight loss associated with venlafaxine hydrochloride extended-release was 0.1% in major depressive disorder studies. In placebo-controlled Social Anxiety Disorder trials, 4% of the venlafaxine hydrochloride extended-release-treated and 1% of the placebo-treated patients sustained a loss of 7% or more of body weight during up to 6 months of treatment. None of the patients receiving venlafaxine hydrochloride extended-release in Social Anxiety Disorder studies discontinued for weight loss.

The safety and efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, have not been established. Coadministration of venlafaxine hydrochloride extended-release and weight loss agents is not recommended. Venlafaxine hydrochloride extended-release is not indicated for weight loss alone or in combination with other products.

Pediatric Patients: Weight loss has been observed in pediatric patients (ages 6 to 17) receiving venlafaxine hydrochloride extended-release. In a pooled analysis of four 8-week, double-blind, placebo-controlled, flexible dose outpatient trials for major depressive disorder (MDD), venlafaxine hydrochloride extended-release-treated patients lost an average of 0.45 kg (n = 333), while placebo-treated patients gained an average of 0.77 kg (n = 333). More patients treated with venlafaxine hydrochloride extended-release than with placebo experienced a weight loss of at least 3.5% in the MDD study (18% of venlafaxine hydrochloride extended-release-treated patients vs. 3.6% of placebo-treated patients; p < 0.001). In a 16-week, double-blind, placebo-controlled, flexible dose outpatient trial for Social Anxiety Disorder, venlafaxine hydrochloride extended-release-treated patients lost an average of 0.75 kg (n = 137), while placebo-treated patients gained a average of 0.76 kg (n = 148). More patients treated with venlafaxine hydrochloride extended-release than with placebo experienced a weight loss of at least 3.5% in the Social Anxiety Disorder study (47% of venlafaxine hydrochloride extended-release-treated patients vs. 14% of placebo-treated patients; p < 0.001). Weight loss was not limited to patients with treatment-emergent anorexia (see PRECAUTIONS: General: *Changes in Appetite*).

The risks associated with longer-term venlafaxine hydrochloride extended-release use were assessed in an open-label MDD study of children and adolescents who received venlafaxine hydrochloride extended-release for up to 6 months. The children and adolescents in the study had increases in weight that were less than expected based on data from age- and sex-matched peers. The difference between observed weight gain and expected weight gain was larger for children (< 12 years old) than for adolescents (> 12 years old).

Changes in Height: *Pediatric Patients:* During the 8-week placebo-controlled MDD studies, venlafaxine hydrochloride extended-release-treated patients grew an average of 0.8 cm (n =146), while placebo-treated patients grew an average of 0.7 cm (n = 147). During the 16-week, placebo-controlled Social Anxiety Disorder study, both the venlafaxine hydrochloride extended-release-treated (n = 109) and the placebo-treated (n = 112) patients each grew an average of 1 cm. In the 6-month open-label MDD study, children and adolescents had height increases that were less than expected based on data from age- and sex-matched peers. The difference between observed growth rates and expected growth rates was larger for children (< 12 years old) than for adolescents (> 12 years old).

Changes in Appetite: *Adult Patients:* Treatment-emergent anorexia was more commonly reported for venlafaxine hydrochloride extended-release-treated (8%) than placebo-treated patients (4%) in the pool of short-term, double-blind, placebo-controlled major depressive disorder studies. The discontinuation rate for anorexia associated with venlafaxine hydrochloride extended-release was 1% in major depressive disorder studies. Treatment-emergent anorexia was more commonly reported for venlafaxine hydrochloride extended-release-treated (17%) than placebo-treated patients (2%) in the pool of short-term, double-blind, placebo-controlled Social Anxiety Disorder studies. The discontinuation rate for anorexia was 0.6% for patients receiving venlafaxine hydrochloride extended-release for up to 12 weeks in Social Anxiety Disorder studies; no patients discontinued for anorexia between week 12 and month 6.

Pediatric Patients: Decreased appetite has been observed in pediatric patients receiving venlafaxine hydrochloride extended-release. In the placebo-controlled trials for MDD, 10% of patients aged 6 to 17 treated with venlafaxine hydrochloride extended-release for up to 8 weeks and 3% of patients treated with placebo reported treatment-emergent anorexia (decreased appetite). None of the patients receiving venlafaxine hydrochloride extended-release discontinued for anorexia or weight loss. In the placebo-controlled trial for Social Anxiety Disorder, 22% and 3% of patients aged 8 to 17 treated for up to 16 weeks with venlafaxine hydrochloride extended-release and placebo, respectively, reported treatment-emergent anorexia (decreased appetite). The discontinuation rates for anorexia were 0.7% and 0.0% for patients receiving venlafaxine hydrochloride extended-release and placebo, respectively; the discontinuation rates for weight loss were 0.7% for patients receiving either venlafaxine hydrochloride extended-release or placebo.

Activation of Mania/Hypomania: During premarketing major depressive disorder studies, mania or hypomania occurred in 0.3% of venlafaxine hydrochloride extended-release-treated patients and no placebo patients. In premarketing Social Anxiety Disorder studies, 0.2% venlafaxine hydrochloride extended-release-treated patients and no placebo-treated patients experienced mania or hypomania. In all premarketing major depressive disorder trials with venlafaxine hydrochloride tablets, mania or hypomania occurred in 0.5% of venlafaxine-treated patients compared with no placebo patients. Mania/hypomania has also been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs to treat major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, venlafaxine hydrochloride extended-release should be used cautiously in patients with a history of mania.

Hyponatremia: Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including venlafaxine hydrochloride extended-release. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk (see PRECAUTIONS: Geriatric Use). Discontinuation of venlafaxine hydrochloride extended-release should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

Seizures: During premarketing experience, no seizures occurred among 705 venlafaxine hydrochloride extended-release-treated patients in the major depressive disorder studies, or among 819 venlafaxine hydrochloride extended-release-treated patients in Social Anxiety Disorder studies. In all premarketing major depressive disorder trials with venlafaxine hydrochloride tablets, seizures were reported at various doses in 0.3% (8/3082) of venlafaxine-treated patients. Venlafaxine hydrochloride extended-release, like many antidepressants, should be used cautiously in patients with a history of seizures and should be discontinued in any patient who develops seizures.

Abnormal Bleeding: SSRIs and SNRIs, including venlafaxine hydrochloride extended-release, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of venlafaxine hydrochloride extended-release and NSAIDs, aspirin, or other drugs that affect coagulation.

Serum Cholesterol Elevation: Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0% of placebo-treated patients treated for at least 3 months in placebo-controlled trials (see ADVERSE REACTIONS: Laboratory Changes). Measurement of serum cholesterol levels should be considered during long-term treatment.

Interstitial Lung Disease and Eosinophilic Pneumonia: Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine therapy have been rarely reported. The possibility of these adverse events should be considered in venlafaxine-treated patients who present with progressive dyspnea, cough or chest discomfort. Such patients should undergo a prompt medical evaluation, and discontinuation of venlafaxine therapy should be considered.

Use in Patients With Concomitant Illness: Premarketing experience with venlafaxine in patients with concomitant systemic illness is limited. Caution is advised in administering venlafaxine hydrochloride extended-release to patients with diseases or conditions that could affect hemodynamic responses or metabolism.

Venlafaxine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during venlafaxine's premarketing testing. The electrocardiograms were analyzed for 275 patients who received venlafaxine hydrochloride extended-release and 220 patients who received placebo in 8- to 12-week double-blind, placebo-controlled trials in major depressive disorder and for 593 patients who received venlafaxine hydrochloride extended-release and 534 patients who received placebo in 12-week double-blind, placebo-controlled trials in Social Anxiety Disorder. The mean change from baseline in corrected QT interval (QTc) for venlafaxine hydrochloride extended-release-treated patients in major depressive disorder studies was increased relative to that for placebo-treated patients (increase of 4.7 msec for venlafaxine hydrochloride extended-release and decrease of 1.9 msec for placebo). The mean change from baseline in QTc interval for venlafaxine hydrochloride extended-release-treated patients in the Social Anxiety Disorder studies was increased relative to that for placebo-treated patients (increase of 3.4 msec for venlafaxine hydrochloride extended-release and decrease of 1.6 msec for placebo).

In these same trials, the mean change from baseline in heart rate for venlafaxine hydrochloride extended-release-treated patients in the major depressive disorder studies was significantly higher than that for placebo (a mean increase of 4 beats per minute for venlafaxine hydrochloride extended-release and 1 beat per minute for placebo). The mean change from baseline in heart rate for venlafaxine hydrochloride extended-release-treated patients in the Social Anxiety Disorder studies was significantly higher than that for placebo (a mean increase of 5 beats per minute for venlafaxine hydrochloride extended-release and no change for placebo).

In a flexible-dose study, with venlafaxine hydrochloride tablets doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, venlafaxine hydrochloride tablets-treated patients had a mean increase in heart rate of 8.5 beats per minute compared with 1.7 beats per minute in the placebo group.

As increases in heart rate were observed, caution should be exercised in patients whose underlying medical conditions might be compromised by increases in heart rate (e.g., patients with hyperthyroidism, heart failure, or recent myocardial infarction).

Evaluation of the electrocardiograms for 769 patients who received immediate-release venlafaxine hydrochloride tablets in 4- to 6-week double-blind, placebo-controlled trials showed that the incidence of trial-emergent conduction abnormalities did not differ from that with placebo.

In patients with renal impairment (GFR = 10 to 70 mL/min) or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, thus prolonging the elimination half-lives of these substances. A lower dose may be necessary (see DOSAGE AND ADMINISTRATION). Venlafaxine hydrochloride extended-release, like all drugs effective in the treatment of major depressive disorder, should be used with caution in such patients.

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 venlafaxine hydrochloride extended-release and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and Other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for venlafaxine hydrochloride extended-release. 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 venlafaxine hydrochloride extended-release.

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 look 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.

Interference with Cognitive and Motor Performance: Clinical studies were performed to examine the effects of venlafaxine on behavioral performance of healthy individuals. The results revealed no clinically significant impairment of psychomotor, cognitive, or complex behavior performance. However, since any psychoactive drug may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that venlafaxine therapy does not adversely affect their ability to engage in such activities.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, including herbal preparations and nutritional supplements, since there is a potential for interactions.

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of venlafaxine hydrochloride extended-release and triptans, tramadol, tryptophan, supplements or other serotonergic agents (see WARNINGS: Serotonin Syndrome and PRECAUTIONS: Drug Interactions: *CNS Active Drugs*).

Patients should be cautioned about the concomitant use of venlafaxine hydrochloride extended-release and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding (see PRECAUTIONS: General: *Abnormal Bleeding*).

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

Allergic Reactions: Patients should be advised to notify their physician if they develop a rash, hives, or a related allergic phenomenon.

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

Nursing: Patients should be advised to notify their physician if they are breast-feeding an infant.

Mydriasis: Mydriasis (prolonged dilation of the pupils of the eye) has been reported with venlafaxine. Patients should be advised to notify their physician if they have a history of glaucoma or a history of increased intraocular pressure (see WARNINGS).

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions: As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

Alcohol: A single dose of ethanol (0.5 g/kg) had no effect on the pharmacokinetics of venlafaxine or O-desmethylvenlafaxine (ODV) when venlafaxine was administered at 150 mg/day in 15 healthy male subjects. Additionally, administration of venlafaxine in a stable regimen did not exaggerate the psychomotor and psychometric effects induced by ethanol in these same subjects when they were not receiving venlafaxine.

Cimetidine: Concomitant administration of cimetidine and venlafaxine in a steady-state study for both drugs resulted in inhibition of first-pass metabolism of venlafaxine in 18 healthy subjects. The oral clearance of venlafaxine was reduced by about 43%, and the exposure (AUC) and maximum concentration (C_{max}) of the drug were increased by about 60%. However, coadministration of cimetidine had no apparent effect on the pharmacokinetics of ODV, which is present in much greater quantity in the circulation than venlafaxine. The overall pharmacological activity of venlafaxine plus ODV is expected to increase only slightly, and no dosage adjustment should be necessary for most normal adults. However, for patients with preexisting hypertension, and for elderly patients or patients with hepatic dysfunction, the interaction associated with the concomitant use of venlafaxine and cimetidine is not known and potentially could be more pronounced. Therefore, caution is advised with such patients.

Diazepam: Under steady-state conditions for venlafaxine administered at 150 mg/day, a single 10 mg dose of diazepam did not appear to affect the pharmacokinetics of either venlafaxine or ODV in 18 healthy male subjects. Venlafaxine also did not have any effect on the pharmacokinetics of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam.

Haloperidol: Venlafaxine administered under steady-state conditions at 150 mg/day in 24 healthy subjects decreased total oral-dose clearance (Cl/F) of a single 2 mg dose of haloperidol by 42%, which resulted in a 70% increase in haloperidol AUC. In addition, the haloperidol C_{max} increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life ($t_{1/2}$) was unchanged. The mechanism explaining this finding is unknown.

Lithium: The steady-state pharmacokinetics of venlafaxine administered at 150 mg/day were not affected when a single 600 mg oral dose of lithium was administered to 12 healthy male subjects. ODV also was unaffected. Venlafaxine had no effect on the pharmacokinetics of lithium (see also *CNS Active Drugs*, below).

Drugs Highly Bound to Plasma Proteins: Venlafaxine is not highly bound to plasma proteins; therefore, administration of venlafaxine hydrochloride extended-release to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin): Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when venlafaxine hydrochloride extended-release is initiated or discontinued.

Drugs that Inhibit Cytochrome P450 Isoenzymes: *CYP2D6 Inhibitors: In vitro* and *in vivo* studies indicate that venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6, the isoenzyme that is responsible for the genetic polymorphism seen in the metabolism of many antidepressants. Therefore, the potential exists for a drug interaction between drugs that inhibit CYP2D6-mediated metabolism of venlafaxine, reducing the metabolism of venlafaxine to ODV, resulting in increased plasma concentrations of venlafaxine and decreased concentrations of the active metabolite. CYP2D6 inhibitors such as quinidine would be expected to do this, but the effect would be similar to what is seen in patients who are genetically CYP2D6 poor metabolizers (see CLINICAL PHARMACOLOGY: Metabolism and Excretion). Therefore, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.

Ketoconazole: A pharmacokinetic study with ketoconazole 100 mg b.i.d with a single dose of venlafaxine 50 mg in extensive metabolizers (EM; n = 14) and 25 mg in poor metabolizers (PM; n = 6) of CYP2D6 resulted in higher plasma concentrations of both venlafaxine and O-desmethylvenlafaxine (ODV) in most subjects following administration of ketoconazole. Venlafaxine C_{max} increased by 26% in EM subjects and 48% in PM subjects. C_{max} values for ODV increased by 14% and 29% in EM and PM subjects, respectively.

Venlafaxine AUC increased by 21% in EM subjects and 70% in PM subjects (range in PMs - 2% to 206%), and AUC values for ODV increased by 23% and 33% in EM and PM subjects (range in PMs - 38% to 105%), respectively. Combined AUCs of venlafaxine and ODV increased on average by approximately 23% in EMs and 53% in PMs (range in PMs - 4% to 134%).

Concomitant use of CYP3A4 inhibitors and venlafaxine may increase levels of venlafaxine and ODV. Therefore, caution is advised if a patient's therapy includes a CYP3A4 inhibitor and venlafaxine concomitantly.

Drugs Metabolized by Cytochrome P450 Isoenzymes: *CYP2D6: In vitro* studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. These findings have been confirmed in a clinical drug interaction study comparing the effect of venlafaxine with that of fluoxetine on the CYP2D6-mediated metabolism of dextromethorphan to dextrorphan.

Imipramine: Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max}, and C_{min} increased by about 35% in the presence of venlafaxine. The 2-OH-desipramine AUC's increased by at least 2.5-fold (with venlafaxine 37.5 mg q12h) and by 4.5-fold (with venlafaxine 75 mg q12h). Imipramine did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of elevated 2-OH-desipramine levels is unknown.

Metoprolol: Concomitant administration of venlafaxine (50 mg every 8 hours for 5 days) and metoprolol (100 mg every 24 hours for 5 days) to 18 healthy male subjects in a pharmacokinetic interaction study for both drugs resulted in an increase of plasma concentrations of metoprolol by approximately 30% to 40% without altering the plasma concentrations of its active metabolite, α-hydroxymetoprolol. Metoprolol did not alter the pharmacokinetic profile of venlafaxine or its active metabolite, O-desmethylvenlafaxine.

Venlafaxine appeared to reduce the blood pressure lowering effect of metoprolol in this study. The clinical relevance of this finding for hypertensive patients is unknown. Caution should be exercised with coadministration of venlafaxine and metoprolol.

Venlafaxine treatment has been associated with dose related increases in blood pressure in some patients. It is recommended that patients receiving venlafaxine hydrochloride extended-release have regular monitoring of blood pressure (see WARNINGS).

Risperidone: Venlafaxine administered under steady-state conditions at 150 mg/day slightly inhibited the CYP2D6-mediated metabolism of risperidone (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32% increase in risperidone AUC. However, venlafaxine coadministration did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone).

CYP3A4: Venlafaxine did not inhibit CYP3A4 *in vitro*. This finding was confirmed *in vivo* by clinical drug interaction studies in which venlafaxine did not inhibit the metabolism of several CYP3A4 substrates, including alprazolam, diazepam, and terfenadine.

Indinavir: In a study of nine healthy volunteers, venlafaxine administered under steady-state conditions at 150 mg/day resulted in a 28% decrease in the AUC of a single 800 mg oral dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of this finding is unknown.

CYP1A2: Venlafaxine did not inhibit CYP1A2 *in vitro*. This finding was confirmed *in vivo* by a clinical drug interaction study in which venlafaxine did not inhibit the metabolism of caffeine, a CYP1A2 substrate.

CYP2C9: Venlafaxine did not inhibit CYP2C9 *in vitro*. *In vivo*, venlafaxine 75 mg by mouth every 12 hours did not alter the pharmacokinetics of a single 500 mg dose of tolbutamide or the CYP2C9 mediated formation of 4-hydroxy-tolbutamide.

CYP2C19: Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see *Diazepam* above).

Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS and WARNINGS.

CNS Active Drugs: The risk of using venlafaxine in combination with other CNS active drugs has not been systematically evaluated (except in the case of those CNS active drugs noted above). Consequently, caution is advised if the concomitant administration of venlafaxine and such drugs is required.

Serotonergic Drugs: Based on the mechanism of action of venlafaxine hydrochloride extended-release and the potential for serotonin syndrome, caution is advised when venlafaxine hydrochloride extended-release is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, SSRIs, other SNRIs, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see WARNINGS: Serotonin Syndrome). If concomitant treatment of venlafaxine hydrochloride extended-release with these drugs is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS: Serotonin Syndrome). The concomitant use of venlafaxine hydrochloride extended-release with tryptophan supplements is not recommended (see WARNINGS: Serotonin Syndrome).

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

Electroconvulsive Therapy: There are no clinical data establishing the benefit of electroconvulsive therapy combined with venlafaxine hydrochloride extended-release capsules treatment.

Post-Marketing Spontaneous Drug Interaction Reports: See ADVERSE REACTIONS: Post-Marketing Reports.

Carcinogenesis, Mutagenesis, Impairment of Fertility: *Carcinogenesis:* Venlafaxine was given by oral

gavage to mice for 18 months at doses up to 120 mg/kg per day, which was 1.7 times the maximum recommended human dose on a mg/m^2 basis. Venlafaxine was also given to rats by oral gavage for 24 months at doses up to 120 mg/kg per day. In rats receiving the 120 mg/kg dose, plasma concentrations of venlafaxine at necropsy were 1 times (male rats) and 6 times (female rats) the plasma concentrations of patients receiving the maximum recommended human dose. Plasma levels of the O-desmethyl metabolite were lower in rats than in patients receiving the maximum recommended dose. Tumors were not increased by venlafaxine treatment in mice or rats.

Mutagenesis: Venlafaxine and the major human metabolite, O-desmethylvenlafaxine (ODV), were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the Chinese hamster ovary/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was also not mutagenic or clastogenic in the *in vitro* BALB/c-3T3 mouse cell transformation assay, the sister chromatid exchange assay in cultured Chinese hamster ovary cells, or in the *in vivo* chromosomal aberration assay in rat bone marrow. ODV was not clastogenic in the *in vitro* Chinese hamster ovary cell chromosomal aberration assay, but elicited a clastogenic response in the *in vivo* chromosomal aberration assay in rat bone marrow.

Impairment of Fertility: Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 2 times the maximum recommended human dose on a mg/m^2 basis.

Pregnancy: ***Teratogenic Effects. Pregnancy Category C:*** Venlafaxine did not cause malformations in offspring of rats or rabbits given doses up to 2.5 times (rat) or 4 times (rabbit) the maximum recommended human daily dose on a mg/m^2 basis. However, in rats, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation, when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. These effects occurred at 2.5 times (mg/m^2) the maximum human daily dose. The no effect dose for rat pup mortality was 0.25 times the human dose on a mg/m^2 basis. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-Teratogenic Effects: Neonates exposed to venlafaxine hydrochloride extended-release, other SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), 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 PRECAUTIONS: Drug Interactions: *CNS Active Drugs*). When treating a pregnant woman with venlafaxine hydrochloride extended-release 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 venlafaxine on labor and delivery in humans is unknown.

Nursing Mothers: Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from venlafaxine hydrochloride extended-release, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk). Two placebo-controlled trials in 766 pediatric patients with MDD have been conducted with venlafaxine hydrochloride extended-release, and the data were not sufficient to support a claim for use in pediatric patients.

Anyone considering the use of venlafaxine hydrochloride extended-release in a child or adolescent must balance the potential risks with the clinical need.

Although no studies have been designed to primarily assess venlafaxine hydrochloride extended-release's impact on the growth, development, and maturation of children and adolescents, the studies that have been done suggest that venlafaxine hydrochloride extended-release may adversely affect weight and height (see PRECAUTIONS: General: *Changes in Height* and *Changes in Weight*). Should the decision be made to treat a pediatric patient with venlafaxine hydrochloride extended-release, regular monitoring of weight and height is recommended during treatment, particularly if it is to be continued long-term. The safety of venlafaxine hydrochloride extended-release treatment for pediatric patients has not been systematically assessed for chronic treatment longer than 6 months in duration.

In the studies conducted in pediatric patients (ages 6 to 17), the occurrence of blood pressure and cholesterol increases considered to be clinically relevant in pediatric patients was similar to that observed in adult patients. Consequently, the precautions for adults apply to pediatric patients (see WARNINGS: Sustained Hypertension, and PRECAUTIONS: General: *Serum Cholesterol Elevation*).

Geriatric Use: Approximately 4% (14/357) and 1% (10/819) of venlafaxine hydrochloride extended-release-treated patients in placebo-controlled premarketing major depressive disorder and Social Anxiety Disorder trials, respectively, were 65 years of age or over. Of 2,897 venlafaxine hydrochloride tablets-treated patients in premarketing phase major depressive disorder studies, 12% (357) were 65 years of age or over. No overall differences in effectiveness or safety were observed between geriatric patients and younger patients, and other reported clinical experience generally has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including venlafaxine hydrochloride extended-release, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see PRECAUTIONS: General: *Hyponatremia*).

The pharmacokinetics of venlafaxine and ODV are not substantially altered in the elderly (see CLINICAL PHARMACOLOGY). No dose adjustment is recommended for the elderly on the basis of age alone, although other clinical circumstances, some of which may be more common in the elderly, such as renal or hepatic impairment, may warrant a dose reduction (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: The information included in the Adverse Findings Observed in Short-Term, Placebo-Controlled Studies with Venlafaxine Hydrochloride Extended-Release subsection is based on data from a pool of three 8- and 12-week controlled clinical trials in major depressive disorder (includes two U.S. trials and one European trial), on data up to 12 weeks from a pool of five controlled clinical trials in Social Anxiety Disorder. Information on additional adverse events associated with venlafaxine hydrochloride extended-release in the entire development program for the formulation and with venlafaxine hydrochloride tablets (the immediate-release formulation of venlafaxine) is included in the Other Adverse Events Observed During the Premarketing Evaluation of Venlafaxine Hydrochloride Tablets and Venlafaxine Hydrochloride Extended-Release subsection (see also WARNINGS and PRECAUTIONS).

Adverse Findings Observed in Short-Term, Placebo-Controlled Studies with Venlafaxine Hydrochloride Extended-Release: ***Adverse Events Associated with Discontinuation of Treatment:*** Approximately 11% of the 357 patients who received venlafaxine hydrochloride extended-release capsules in placebo-controlled clinical trials for major depressive disorder discontinued treatment due to an adverse experience, compared with 6% of the 285 placebo-treated patients in those studies. Approximately 15% of the 819 patients who received venlafaxine hydrochloride extended-release capsules in placebo-controlled clinical trials for Social Anxiety Disorder discontinued treatment due to an adverse experience, compared with 5% of the 695 placebo-treated patients in those studies. The most common events leading to discontinuation and considered to be drug-related (i.e., leading to discontinuation in at least 1% of the venlafaxine hydrochloride extended-release-treated patients at a rate at least twice that of placebo for either indication) are shown in Table 6.

Table 6: Common Adverse Events Leading to Discontinuation of Treatment in Placebo-Controlled Trials[1]

	Percentage of Patients Discontinuing Due to Adverse Event			
Adverse Event	Major Depressive Disorder Indication[2]		Social Anxiety Disorder Indication[3]	
	Venlafaxine HCl ER n = 357	Placebo n = 285	Venlafaxine HCl ER n = 819	Placebo n = 695
Body as a Whole				
Asthenia	—	—	2%	< 1%
Headache	—	—	1%	< 1%
Digestive System				
Nausea	4%	< 1%	3%	< 1%
Anorexia	1%	< 1%	—	—
Dry Mouth	1%	0%	—	—
Vomiting	—	—	—	—
Nervous System				
Dizziness	2%	1%	2%	< 1%
Insomnia	1%	< 1%	2%	< 1%
Somnolence	2%	< 1%	2%	< 1%
Nervousness	—	—	—	—
Tremor	—	—	—	—
Skin				
Sweating	—	—	—	—
Urogenital System				
Impotence[4]	—	—	2%	0%

[1] Two of the major depressive disorder studies were flexible dose and one was fixed dose. Four of the Social Anxiety Disorder studies were flexible dose and one was fixed/flexible dose.

[2] In U.S. placebo-controlled trials for major depressive disorder, the following were also common events leading to discontinuation and were considered to be drug-related for venlafaxine hydrochloride extended-release-treated patients (% venlafaxine hydrochloride extended-release [n = 192], % Placebo [n = 202]): hypertension (1%, < 1%); diarrhea (1%, 0%); paresthesia (1%, 0%); tremor (1%, 0%); abnormal vision, mostly blurred vision (1%, 0%); and abnormal, mostly delayed, ejaculation (1%, 0%).

[3] In a 6-month placebo-controlled trial for Social Anxiety Disorder, the following was also a common event leading to discontinuation and was considered to be drug-related for venlafaxine hydrochloride extended-release-treated patients (% venlafaxine hydrochloride extended-release [n = 257], % Placebo [n = 129]: depression (5%, 0%), libido decrease (1%, 0%), and nervousness (3%, 0%).

[4] Incidence is based on the number of men (venlafaxine hydrochloride extended-release = 454, placebo = 357).

Adverse Events Occurring at an Incidence of 2% or More Among Venlafaxine Hydrochloride Extended-Release-Treated Patients: Tables 7 and 8 enumerate the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of major depressive disorder (up to 12 weeks; dose range of 75 to 225 mg/day) and Social Anxiety Disorder (up to 12 weeks; dose range of 75 to 225 mg/day), respectively, in 2% or more of patients treated with venlafaxine hydrochloride extended-release where the incidence in patients treated with venlafaxine hydrochloride extended-release was greater than the incidence for the respective placebo-treated patients. The table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

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

Commonly Observed Adverse Events from Tables 7 and 8: *Major Depressive Disorder:* Note in particular the following adverse events that occurred in at least 5% of the venlafaxine hydrochloride extended-release patients and at a rate at least twice that of the placebo group for all placebo-controlled trials for the major depressive disorder indication (Table 7): Abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, and anorexia), CNS complaints (dizziness, somnolence, and abnormal dreams), and sweating. In the two U.S. placebo-controlled trials, the following additional events occurred in at least 5% of venlafaxine hydrochloride extended-release-treated patients (n = 192) and at a rate at least twice that of the placebo group: Abnormalities of sexual function (impotence in men, anorgasmia in women, and libido decreased), gastrointestinal complaints (constipation and flatulence), CNS complaints (insomnia, nervousness, and tremor), problems of special senses (abnormal vision), cardiovascular effects (hypertension and vasodilatation), and yawning.

Social Anxiety Disorder: Note in particular the following adverse events that occurred in at least 5% of the venlafaxine hydrochloride extended-release patients and at a rate at least twice that of the placebo group for the five placebo-controlled trials for the Social Anxiety Disorder indication (Table 8): asthenia, gastrointestinal complaints (anorexia, constipation, dry mouth, nausea), CNS complaints (insomnia, libido decreased, nervousness, somnolence, tremor), abnormalities of sexual function (abnormal ejaculation, impotence), yawn and sweating.

In the 6-month trial, the following adverse events occurred twice as often in the 150 to 225 mg/day venlafaxine hydrochloride extended-release group compared to the 75 mg/day venlafaxine hydrochloride extended-release group and placebo: vasodilation, libido decreased, tremor, yawn, abnormal vision, and impotence.

Table 7: Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Venlafaxine Hydrochloride Extended-Release Clinical Trials in Patients with Major Depressive Disorder[1,2]

	% Reporting Event	
Body System Preferred Term	**Venlafaxine HCl ER** (n = 357)	**Placebo** (n = 285)
Body as a Whole		
Asthenia	8%	7%
Cardiovascular System		
Vasodilatation[3]	4%	2%
Hypertension	4%	1%
Digestive System		
Nausea	31%	12%
Constipation	8%	5%
Anorexia	8%	4%
Vomiting	4%	2%
Flatulence	4%	3%
Metabolic/Nutritional		
Weight Loss	3%	0%
Nervous System		
Dizziness	20%	9%
Somnolence	17%	8%
Insomnia	17%	11%
Dry Mouth	12%	6%
Nervousness	10%	5%
Abnormal Dreams[4]	7%	2%
Tremor	5%	2%
Depression	3%	< 1%
Paresthesia	3%	1%
Libido Decreased	3%	< 1%
Agitation	3%	1%
Respiratory System		
Pharyngitis	7%	6%
Yawn	3%	0%
Skin		
Sweating	14%	3%
Special Senses		
Abnormal Vision[5]	4%	< 1%
Urogenital System		
Abnormal Ejaculation (male)[6,7]	16%	< 1%
Impotence[7]	4%	< 1%
Anorgasmia (female)[8,9]	3%	< 1%

[1] Incidence, rounded to the nearest %, for events reported by at least 2% of patients treated with venlafaxine hydrochloride extended-release, except the following events which had an incidence equal to or less than placebo: abdominal pain, accidental injury, anxiety, back pain, bronchitis, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, pain, palpitation, rhinitis, and sinusitis.

[2] < 1% indicates an incidence greater than zero but less than 1%.

[3] Mostly "hot flashes."

[4] Mostly "vivid dreams," "nightmares," and "increased dreaming."

[5] Mostly "blurred vision" and "difficulty focusing eyes."

[6] Mostly "delayed ejaculation."

[7] Incidence is based on the number of male patients.

[8] Mostly "delayed orgasm" or "anorgasmia."

[9] Incidence is based on the number of female patients.

Table 8: Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Venlafaxine Hydrochloride Extended-Release Clinical Trials in Social Anxiety Disorder Patients[1,2]

	% Reporting Event	
Body System Preferred Term	**Venlafaxine HCl ER** (n = 819)	**Placebo** (n = 695)
Body as a Whole		
Headache	38%	34%
Asthenia	19%	9%
Abdominal Pain	6%	4%
Accidental Injury	4%	3%
Cardiovascular System		
Hypertension	5%	3%
Vasodilatation[3]	3%	2%
Palpitation	3%	1%
Digestive System		
Nausea	31%	9%
Anorexia[4]	17%	2%
Constipation	9%	3%
Diarrhea	8%	6%
Dyspepsia	7%	6%
Vomiting	3%	2%
Metabolic/Nutritional		
Weight Loss	2%	< 1%
Nervous System		
Insomnia	24%	8%
Somnolence	20%	8%
Dry Mouth	17%	4%
Dizziness	16%	8%
Nervousness	10%	5%
Libido Decreased	8%	2%
Anxiety	5%	4%
Tremor	5%	2%
Agitation	3%	1%
Abnormal Dreams[5]	3%	< 1%
Twitching	3%	< 1%
Respiratory System		
Yawn	5%	< 1%
Skin		
Sweating	13%	4%
Special Senses		
Abnormal Vision[6]	4%	2%
Urogenital System		
Abnormal Ejaculation[7,8]	19%	< 1%
Impotence[8]	6%	< 1%
Orgasmic Dysfunction[9,10]	5%	< 1%

continued

[1] Adverse events for which the venlafaxine hydrochloride extended-release reporting rate was less than or equal to the placebo rate are not included. These events are: arthralgia, back pain, dysmenorrhea, flu syndrome, infection, pain, pharyngitis, rhinitis, and upper respiratory infection.

[2] < 1% means greater than zero but less than 1%.

[3] Mostly "hot flashes."

[4] Mostly "decreased appetite" and "loss of appetite."

[5] Mostly "vivid dreams," "nightmares," and "increased dreaming."

[6] Mostly "blurred vision."

[7] Includes "delayed ejaculation" and "anorgasmia."

[8] Percentage based on the number of males (venlafaxine hydrochloride extended-release = 454, placebo = 357).

[9] Includes "abnormal orgasm" and "anorgasmia."

[10] Percentage based on the number of females (venlafaxine hydrochloride extended-release = 365, placebo = 338).

Vital Sign Changes: Venlafaxine hydrochloride extended-release capsules treatment for up to 12 weeks in premarketing placebo-controlled major depressive disorder trials was associated with a mean final on-therapy increase in pulse rate of approximately 2 beats per minute, compared with 1 beat per minute for placebo. Venlafaxine hydrochloride extended-release treatment for up to 12 weeks in premarketing placebo-controlled Social Anxiety Disorder trials was associated with a mean final on-therapy increase in pulse rate of approximately 3 beats per minute, compared with an increase of 1 beat per minute for placebo. (See the Sustained Hypertension and Elevations in Systolic and Diastolic Blood Pressure sections of WARNINGS for effects on blood pressure.)

In a flexible-dose study, with venlafaxine hydrochloride tablets doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, the mean pulse was increased by about 2 beats per minute compared with a decrease of about 1 beat per minute for placebo.

Laboratory Changes: *Serum Cholesterol:* Venlafaxine hydrochloride extended-release capsules treatment for up to 12 weeks in premarketing placebo-controlled trials for major depressive disorder was associated with a mean final on-therapy increase in serum cholesterol concentration of approximately 1.5 mg/dL compared with a mean final decrease of 7.4 mg/dL for placebo. Venlafaxine hydrochloride extended-release treatment for up to 12 weeks and up to 6 months in premarketing placebo-controlled Social Anxiety Disorder trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 7.9 mg/dL and 5.6 mg/dL, respectively, compared with mean final decreases of 2.9 and 4.2 mg/dL, respectively, for placebo.

Patients treated with venlafaxine hydrochloride tablets (the immediate-release form of venlafaxine) for at least 3 months in placebo-controlled 12-month extension trials had a mean final on-therapy increase in total cholesterol of 9.1 mg/dL compared with a decrease of 7.1 mg/dL among placebo-treated patients. This increase was duration dependent over the study period and tended to be greater with higher doses. Clinically relevant increases in serum cholesterol, defined as 1) a final on-therapy increase in serum cholesterol ≥ 50 mg/dL from baseline and to a value ≥ 261 mg/dL, or 2) an average on-therapy increase in serum cholesterol ≥ 50 mg/dL from baseline and to a value ≥ 261 mg/dL, were recorded in 5.3% of venlafaxine-treated patients and 0% of placebo-treated patients (see PRECAUTIONS: General: *Serum Cholesterol Elevation*).

Serum Triglycerides: Venlafaxine hydrochloride extended-release treatment for up to 12 weeks in pooled premarketing Social Anxiety Disorder trials was associated with a mean final on-therapy increase in fasting serum triglyceride concentration of approximately 8.2 mg/dL, compared with a mean final increase of 0.4 mg/dL for placebo. Venlafaxine hydrochloride extended-release treatment for up to 6 months in a premarketing Social Anxiety Disorder trial was associated with a mean final on-therapy increase in fasting serum triglyceride concentration of approximately 11.8 mg/dL, compared with a mean final on-therapy increase of 1.8 mg/dL for placebo.

ECG Changes: In a flexible-dose study, with venlafaxine hydrochloride tablet doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, the mean change in heart rate was 8.5 beats per minute compared with 1.7 beats per minute for placebo.

(See PRECAUTIONS: *Use in Patients with Concomitant Illness.*)

Other Adverse Events Observed During the Premarketing Evaluation of Venlafaxine Hydrochloride Tablets and Venlafaxine Hydrochloride Extended-Release Capsules: During its premarketing assessment, multiple doses of venlafaxine hydrochloride extended-release capsules were administered to 705 patients in Phase 3 major depressive disorder studies and venlafaxine hydrochloride tablets were administered to 96 patients. During its premarketing assessment, multiple doses of venlafaxine hydrochloride extended-release capsules were also administered to 819 patients in Phase 3 Social Anxiety Disorder studies. In addition, in premarketing assessment of venlafaxine hydrochloride tablets, multiple doses were administered to 2,897 patients in Phase 2 to Phase 3 studies for major depressive disorder. The conditions and duration of exposure to venlafaxine in both development programs varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient (venlafaxine hydrochloride tablets only) and outpatient studies, fixed-dose, and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 7,212 patients exposed to multiple doses of either formulation of venlafaxine who experienced an event of the type cited on at least one occasion while receiving venlafaxine. All reported events are included except those already listed in Tables 7 and 8 and those events for which a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. It is important to emphasize that, although the events reported occurred during treatment with venlafaxine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as those occurring on one or more occasions 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 1/1,000 patients.

Body as a Whole: *Frequent:* chest pain substernal, chills, fever, neck pain; *Infrequent:* face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; *Rare:* appendicitis, bacteremia, carcinoma, cellulitis, granuloma.

Cardiovascular System: *Frequent:* migraine, tachycardia; *Infrequent:* angina pectoris, arrhythmia, bradycardia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), postural hypotension, syncope; *Rare:* aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, sinus arrhythmia, thrombophlebitis.

Digestive System: *Frequent:* increased appetite; *Infrequent:* bruxism, colitis, dysphagia, tongue edema, eructation, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; *Rare:* abdominal distension, biliary pain, cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration.

Endocrine System: *Rare:* galactorrhoea, goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis.

Hemic and Lymphatic System: *Frequent:* ecchymosis; *Infrequent:* anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia; *Rare:* basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia.

Metabolic and Nutritional: *Frequent:* edema, weight gain; *Infrequent:* alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipidemia, hypokalemia, SGOT (AST) increased, SGPT (ALT) increased, thirst; *Rare:* alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia.

Musculoskeletal System: *Infrequent:* arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; *Rare:* bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture.

Nervous System: *Frequent:* amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; *Infrequent:* akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, libido increased, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; *Rare:* abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barre Syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis.

Respiratory System: *Frequent:* cough increased, dyspnea; *Infrequent:* asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; *Rare:* atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea.

Skin and Appendages: *Frequent:* pruritus; *Infrequent:* acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; *Rare:* brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased.

Special Senses: *Frequent:* abnormality of accommodation, mydriasis, taste perversion; *Infrequent:* conjunctivitis, diplopia, dry eyes, eye pain, otitis media, parosmia, photophobia, taste loss; *Rare:* blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, hyperacusis, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis, visual field defect.

Urogenital System: *Frequent:* albuminuria, urination impaired, *Infrequent:* amenorrhea,* cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea,* menorrhagia, * metrorrhagia, * nocturia, breast pain, polyuria, pyuria, prostatic disorder (prostatitis, enlarged prostate, and prostate irritability),* urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage,* vaginitis*; *Rare:* abortion,* anuria, breast discharge, breast engorgement, balanitis,* breast enlargement, endometriosis,* female lactation,* fibrocystic breast, calcium crystalluria, cervicitis,* orchitis,* ovarian cyst,* bladder pain, prolonged erection,* gynecomastia (male),* hypomenorrhea,* kidney function abnormal, mastitis, menopause,* pyelonephritis, oliguria, salpingitis,* urolithiasis, uterine hemorrhage,* uterine spasm,* vaginal dryness.*

*Based on the number of men and women as appropriate.

Post-Marketing Reports: ***Adverse Events:*** Voluntary reports of other adverse events temporally associated with the use of venlafaxine that have been received since market introduction and that may have no causal relationship with the use of venlafaxine include the following: agranulocytosis, anaphylaxis, angioedema, aplastic anemia, catatonia, congenital anomalies, impaired coordination and balance, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including Torsades de pointes; toxic epidermal necrolysis/Stevens-Johnson Syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), interstitial lung disease, involuntary movements, LDH increased, neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, renal failure, rhabdomyolysis, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and syndrome of inappropriate antidiuretic hormone secretion (usually in the elderly).

Drug Interactions: There have been reports of elevated clozapine levels that were temporally associated with adverse events, including seizures, following the addition of venlafaxine. There have been reports of increases in prothrombin time, partial thromboplastin time, or INR when venlafaxine was given to patients receiving warfarin therapy.

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: Venlafaxine hydrochloride extended-release capsules are not a controlled substance.

Physical and Psychological Dependence: *In vitro* studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors.

Venlafaxine was not found to have any significant CNS stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

Discontinuation effects have been reported in patients receiving venlafaxine (see DOSAGE AND ADMINISTRATION).

While venlafaxine has not been systematically studied in clinical trials 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 history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of venlafaxine (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE: Human Experience: Among the patients included in the premarketing evaluation of venlafaxine hydrochloride extended-release, there were two reports of acute overdosage with venlafaxine hydrochloride extended-release in major depressive disorder trials, either alone or in combination with other drugs. One patient took a combination of 6 g of venlafaxine hydrochloride extended-release and 2.5 mg of lorazepam. This patient was hospitalized, treated symptomatically, and recovered without any untoward effects. The other patient took 2.85 g of venlafaxine hydrochloride extended-release. This patient reported paresthesia of all four limbs but recovered without sequelae.

There were no reports of acute overdose with venlafaxine hydrochloride extended-release in Social Anxiety Disorder trials.

Among the patients included in the premarketing evaluation with venlafaxine hydrochloride tablets, there were 14 reports of acute overdose with venlafaxine, either alone or in combination with other drugs and/or alcohol. The majority of the reports involved ingestion in which the total dose of venlafaxine taken was estimated to be no more than several-fold higher than the usual therapeutic dose. The three patients who took the highest doses were estimated to have ingested approximately 6.75 g, 2.75 g, and 2.5 g. The resultant peak plasma levels of venlafaxine for the latter two patients were 6.24 and 2.35 mcg/mL, respectively, and the peak plasma levels of O-desmethylvenlafaxine were 3.37 and 1.30 mcg/mL, respectively. Plasma venlafaxine levels were not obtained for the patient who ingested 6.75 g of venlafaxine. All 14 patients recovered without sequelae. Most patients reported no symptoms. Among the remaining patients, somnolence was the most commonly reported symptom. The patient who ingested 2.75 g of venlafaxine was observed to have two generalized convulsions and a prolongation of QTc to 500 msec, compared with 405 msec at baseline. Mild sinus tachycardia was reported in two of the other patients.

In post-marketing experience, overdose with venlafaxine has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported.

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher preexisting burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage as opposed to some characteristic(s) of venlafaxine-treated patients is not clear. Prescriptions for venlafaxine hydrochloride extended-release should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Management of Overdosage: Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. 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 should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known.

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

DOSAGE AND ADMINISTRATION: Venlafaxine hydrochloride extended-release capsules should be administered in a single dose with food either in the morning or in the evening at approximately the same time each day. Each capsule should be swallowed whole with fluid and not divided, crushed, chewed, or placed in water, or it may be administered by carefully opening the capsule and sprinkling the entire contents on a spoonful of applesauce. This drug/food mixture should be swallowed immediately without chewing and followed with a glass of water to ensure complete swallowing of the pellets.

Initial Treatment: ***Major Depressive Disorder:*** For most patients, the recommended starting dose for venlafaxine hydrochloride extended-release capsules is 75 mg/day, administered in a single dose. In the clinical trials establishing the efficacy of venlafaxine hydrochloride extended-release capsules in moderately depressed outpatients, the initial dose of venlafaxine was 75 mg/day. For some patients, it may be desirable to start at 37.5 mg/day for 4 to 7 days, to allow new patients to adjust to the medication before increasing to 75 mg/day. While the relationship between dose and antidepressant response for venlafaxine hydrochloride extended-release capsules has not been adequately explored, patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days, since steady state plasma levels of venlafaxine and its major metabolites are achieved in most patients by day 4. In the clinical trials establishing efficacy, upward titration was permitted at intervals of 2 weeks or more; the average doses were about 140 to 180 mg/day (see CLINICAL PHARMACOLOGY: Clinical Trials).

It should be noted that, while the maximum recommended dose for moderately depressed outpatients is also 225 mg/day for venlafaxine hydrochloride tablets (the immediate-release form of venlafaxine) more severely depressed inpatients in one study of the development program for that product responded to a mean dose of 350 mg/day (range of 150 to 375 mg/day). Whether or not higher doses of venlafaxine hydrochloride extended-release capsules are needed for more severely depressed patients is unknown; however, the experience with venlafaxine hydrochloride extended-release capsules doses higher than 225 mg/day is very limited. (See PRECAUTIONS: General: *Use in Patients with Concomitant Illness.*)

Social Anxiety Disorder (Social Phobia): The recommended dose is 75 mg/day, administered in a single dose. There was no evidence that higher doses confer any additional benefit. (See PRECAUTIONS: Use in Patients with Concomitant Illness.)

Switching Patients from Venlafaxine Hydrochloride Tablets: Depressed patients who are currently being treated at a therapeutic dose with venlafaxine hydrochloride tablets may be switched to venlafaxine hydrochloride extended-release capsules at the nearest equivalent dose (mg/day), e.g., 37.5 mg venlafaxine 2 times a day to 75 mg venlafaxine hydrochloride extended-release capsules once daily. However, individual dosage adjustments may be necessary.

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

Patients with Hepatic Impairment: Given the decrease in clearance and increase in elimination half-life for both venlafaxine and ODV that is observed in patients with hepatic cirrhosis and mild and moderate hepatic impairment compared with normal subjects (see CLINICAL PHARMACOLOGY), it is recommended that the total daily dose be reduced by 50% in patients with mild to moderate hepatic impairment. Since there was much individual variability in clearance between subjects with cirrhosis, it may be necessary to reduce the dose even more than 50%, and individualization of dosing may be desirable in some patients.

Patients with Renal Impairment: Given the decrease in clearance for venlafaxine and the increase in elimination half-life for both venlafaxine and ODV that is observed in patients with renal impairment (GFR = 10 to 70 mL/min) compared with normal subjects (see CLINICAL PHARMACOLOGY), it is recommended that the total daily dose be reduced by 25% to 50%. In patients undergoing hemodialysis, it is recommended that the total daily dose be reduced by 50%. Because there was much individual variability in clearance between patients with renal impairment, individualization of dosage may be desirable in some patients.

Elderly Patients: No dose adjustment is recommended for elderly patients solely on the basis of age. As with any drug for the treatment of major depressive disorder or Social Anxiety Disorder, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

Maintenance Treatment: There is no body of evidence available from controlled trials to indicate how long patients with major depressive disorder or Social Anxiety Disorder should be treated with venlafaxine hydrochloride extended-release capsules.

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacological therapy beyond response to the acute episode. In one study, in which patients responding during 8 weeks of acute treatment with venlafaxine hydrochloride extended-release capsules were assigned randomly to placebo or to the same dose of venlafaxine hydrochloride extended-release capsules (75, 150, or 225 mg/day, qAM) during 26 weeks of maintenance treatment as they had received during the acute stabilization phase, longer-term efficacy was demonstrated. A second longer-term study has demonstrated the efficacy of venlafaxine hydrochloride tablets in maintaining a response in patients with recurrent major depressive disorder who had responded and continued to be improved during an initial 26 weeks of treatment and were then randomly assigned to placebo or venlafaxine hydrochloride tablets for periods of up to 52 weeks on the same dose (100 to 200 mg/day, on a b.i.d. schedule) (see CLINICAL PHARMACOLOGY: Clinical Trials). Based on these limited data, it is not known whether or not the dose of venlafaxine hydrochloride tablets/venlafaxine hydrochloride extended-release capsules needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

In patients with Social Anxiety Disorder, venlafaxine hydrochloride extended-release has been shown to be effective in a 6-month clinical trial. The need for continuing medication in patients with Social Anxiety Disorder who improve with venlafaxine hydrochloride extended-release capsule treatment should be periodically reassessed.

Discontinuing Venlafaxine Hydrochloride Extended-Release Capsules: Symptoms associated with discontinuation of venlafaxine hydrochloride extended-release capsules, other SNRIs, and SSRIs, 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. In clinical trials with venlafaxine hydrochloride extended-release capsules, tapering was achieved by reducing the daily dose by 75 mg at one week intervals. Individualization of tapering may be necessary.

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 venlafaxine hydrochloride extended-release capsules. In addition, at least 7 days should be allowed after stopping venlafaxine hydrochloride extended-release capsules before starting an MAOI (see CONTRAINDICATIONS and WARNINGS).

HOW SUPPLIED: Venlafaxine Hydrochloride Extended-Release Capsules are available containing venlafaxine hydrochloride, USP equivalent to 37.5 mg, 75 mg or 150 mg of venlafaxine.

The 37.5 mg capsule is a hard-shell gelatin capsule with a light blue opaque cap and a white opaque body filled with white to off-white pellets and axially printed with **MYLAN** over **5131** in black ink on both the cap and the body. They are available as follows:

NDC 0378-5131-01
bottles of 100 capsules

NDC 0378-5131-05
bottles of 500 capsules

The 75 mg capsule is a hard-shell gelatin capsule with a lavender opaque cap and a white opaque body filled with white to off-white pellets and axially printed with **MYLAN** over **5132** in black ink on both the cap and the body. They are available as follows:

NDC 0378-5132-01
bottles of 100 capsules

NDC 0378-5132-05
bottles of 500 capsules

The 150 mg capsule is a hard-shell gelatin capsule with an orange opaque cap and white opaque body filled with white to off-white pellets and axially printed with **MYLAN** over **5133** in black ink on both the cap and the body. They are available as follows:

NDC 0378-5133-01
bottles of 100 capsules

NDC 0378-5133-05
bottles of 500 capsules

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

PHARMACIST: Dispense a Medication Guide with each prescription.

Mylan®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

MARCH 2011
VNLAER:R1mc

Medication Guide
Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines.

Talk to your, or your family member's, healthcare provider about:

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
    - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
    - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
    - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

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

Revised 1/2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078789

LABELING REVIEWS

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	078789
Date of Submission:	March 18, 2011 (received March 21, 2011)
Applicant's Name:	Mylan Pharmaceuticals, Inc.
Established Name:	Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg (base), 75 mg (base) and 150 mg (base)
Proposed Proprietary Name:	None

REMS required?
☐ Yes ☒ No ☐ n/a

MedGuides and/or PPIs (505-1(e))	☐ Yes	☒ No
Communication plan (505-1(e))	☐ Yes	☒ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☒ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☒ No
Timetable for assessment (505-1(d))	☐ Yes	☒ No

ANDA REMS acceptable?
☐ Yes ☐ No ☒ n/a

Final Printed Labels and Labeling provided electronically

1. CONTAINER – bottles of 100s and 500s

   Satisfactory in final print as of the March 18, 2011 amendment

2. PHYSICIAN INSERT/MEDICATION GUIDE

   Satisfactory in final print as of the March 18, 2011 amendment
   Mylan is participating in the distribution of Medication Guides with the Hibbert Group.

Revisions needed pre-approval: Yes

INSERT

a. When the RLD specifies immediate release throughout the labeling [i.e. Effexor (immediate release)], please also specify immediate release in your labeling [i.e. venlafaxine hydrochloride tablets (immediate release)].

b. PRECAUTIONS, General, Changes in Weight, Pediatric Patients, 4th sentence – Revise to read "…gained an average of 0.76 kg…" rather than "…gained a average of 0.76 kg…".

NOTE TO THE CHEMIST:

From: Sun, Zhigang
Sent: Tuesday, April 12, 2011 9:26 AM
To: Kwok, Lisa
Subject: RE: ANDA 078789 Mylan's Venlafaxine ER Cap

Lisa,

For ANDA 78789, the pellet size of the final blend is controlled by the [redacted] (b) (4) process [redacted] (b) (4) In addition, in the in-process specifications, the proposed limit for the pellet size [redacted] (b) (4)) will ensure to meet our requirement.

Thanks,

zhigang

From: Kwok, Lisa
Sent: Tuesday, April 12, 2011 9:08 AM
To: Sun, Zhigang
Subject: ANDA 078789 Mylan's Venlafaxine ER Cap

Hi Zhigang,

Can you comment on if the firm provided adequate information on the pellet size ([redacted] (b) (4)) to ensure that the patient will be able to swallow the drug/food mixture without stimulating the urge to chew?

Thanks,
Lisa

FOR THE RECORD: (Portions of review from previous reviewer)

1. MODEL LABELING

The RLD is NDA 020699 Effexor XR (venlafaxine hydrochloride) Extended Release Capsules by Wyeth Pharmaceuticals, Inc. The model RLD labeling used for this review is NDA 020699/S-090 approved January 6, 2010.

NDA 020699/S-089 was submitted on 5/14/09, providing for a Comprehensive Medication Guide for Effexor XR. An acceptable labeling review for S-089 is in DARRTS as of 4/7/2011. However, OND has not yet issued an approval letter for S-089. Thus, S-090 remains the model labeling.

2. PATENT/EXCLUSIVITIES

PATENT 20-699

Number	Expiration	Use Code	Description	*Patent certification*	Labeling Impact
5916923/*PED	6-28-13 / 12-28-13	U-398	Tx of GAD	MOU	Carved out
6274171/*PED	3-20-17 / 9-20-17			IV	None
6403120/*PED	3-20-17 / 9-20-17	U-451	Tx of Depression	IV	None
			Tx of GAD	MOU	Carved out
		U-535	Tx of SAD	IV	None
6419958/*PED	3-20-17 / 9-20-17	U-459	Tx of Depression	IV	None
			Tx of GAD	MOU	Carved out
		U-535	Tx of SAD	IV	None
6444708/*PED	6-28-13 / 12-28-13	U-398	Tx of GAD	MOU	Carved out
6310101	6-28-13	U-46	Tx of Panic Disorder	MOU	Carved out

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
Morgantown, WV 26505

4. USP: Drug product not subject to a USP 33 monograph (checked 4/11/11).
The drug substance currently is not USP. However, the USP monograph for venlafaxine hydrochloride will become effective on May 1, 2011, under USP 34.

USP 34: Packaging and Storage - Preserve in well-closed containers and store at controlled room temperature.

Please note that Mylan's revised labeling reflects the implementation of the USP monograph for the drug substance which will become effective on May 1, 2011. The container label states on the left side panel "Each capsule contains venlafaxine hydrochloride, USP equivalent to xx mg of venlafaxine." This is acceptable since Mylan will not market until June 1, 2011.

5. PF – None

6. INACTIVE INGREDIENTS
The list of inactive ingredients in the DESCRIPTION section is accurate.

Per Chemistry Review #1
Iron oxide is a component of the black imprinting inks and per the following calculation, meets the requirements of 21 CFR 73.1200 of not more than 5mg elemental iron per day. Since the quantity of iron oxide in [redacted] (b) (4), the quantity of iron oxide in [redacted] (b) (4) ([redacted] (b) (4) %) is used in calculating the daily intake of elemental iron. Based on a maximum daily dose of 350mg venlafaxine HCl, the maximum daily intake of elemental iron is (see Section 3.2.P.1 for further information): 9 capsules (37.5mg strength) x [redacted] (b) (4)

7. PACKAGING CONFIGURATIONS
RLD – Bottles of 15s, 30s, 90s, 100s and Blister carton of 100s
ANDA –Bottles of 100s, 500s

8. DISPENSING/STORAGE TEMPERATURE STATEMENT COMPARISION
RLD: Store at controlled room temperature, 20° to 25°C (68°F to 77°F).
Note to authorized dispenser: Each time Effexor XR is dispensed, give the patient the attached Medication Guide.
ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]
Pharmacist: Dispense the Medication Guide provided separately to each patient.

9. CONTAINER/CLOSURE

Fill Size	Component Description
Bottle, 100's for 37.5 mg	[redacted] (b) (4)
Bottle, 100's for 75 mg	[redacted]
Bottle, 100's for 150 mg	[redacted]

Fill Size	Component Description
Bottle, 500's for 37.5 mg	(b) (4)
Bottle, 500's for 75 mg	
Bottle, 500's for 150 mg	

10. IMPRINTINGS

The capsule imprinting as described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95. has been accurately described.

37.5 mg: A light blue opaque cap / white opaque body, hard-shell gelatin capsules filled with white to off-white pellets. The capsule is axially printed with MYLAN over 5131 in black ink on both the cap and the body.

75 mg: A lavender opaque cap / white opaque body, hard-shell gelatin capsule filled with white to off-white pellets. The capsule is axially printed with MYLAN over 5132 in black ink on both the cap and the body.

150 mg: An orange opaque / white opaque body, hard-shell gelatin capsule filled with white to off-white pellets. The capsule is axially printed with MYLAN over 5133 in black ink on both the cap and the body.

11. MEDICATION GUIDE

Mylan is participating in the distribution of Medication Guides with the Hibbert Group.

12. SPECIAL CONSIDERATION

The RLD uses pellets to fill the capsules. The ANDA drug product also consists of pellets.

From the DOSAGE AND ADMINISTRATION section:

> *"Each capsule should be swallowed whole with fluid and not divided, crushed, chewed, or placed in water, or it may be administered by carefully opening the capsule and sprinkling the entire contents on a spoonful of applesauce. This drug/food mixture should be swallowed immediately without chewing and followed with a glass of water to ensure complete swallowing of the pellets."*

Per Bio Review dated 4/16/08, the fed and fed sprinkle studies are acceptable for approval.

The draft Guidance for Industry on 'Size of Beads in Drug Products Labeled for Sprinkle' recommends that pellets not be larger than 2 mm in size based on studies that demonstrate that food is chewed to approximately 2 mm in median particle size before swallowing.

Per Chemist: For ANDA 78789, the pellet size of the final blend is controlled by the (b) (4) process ((b) (4) In addition, in the in-process specifications, the proposed limit for the pellet size ((b) (4) will ensure to meet our requirement.

13. MEDWATCH

January 2010: Contraindications and Adverse Reaction- Postmarketing Reports sections revised.
January 2009: Warnings section revised.
These changes are reflected in the latest RLD labeling for NDA 020699/S-090, XR (venlafaxine hydrochloride) Extended Release Capsules by Wyeth Pharmaceuticals, Inc. approved on January 6, 2010.

Date of review:	April 12, 2011
Primary Reviewer:	Lisa Kwok
Team Leader:	Lillie Golson

Review 03.AP

N
3 0378-5131-01 4

*Each capsule contains venlafaxine hydrochloride, USP equivalent to 37.5 mg of venlafaxine.

37.5 mg*

Mylan®

NDC 0378-5131-01

Venlafaxine HCl
Extended-release

Capsules

37.5 mg*

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

Rx only 100 CAPSULES

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Usual Dosage: See accompanying prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan®
www.mylan.com

RM5131A

N
3 0378-5131-05 2

37.5 mg*

*Each capsule contains venlafaxine hydrochloride, USP equivalent to 37.5 mg of venlafaxine.

Mylan®

NDC 0378-5131-05

Venlafaxine HCl Extended-release

Capsules

37.5 mg*

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

Rx only 500 CAPSULES

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

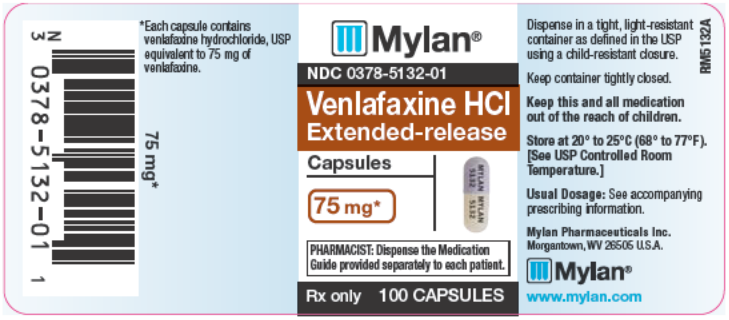
Usual Dosage: See accompanying prescribing information.

This container is not intended for dispensing for household use.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan® www.mylan.com

RM5131B


N
3 0378-5132-01 1
*Each capsule contains venlafaxine hydrochloride, USP equivalent to 75 mg of venlafaxine.
75 mg*
Mylan®
NDC 0378-5132-01
Venlafaxine HCl
Extended-release
Capsules
75 mg*
PHARMACIST: Dispense the Medication Guide provided separately to each patient.
Rx only 100 CAPSULES
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Usual Dosage: See accompanying prescribing information.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Mylan®
www.mylan.com
RM5 132A

*Each capsule contains venlafaxine hydrochloride, USP equivalent to 75 mg of venlafaxine.

75 mg*

Mylan®

NDC 0378-5132-05

Venlafaxine HCl Extended-release

Capsules

75 mg*

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

Rx only 500 CAPSULES

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

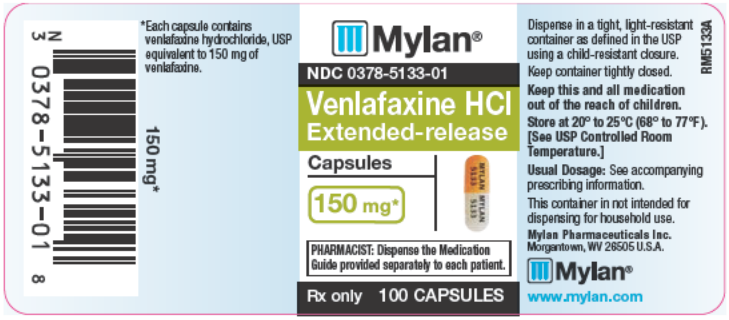
Usual Dosage: See accompanying prescribing information.

This container is not intended for dispensing for household use.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan® www.mylan.com

RM5132B


N
3 0378-5133-01 8
150 mg*
*Each capsule contains venlafaxine hydrochloride, USP equivalent to 150 mg of venlafaxine.
Mylan®
NDC 0378-5133-01
Venlafaxine HCl
Extended-release
Capsules
150 mg*
PHARMACIST: Dispense the Medication Guide provided separately to each patient.
Rx only 100 CAPSULES
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Usual Dosage: See accompanying prescribing information.
This container in not intended for dispensing for household use.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Mylan®
www.mylan.com
RM5133A

150 mg*

*Each capsule contains venlafaxine hydrochloride, USP equivalent to 150 mg of venlafaxine.

Mylan®

NDC 0378-5133-05

Venlafaxine HCl Extended-release

Capsules

150 mg*

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

Rx only 500 CAPSULES

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Usual Dosage: See accompanying prescribing information.

This container is not intended for dispensing for household use.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan® www.mylan.com

RM5133B

VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES

37.5 mg, 75 mg and 150 mg

℞ only

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of venlafaxine hydrochloride extended-release or any other antidepressant in a child, adolescent or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24. There was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with the increase in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and 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. Venlafaxine hydrochloride extended-release is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients and PRESCRIBING INFORMATION: Pediatric Use.)

DESCRIPTION Venlafaxine hydrochloride extended-release capsules are oral administration capsules containing venlafaxine hydrochloride as a racemic mixture and a bioenzyme. It is designated as 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride (Ω). Its empirical formula is $C_{17}H_{27}NO_2 \cdot HCl$. Its molecular weight is 313.9. The structural formula is shown below:

VNLAER:R1 mo

Venlafaxine Hydrochloride

Venlafaxine Hydrochloride USP is a white to off-white powder that is very soluble in water, freely soluble in ethanol and chloroform. It has a solubility of 52.7 mg/mL in water (adjusted to ionic strength of 0.2 M with sodium chloride). It contains one ionizable group with a pKa of 9.4.

Venlafaxine Hydrochloride extended-release capsules are for oral administration. Drug release is controlled by diffusion through the rate-limiting membrane on the spherules and in the gel hydrated matrix. Capsules contain venlafaxine hydrochloride equivalent to 37.5 mg, 75 mg or 150 mg of venlafaxine. Inactive ingredients consist of ethylcellulose, hypromellose, polydextrose, glycerol, sugar spheres, and talc. In addition, each of the capsule strengths contains an ink for marking, gelatin, titanium dioxide and also the 37.5 mg and the 75 mg colorant also contains:

37.5 mg FD&C Blue No. 1 and FD&C Red No. 3

75 mg D&C Red No. 28 and FD&C Blue No. 1

150 mg D&C Red No. 28, D&C Yellow No. 10 and FD&C Red No. 40

This imprinting ink contains the following: black iron oxide, D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, propylene glycol and shellac gloss.

CLINICAL PHARMACOLOGY **Pharmacodynamics** The mechanism of the antidepressant action of venlafaxine in humans is believed to be associated with its potent and selective inhibition of neuronal uptake of the CNS. Preclinical studies have shown that venlafaxine and its active metabolite O-desmethylvenlafaxine (ODV) are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic cholinergic, histaminergic, dopaminergic, adrenergic receptors in vitro. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

Pharmacokinetics Steady state concentrations of venlafaxine and ODV in plasma are attained within 3 days of administration of immediate-release venlafaxine and ODV exhibited linear kinetics over the dose range of 75 to 450 mg/day. About a 50 % steady state plasma concentration of venlafaxine and ODV is 1.3 and 1.6 and 0.4 and 0.2 L/kg, respectively, given a dosing interval of 12 hours, respectively, and given a dosing interval of 24 hours. Steady state volumes of distribution for ODV are 5.7 and 7.5 L/kg, respectively, for venlafaxine and ODV given a dosing interval of 12 hours. Plasma protein binding of venlafaxine and ODV is approximately 30 percent and 27 percent, respectively, for venlafaxine and ODV.

Absorption Venlafaxine is well absorbed and extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the only major active metabolite. On the basis of mass balance studies, at least 92% of a single oral dose of venlafaxine is absorbed. The absolute bioavailability of venlafaxine is about 45%.

After administration of venlafaxine hydrochloride extended-release capsules (150 mg, q24h) found generally steady state levels of venlafaxine (C_{max}) (150 ng/mL) for venlafaxine and 300 ng/mL for ODV and better (T_{max}) (5.5 hours for venlafaxine and 9 hours for ODV) than for immediate-release venlafaxine in adults (C_{max} for immediate-release 75 mg q12 hours was a 235 ng/mL for venlafaxine and 296 ng/mL for ODV; T_{max} 2 hours for venlafaxine and 3 hours for ODV). When equal daily doses of venlafaxine are administered as either an immediate-release tablet or the extended-release capsule, the exposure to both venlafaxine and ODV was similar for the two treatments and the fluctuations in plasma concentrations was slight lower with the venlafaxine hydrochloride extended-release capsule. Venlafaxine hydrochloride extended-release formulation provides a slower rate of absorption but the same amount of absorption compared with the immediate-release tablet.

Food did not affect the bioavailability of venlafaxine and its active metabolite ODV. Time of administration (AM or PM) did not affect the pharmacokinetics of venlafaxine and ODV from the 75 mg extended-release hydrochloride extended-release capsule.

Metabolism and Excretion Following oral administration, venlafaxine undergoes extensive presystemic metabolism. In the liver, primarily by CYP2D6, to the active metabolite O-desmethylvenlafaxine (ODV) and other minor metabolites. In vitro studies indicate that the formation of ODV is catalyzed by CYP2D6. This has been confirmed in a clinical study showing that patients with poor CYP2D6 levels ("poor metabolizers") had increased levels of venlafaxine and reduced levels of ODV compared to people with normal CYP2D6 ("extensive metabolizers"). The differences between the CYP2D6 poor and extensive metabolizers were not expected to be of a clinical importance because the sum of venlafaxine and ODV is similar in the two groups and venlafaxine and ODV are pharmacologically approximately equipotent and equipotent.

Approximately 87% of venlafaxine dose is recovered in the urine within 48 hours as unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (21%), or a lesser minor less active metabolites (27%). Renal elimination of venlafaxine and its metabolites is thus the primary route of excretion.

Special Populations **Age and Gender** A population pharmacokinetic analysis of 404 venlafaxine hydrochloride patients from two studies involving both b.i.d. and t.i.d. regimens showed that dose normalized bioavailability across weeks of either venlafaxine or ODV was unaffected by age or gender of the female. Dosage adjustment based on the basis of age or gender of a patient is generally not necessary (see DOSAGE AND ADMINISTRATION).

Extensive/Poor Metabolizers Plasma concentration levels of venlafaxine were higher in CYP2D6 poor metabolizers than extensive metabolizers. Because the sum of venlafaxine (VLAF) and venlafaxine and ODV was similar in poor and extensive metabolizer groups, however, there is no need for different dosage regimens for these two groups.

Liver Disease In mild to moderate cirrhosis of the liver, the pharmacokinetics of oral venlafaxine and its active metabolite ODV were significantly altered after a single administration of venlafaxine. Plasma levels of venlafaxine were about 50% and 60% higher than in healthy subjects, and the elimination half-life was prolonged by about 50% and clearance was reduced by about 30% and 60% in mild and moderate cirrhosis, respectively. Plasma levels of ODV were about 50% and 60% higher than in healthy subjects, and the elimination half-life was prolonged by about 30% and clearance was reduced by about 30% and 60% in mild and moderate cirrhosis, respectively. Dosage adjustment is necessary in these hepatic impairment patients (see DOSAGE AND ADMINISTRATION).

Renal Disease In a renal impairment study, venlafaxine elimination half-life was prolonged by about 50% and clearance was reduced by about 24% in analog impaired patients (CR ≤ 10 ± 70 mL/min) compared to normal subjects. In dialysis patients, venlafaxine elimination half-life was prolonged by about 100% and clearance was reduced by about 57% compared to normal subjects. Similarly, ODV elimination half-life was prolonged by about 40% and clearance was unchanged in patients with renal impairment (CR ≤ 10 ± 70 mL/min) compared to normal subjects. In dialysis patients, ODV elimination half-life was prolonged by about 142% and clearance was reduced by about 56% compared to normal subjects. A single dose of venlafaxine extended-release capsules should not be administered to patients on dialysis.

Clinical Trials **Major Depressive Disorder** The efficacy of venlafaxine hydrochloride extended-release capsules as a treatment for major depressive disorder was established in five placebo-controlled short-term Fixed-dose studies in adult outpatients meeting DSM-IV criteria for major depressive disorder.

A 12 week study utilizing venlafaxine hydrochloride extended-release doses in a range 75 to 150 mg/day (mean dose for completers was 136 mg/day) and an 8 week study utilizing venlafaxine hydrochloride extended-release doses in a range 75 to 225 mg/day (mean dose for completers was 177 mg/day) both demonstrated superiority of venlafaxine hydrochloride extended-release over placebo on the HAM-D total score. HAM-D Responder Mixed Item the MADRS total score, the Clinical Global Impressions (CGI) Severity of Illness item and the CGI Global Improvement item in both studies. Venlafaxine hydrochloride extended-release was also significantly better than placebo for certain factors of the HAM-D, including the anxiety/somatic factor, the cognitive disturbance factor and the anxiety factor as well as for the psychic anxiety.

A 4 week study of inpatients meeting DSM-IV criteria for major depressive disorder with melancholia (a distinct subset within major depressive disorder characterized by a loss of pleasure in all or almost all activities, lack of responsiveness to pleasure, distinct quality of depressed mood, depression worse in the morning, early morning awakening, psychomotor retardation, excessive guilt, and loss of appetite) showed that venlafaxine hydrochloride extended-release capsules were also significantly better than placebo for certain factors of the HAM-D, including the anxiety/somatic factor, the cognitive disturbance factor and the anxiety factor as well as for the psychic anxiety.

A 4 week study of inpatients meeting DSM-IV criteria for major depressive disorder with melancholia utilizing venlafaxine hydrochloride extended-release (the immediate-release form of venlafaxine) in a range of 150 ± 375 mg/day (1 ± 3 tablets) demonstrated superiority of venlafaxine hydrochloride extended-release over placebo. The mean dose in comparison was 350 mg/day.

Examination of gender subsets of the population studied did not reveal any differences in response across the basis of gender.

In one longer-term study, adult outpatients meeting DSM-IV criteria for major depressive disorder who had responded during an 8 week open-label run-in period on venlafaxine hydrochloride extended-release capsules 75 mg, 150 mg or 225 mg (q24h) were randomized to continuation of their same venlafaxine hydrochloride extended-release dose or to placebo for up to 26 weeks of treatment on or relapse. Response during the open-label period was defined as a CGI Severity of Illness score of ≤ 3 and a HAM-D 17 total score of ≤ 18 at the end-of-the-open-label-period. Relapse during the double-blind phase was defined as follows: (1) an appearance of major depressive disorder as defined by DSM-IV criteria and a CGI Severity of Illness item score of ≥ 4 (moderately ill); (2) two consecutive CGI Severity of Illness item scores of ≥ 4 or 3 if the CGI Severity of Illness item score of ≥ 4 for any patient who withdrew from the study for any reason. Patients who in any one round venlafaxine hydrochloride extended-release treatment experienced greater clinical improvement and were more likely to remain in remission than those who were receiving a placebo.

In a second longer term trial adult outpatients meeting DSM-IV criteria for major depressive disorder, recurrent, who had responded (HAM-D 22 total score ≤ 12 at the step 6 exit criterion) and continued to be improved (defined as the following criteria: a HAM-D total score ≤ 7 for at least 5 through 180 (3) to HAM-D 21 a decrease ≥ 50 (Clinical Global Impressions ≤ 10 and 3 (Clinical Global Impressions ≤ 10 and 3 (Clinical Global Impressions Severity of Illness item score ≤ 4 moderately ill) during an initial 24 weeks of treatment on venlafaxine hydrochloride tablets (100 to 200 mg/day) on a b.i.d. basis were randomized to continuation of their same venlafaxine hydrochloride tablet dose or a placebo. The relapse criteria used for this study were the criteria defined as a CGI Severity of Illness item score ≥ 4 was for up to 52 weeks. Patients receiving an immediate-release venlafaxine hydrochloride tablet dose of 100 ± 200 mg/day

gavage to mice for 18 months at doses up to 120 mg/kg per day, which was 1.7 times the maximum recommended human dose on a mg/m^2 basis. Venlafaxine was also given to rats by oral gavage for 24 months at doses up to 120 mg/kg per day. In rats receiving the 120 mg/kg dose, plasma concentrations of venlafaxine at necropsy were 1 times (male rats) and 6 times (female rats) the plasma concentrations of patients receiving the maximum recommended human dose. Plasma levels of the O-desmethyl metabolite were lower in rats than in patients receiving the maximum recommended dose. Tumors were not increased by venlafaxine treatment in mice or rats.

Mutagenesis: Venlafaxine and the major human metabolite, O-desmethylvenlafaxine (ODV), were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the Chinese hamster ovary/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was also not mutagenic or clastogenic in the *in vitro* BALB/c-3T3 mouse cell transformation assay, the sister chromatid exchange assay in cultured Chinese hamster ovary cells, or in the *in vivo* chromosomal aberration assay in rat bone marrow. ODV was not clastogenic in the *in vitro* Chinese hamster ovary cell chromosomal aberration assay, but elicited a clastogenic response in the *in vivo* chromosomal aberration assay in rat bone marrow.

Impairment of Fertility: Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 2 times the maximum recommended human dose on a mg/m^2 basis.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Venlafaxine did not cause malformations in offspring of rats or rabbits given doses up to 2.5 times (rat) or 4 times (rabbit) the maximum recommended human daily dose on a mg/m^2 basis. However, in rats, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation, when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. These effects occurred at 2.5 times (mg/m^2) the maximum human daily dose. The no effect dose for rat pup mortality was 0.25 times the human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-Teratogenic Effects: Neonates exposed to venlafaxine hydrochloride extended release, other SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), 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 PRECAUTIONS, Drug Interactions, *CNS-Active Drugs*). When treating a pregnant woman with venlafaxine hydrochloride extended release 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 venlafaxine on labor and delivery in humans is unknown.

Nursing Mothers: Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from venlafaxine hydrochloride extended release, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Two placebo-controlled trials in 766 pediatric patients with MDD have been conducted with venlafaxine hydrochloride extended release, and the data were not sufficient to support a claim for use in pediatric patients.

Anyone considering the use of venlafaxine hydrochloride extended release in a child or adolescent must balance the potential risks with the clinical need.

Although no studies have been designed to primarily assess venlafaxine hydrochloride extended release's impact on the growth, development, and maturation of children and adolescents, the studies that have been done suggest that venlafaxine hydrochloride extended release may adversely affect weight and height (see PRECAUTIONS, General, *Changes in Height* and *Changes in Weight*). Should the decision be made to treat a pediatric patient with venlafaxine hydrochloride extended release, regular monitoring of weight and height is recommended during treatment, particularly if it is to be continued long term. The safety of venlafaxine hydrochloride extended release treatment for pediatric patients has not been systematically assessed for chronic treatment longer than 6 months in duration.

In the studies conducted in pediatric patients (ages 6 to 17), the occurrence of blood pressure and cholesterol increases considered to be clinically relevant in pediatric patients was similar to that observed in adult patients. Consequently, the precautions for adults apply to pediatric patients (see WARNINGS, Sustained Hypertension, and PRECAUTIONS, General, *Serum Cholesterol Elevation*).

Geriatric Use: Approximately 4% (14/357) and 1% (10/819) of venlafaxine hydrochloride extended release treated patients in placebo-controlled premarketing major depressive disorder and Social Anxiety Disorder trials, respectively, were 65 years of age or over. Of 2,897 venlafaxine hydrochloride tablets treated patients in premarketing phase major depressive disorder studies, 12% (357) were 65 years of age or over. No overall differences in effectiveness or safety were observed between geriatric patients and younger patients, and other reported clinical experience generally has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including venlafaxine hydrochloride extended release, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see PRECAUTIONS, General, *Hyponatremia*).

The pharmacokinetics of venlafaxine and ODV are not substantially altered in the elderly (see CLINICAL PHARMACOLOGY). No dose adjustment is recommended for the elderly on the basis of age alone, although other clinical circumstances, some of which may be more common in the elderly, such as renal or hepatic impairment, may warrant a dose reduction (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS The information included in the Adverse Findings Observed in Short-Term Placebo-Controlled Studies with Venlafaxine Hydrochloride Extended Release subsection is based on data from a pool of three 8- and 12-week controlled clinical trials in major depressive disorder (includes two U.S. trials and one European trial), on data up to 12 weeks from a pool of five controlled clinical trials in Social Anxiety Disorder. Information on additional adverse events associated with venlafaxine hydrochloride extended release in the entire development program for the formulation and with venlafaxine hydrochloride tablets (the immediate release formulation of venlafaxine) is included in the Other Adverse Events Observed During the Premarketing Evaluation of Venlafaxine Hydrochloride Tablets and Venlafaxine Hydrochloride Extended Release subsection (see also WARNINGS and PRECAUTIONS).

Adverse Findings Observed in Short-Term Placebo-Controlled Studies with Venlafaxine Hydrochloride Extended Release: ***Adverse Events Associated with Discontinuation of Treatment:*** Approximately 11% of the 357 patients who received venlafaxine hydrochloride extended release capsules in placebo-controlled clinical trials for major depressive disorder discontinued treatment due to an adverse experience, compared with 6% of the 285 placebo-treated patients in those studies. Approximately 15% of the 819 patients who received venlafaxine hydrochloride extended release capsules in placebo-controlled clinical trials for Social Anxiety Disorder discontinued treatment due to an adverse experience, compared with 5% of the 695 placebo-treated patients in those studies. The most common events leading to discontinuation and considered to be drug-related (i.e., leading to discontinuation in at least 1% of the venlafaxine hydrochloride extended release treated patients at a rate at least twice that of placebo for either indication) are shown in Table 6.

Table 6. Common Adverse Events Leading to Discontinuation of Treatment in Placebo-Controlled Trials[1]

Percentage of Patients Discontinuing Due to Adverse Event				
Adverse Event	Major Depressive Disorder Indication[2]		Social Anxiety Disorder Indication[3]	
	Venlafaxine HCl ER n = 357	Placebo n = 285	Venlafaxine HCl ER n = 819	Placebo n = 695
Body as a Whole				
Asthenia			2%	<1%
Headache			1%	<1%
Digestive System				
Nausea	4%	<1%	3%	<1%
Anorexia	1%	<1%		
Dry Mouth	1%	0%		
Vomiting				
Nervous System				
Dizziness	2%	1%	2%	<1%
Insomnia	1%	<1%	2%	<1%
Somnolence	2%	<1%	2%	<1%
Nervousness				
Tremor				
Skin				
Sweating				
Urogenital System				
Impotence[4]			2%	0%

[1] Two of the major depressive disorder studies were flexible dose and one was fixed dose. Four of the Social Anxiety Disorder studies were flexible dose and one was fixed/flexible dose.

[2] In U.S. placebo-controlled trials for major depressive disorder, the following were also common events leading to discontinuation and were considered to be drug-related for venlafaxine hydrochloride extended release treated patients (% venlafaxine hydrochloride extended release [n = 192], % Placebo [n = 202]): hypertension (1%, <1%); diarrhea (1%, 0%); paresthesia (1%, 0%); tremor (1%, 0%); abnormal vision, mostly blurred vision (1%, 0%); and abnormal, mostly delayed, ejaculation (1%, 0%).

[3] In a 6-month placebo-controlled trial for Social Anxiety Disorder, the following was also a common event leading to discontinuation and was considered to be drug-related for venlafaxine hydrochloride extended release treated patients (% venlafaxine hydrochloride extended release [n = 257], % Placebo [n = 128]): depression (5%, 0%); libido decrease (1%, 0%); and nervousness (1%, 0%).

[4] Incidence is based on the number of men (venlafaxine hydrochloride extended release = 454, placebo = 357).

Adverse Events Occurring at an Incidence of 2% or More Among Venlafaxine Hydrochloride Extended Release-Treated Patients: Tables 7 and 8 enumerate the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of major depressive disorder (up to 12 weeks; dose range of 75 to 225 mg/day) and Social Anxiety Disorder (up to 12 weeks; dose range of 75 to 225 mg/day), respectively, in 2% or more of patients treated with venlafaxine hydrochloride extended release where the incidence in patients treated with venlafaxine hydrochloride extended release was greater than the incidence for the respective placebo-treated patients. The table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

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

Commonly Observed Adverse Events from Tables 7 and 8: Major Depressive Disorder: Note in particular the following adverse events that occurred in at least 5% of the venlafaxine hydrochloride extended release patients and at a rate at least twice that of the placebo group for all placebo-controlled trials for the major depressive disorder indication (Table 7): Abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, and anorexia), CNS complaints (dizziness, somnolence, and abnormal dreams), and sweating. In the two U.S. placebo-controlled trials, the following additional events occurred in at least 5% of venlafaxine hydrochloride extended release treated patients (n = 192) and at a rate at least twice that of the placebo group: Abnormalities of sexual function (impotence in men, anorgasmia in women, and libido decreased), gastrointestinal complaints (constipation and flatulence), CNS complaints (insomnia, nervousness, and tremor), problems of special senses (abnormal vision), cardiovascular effects (hypertension and vasodilatation), and yawning.

Social Anxiety Disorder: Note in particular the following adverse events that occurred in at least 5% of the venlafaxine hydrochloride extended release patients and at a rate at least twice that of the placebo group for the five placebo-controlled trials for the Social Anxiety Disorder indication (Table 8): asthenia, gastrointestinal complaints (anorexia, constipation, dry mouth, nausea), CNS complaints (insomnia, libido decreased, nervousness, somnolence, tremor), abnormalities of sexual function (abnormal ejaculation, impotence), yawn, and sweating.

In the 6-month trial, the following adverse events occurred twice as often in the 150 to 225 mg/day venlafaxine hydrochloride extended release group compared to the 75 mg/day venlafaxine hydrochloride extended release group and placebo: vasodilatation, libido decreased, tremor, yawn, abnormal vision, and impotence.

Table 7. Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Venlafaxine Hydrochloride Extended Release Clinical Trials in Patients with Major Depressive Disorder[1,2]

Body System Preferred Term	% Reporting Event Venlafaxine HCl ER (n = 357)	Placebo (n = 285)
Body as a Whole		
Asthenia	8%	7%
Cardiovascular System		
Vasodilatation[3]	4%	2%
Hypertension	4%	1%
Digestive System		
Nausea	31%	12%
Constipation	8%	5%
Anorexia	8%	4%
Vomiting	4%	2%
Flatulence	4%	3%
Metabolic/Nutritional		
Weight Loss	3%	0%
Nervous System		
Dizziness	20%	9%
Somnolence	17%	8%
Insomnia	17%	11%
Dry Mouth	12%	6%
Nervousness	10%	5%
Abnormal Dreams[4]	7%	2%
Tremor	5%	2%
Depression	3%	<1%
Paresthesia	3%	1%
Libido Decreased	3%	<1%
Agitation	3%	1%
Respiratory System		
Pharyngitis	7%	6%
Yawn	3%	0%
Skin		
Sweating	14%	3%
Special Senses		
Abnormal Vision[5]	4%	<1%
Urogenital System		
Abnormal Ejaculation (male)[6,7]	16%	<1%
Impotence[7]	4%	<1%
Anorgasmia (female)[8,9]	3%	<1%

[1] Incidence, rounded to the nearest %, for events reported by at least 2% of patients treated with venlafaxine hydrochloride extended release, except the following events which had an incidence equal to or less than placebo: abdominal pain, accidental injury, anxiety, back pain, bronchitis, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, pain, palpitation, rhinitis, and sinusitis.

[2] <1% indicates an incidence greater than zero but less than 1%.

[3] Mostly "hot flashes."

[4] Mostly "vivid dreams," "nightmares," and "increased dreaming."

[5] Mostly "blurred vision" and "difficulty focusing eyes."

[6] Mostly "delayed ejaculation."

[7] Incidence is based on the number of male patients.

[8] Mostly "delayed orgasm" or "anorgasmia."

[9] Incidence is based on the number of female patients.

Table 8. Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Venlafaxine Hydrochloride Extended Release Clinical Trials in Social Anxiety Disorder Patients[1,2]

Body System Preferred Term	% Reporting Event Venlafaxine HCl ER (n = 819)	Placebo (n = 695)
Body as a Whole		
Headache	38%	34%
Asthenia	19%	9%
Abdominal Pain	6%	4%
Accidental Injury	4%	3%
Cardiovascular System		
Hypertension	5%	3%
Vasodilatation[3]	3%	2%
Palpitation	3%	1%
Digestive System		
Nausea	31%	9%
Anorexia[4]	17%	2%
Constipation	9%	3%
Diarrhea	8%	6%
Dyspepsia	7%	6%
Vomiting	3%	2%
Metabolic/Nutritional		
Weight Loss	2%	<1%
Nervous System		
Insomnia	24%	8%
Somnolence	20%	8%
Dry Mouth	17%	4%
Dizziness	16%	8%
Nervousness	10%	5%
Libido Decreased	8%	2%
Anxiety	5%	4%
Tremor	5%	2%
Agitation	3%	1%
Abnormal Dreams[5]	3%	<1%
Twitching	3%	<1%
Respiratory System		
Yawn	5%	<1%
Skin		
Sweating	13%	4%
Special Senses		
Abnormal Vision[6]	4%	2%
Urogenital System		
Abnormal Ejaculation[7,8]	19%	<1%
Impotence[8]	6%	<1%
Orgasmic Dysfunction[9,10]	5%	<1%

continued

[1] Adverse events for which the venlafaxine hydrochloride extended release reporting rate was less than or equal to the placebo rate are not included. These events are: arthralgia, back pain, dysmenorrhea, flu syndrome, infection, pain, pharyngitis, rhinitis, and upper respiratory infection.

[2] <1% means greater than zero but less than 1%.

[3] Mostly "hot flashes."

[4] Mostly "decreased appetite" and "loss of appetite."

[5] Mostly "vivid dreams," "nightmares," and "increased dreaming."

[6] Mostly "blurred vision."

[7] Includes "delayed ejaculation" and "anorgasmia."

[8] Percentage based on the number of males (venlafaxine hydrochloride extended release = 454, placebo = 357).

[9] Includes "abnormal orgasm" and "anorgasmia."

[10] Percentage based on the number of females (venlafaxine hydrochloride extended release = 365, placebo = 338).

Vital Sign Changes: Venlafaxine hydrochloride extended release capsules treatment for up to 12 weeks in premarketing placebo-controlled major depressive disorder trials was associated with a mean final on-therapy increase in pulse rate of approximately 2 beats per minute, compared with 1 beat per minute for placebo. Venlafaxine hydrochloride extended release treatment for up to 12 weeks in premarketing placebo-controlled Social Anxiety Disorder trials was associated with a mean final on-therapy increase in pulse rate of approximately 3 beats per minute, compared with an increase of 1 beat per minute for placebo. (See the Sustained Hypertension and Elevations in Systolic and Diastolic Blood Pressure sections of WARNINGS for effects on blood pressure.)

In a flexible-dose study, with venlafaxine hydrochloride tablets doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, the mean pulse was increased by about 2 beats per minute compared with a decrease of about 1 beat per minute for placebo.

Laboratory Changes: *Serum Cholesterol:* Venlafaxine hydrochloride extended release capsules treatment for up to 12 weeks in premarketing placebo-controlled trials for major depressive disorder was associated with a mean final on-therapy increase in serum cholesterol concentration of approximately 1.5 mg/dL compared with a mean final decrease of 7.4 mg/dL for placebo. Venlafaxine hydrochloride extended release treatment for up to 12 weeks and up to 6 months in premarketing placebo-controlled Social Anxiety Disorder trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 7.9 mg/dL and 5.6 mg/dL, respectively, compared with mean final decreases of 2.9 and 4.2 mg/dL, respectively, for placebo.

Patients treated with venlafaxine hydrochloride tablets (the immediate-release form of venlafaxine) for at least 3 months in placebo-controlled 12-month extension trials had a mean final on-therapy increase in total cholesterol of 9.1 mg/dL compared with a decrease of 7.1 mg/dL among placebo-treated patients. This increase was duration dependent over the study period and tended to be greater with higher doses. Clinically relevant increases in serum cholesterol, defined as 1) a final on-therapy increase in serum cholesterol ≥ 50 mg/dL from baseline and to a value ≥ 261 mg/dL, or 2) an average on-therapy increase in serum cholesterol ≥ 50 mg/dL from baseline and to a value ≥ 261 mg/dL, were recorded in 5.3% of venlafaxine-treated patients and 0% of placebo-treated patients (see PRECAUTIONS, General, *Serum Cholesterol Elevation*).

Serum Triglycerides: Venlafaxine hydrochloride extended release treatment for up to 12 weeks in pooled premarketing Social Anxiety Disorder trials was associated with a mean final on-therapy increase in fasting serum triglyceride concentration of approximately 8.2 mg/dL, compared with a mean final increase of 0.4 mg/dL for placebo. Venlafaxine hydrochloride extended release treatment for up to 6 months in a premarketing Social Anxiety Disorder trial was associated with a mean final on-therapy increase in fasting serum triglyceride concentration of approximately 11.8 mg/dL, compared with a mean final on-therapy increase of 1.8 mg/dL for placebo.

ECG Changes: In a flexible-dose study, with venlafaxine hydrochloride tablet doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, the mean change in heart rate was 8.5 beats per minute compared with 1.7 beats per minute for placebo.

(See PRECAUTIONS, *Use in Patients with Concomitant Illness*.)

Other Adverse Events Observed During the Premarketing Evaluation of Venlafaxine Hydrochloride Tablets and Venlafaxine Hydrochloride Extended Release Capsules: During its premarketing assessment, multiple doses of venlafaxine hydrochloride extended release capsules were administered to 705 patients in Phase 3 major depressive disorder studies and venlafaxine hydrochloride tablets were administered to 96 patients. During its premarketing assessment, multiple doses of venlafaxine hydrochloride extended release capsules were also administered to 819 patients in Phase 3 Social Anxiety Disorder studies. In addition, in premarketing assessment of venlafaxine hydrochloride tablets, multiple doses were administered to 2,897 patients in Phase 2 to Phase 3 studies for major depressive disorder. The conditions and duration of exposure to venlafaxine in both development programs varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient (venlafaxine hydrochloride tablets only) and outpatient studies, fixed-dose, and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 7,212 patients exposed to multiple doses of either formulation of venlafaxine who experienced an event of the type cited on at least one occasion while receiving venlafaxine. All reported events are included except those already listed in Tables 7 and 8 and those events for which a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. It is important to emphasize that, although the events reported occurred during treatment with venlafaxine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as those occurring on one or more occasions 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.

Body as a Whole – Frequent: chest pain substernal, chills, fever, neck pain; *Infrequent:* face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; *Rare:* appendicitis, bacteremia, carcinoma, cellulitis, granuloma.

Cardiovascular System – Frequent: migraine, tachycardia; *Infrequent:* angina pectoris, arrhythmia, bradycardia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), postural hypotension, syncope; *Rare:* aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, sinus arrhythmia, thrombophlebitis.

Digestive System – Frequent: increased appetite; *Infrequent:* bruxism, colitis, dysphagia, tongue edema, eructation, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; *Rare:* abdominal distension, biliary pain, cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration.

Endocrine System – Rare: galactorrhea, goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis.

Hemic and Lymphatic System – Frequent: ecchymosis; *Infrequent:* anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia; *Rare:* basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia.

Metabolic and Nutritional – Frequent: edema, weight gain; *Infrequent:* alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipidemia, hypokalemia, SGOT (AST) increased, SGPT (ALT) increased, thirst; *Rare:* alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia.

Musculoskeletal System – Infrequent: arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; *Rare:* bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture.

Nervous System – Frequent: amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; *Infrequent:* akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, libido increased, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; *Rare:* abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barre Syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis.

Respiratory System – Frequent: cough increased, dyspnea; *Infrequent:* asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; *Rare:* atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea.

Skin and Appendages – Frequent: pruritus; *Infrequent:* acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; *Rare:* brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased.

Special Senses – Frequent: abnormality of accommodation, mydriasis, taste perversion; *Infrequent:* conjunctivitis, diplopia, dry eyes, eye pain, otitis media, parosmia, photophobia, taste loss; *Rare:* blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, hyperacusis, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis, visual field defect.

Urogenital System – Frequent: albuminuria, urination impaired; *Infrequent:* amenorrhea*, cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea*, menorrhagia*, metrorrhagia*, nocturia, breast pain, polyuria, pyuria, prostatic disorder*, prostatitis*, enlarged prostate* and prostate irritability*, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage*, vaginitis*; *Rare:* abortion*, anuria, breast discharge, breast engorgement, balanitis*, breast enlargement, endometriosis*, female lactation*, fibrocystic breast, calcium crystalluria, cervicitis*, orchitis*, ovarian cyst*, bladder pain, prolonged erection*, gynecomastia (male)*, hypomenorrhea*, kidney function abnormal, mastitis, menopause*, pyelonephritis, oliguria, salpingitis*, urolithiasis, uterine hemorrhage*, uterine spasm*, vaginal dryness*.

*Based on the number of men and women as appropriate.

Post-Marketing Reports: *Adverse Events:* Voluntary reports of other adverse events temporally associated with the use of venlafaxine that have been received since market introduction and that may have no causal relationship with the use of venlafaxine include the following: agranulocytosis, anaphylaxis, angioedema, aplastic anemia, catatonia, congenital anomalies, impaired coordination and balance, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; toxic epidermal necrolysis/Stevens-Johnson Syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), interstitial lung disease, involuntary movements, LDH increased, neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, renal failure, rhabdomyolysis, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and syndrome of inappropriate antidiuretic hormone secretion (usually in the elderly).

Drug Interactions: There have been reports of elevated clozapine levels that were temporally associated with adverse events, including seizures, following the addition of venlafaxine. There have been reports of increases in prothrombin time, partial thromboplastin time, or INR when venlafaxine was given to patients receiving warfarin therapy.

DRUG ABUSE AND DEPENDENCE **Controlled Substance Class:** Venlafaxine hydrochloride extended release capsules are not a controlled substance.

Physical and Psychological Dependence: *In vitro* studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors.

Venlafaxine was not found to have any significant CNS stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

Discontinuation effects have been reported in patients receiving venlafaxine (see DOSAGE AND ADMINISTRATION).

While venlafaxine has not been systematically studied in clinical trials 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 history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of venlafaxine (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE **Human Experience:** Among the patients included in the premarketing evaluation of venlafaxine hydrochloride extended release, there were two reports of acute overdosage with venlafaxine hydrochloride extended release in major depressive disorder trials, either alone or in combination with other drugs. One patient took a combination of 6 g of venlafaxine hydrochloride extended release and 2.5 mg of lorazepam. This patient was hospitalized, treated symptomatically, and recovered without any untoward effects. The other patient took 2.85 g of venlafaxine hydrochloride extended release. This patient reported paresthesia of all four limbs but recovered without sequelae.

There were no reports of acute overdose with venlafaxine hydrochloride extended release in Social Anxiety Disorder trials.

Among the patients included in the premarketing evaluation with venlafaxine hydrochloride tablets, there were 14 reports of acute overdose with venlafaxine, either alone or in combination with other drugs and/or alcohol. The majority of the reports involved ingestion in which the total dose of venlafaxine taken was estimated to be no more than several-fold higher than the usual therapeutic dose. The 3 patients who took the highest doses were estimated to have ingested approximately 6.75 g, 2.75 g, and 2.5 g. The resultant peak plasma levels of venlafaxine for the latter 2 patients were 6.24 and 2.35 mcg/mL, respectively, and the peak plasma levels of O-desmethylvenlafaxine were 3.37 and 1.30 mcg/mL, respectively. Plasma venlafaxine levels were not obtained for the patient who ingested 6.75 g of venlafaxine. All 14 patients recovered without sequelae. Most patients reported no symptoms. Among the remaining patients, somnolence was the most commonly reported symptom. The patient who ingested 2.75 g of venlafaxine was observed to have two generalized convulsions and a prolongation of QTc to 500 msec, compared with 405 msec at baseline. Mild sinus tachycardia was reported in two of the other patients.

In postmarketing experience, overdose with venlafaxine has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported.

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage as opposed to some characteristic(s) of venlafaxine-treated patients is not clear. Prescriptions for venlafaxine hydrochloride extended release should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Management of Overdosage: Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. 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 should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known.

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

DOSAGE AND ADMINISTRATION Venlafaxine hydrochloride extended release capsules should be administered in a single dose with food either in the morning or in the evening at approximately the same time each day. Each capsule should be swallowed whole with fluid and not divided, crushed, chewed, or placed in water, or it may be administered by carefully opening the capsule and sprinkling the entire contents on a spoonful of applesauce. This drug/food mixture should be swallowed immediately without chewing and followed with a glass of water to ensure complete swallowing of the pellets.

Initial Treatment: ***Major Depressive Disorder:*** For most patients, the recommended starting dose for venlafaxine hydrochloride extended release capsules is 75 mg/day, administered in a single dose. In the clinical trials establishing the efficacy of venlafaxine hydrochloride extended release capsules in moderately depressed outpatients, the initial dose of venlafaxine was 75 mg/day. For some patients, it may be desirable to start at 37.5 mg/day for 4 to 7 days, to allow new patients to adjust to the medication before increasing to 75 mg/day. While the relationship between dose and antidepressant response for venlafaxine hydrochloride extended release capsules has not been adequately explored, patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days, since steady-state plasma levels of venlafaxine and its major metabolites are achieved in most patients by day 4. In the clinical trials establishing efficacy, upward titration was permitted at intervals of 2 weeks or more; the average doses were about 140 to 180 mg/day (see CLINICAL PHARMACOLOGY, Clinical Trials).

It should be noted that, while the maximum recommended dose for moderately depressed outpatients is also 225 mg/day for venlafaxine hydrochloride tablets (the immediate release form of venlafaxine), more severely depressed inpatients in one study of the development program for that product responded to a mean dose of 350 mg/day (range of 150 to 375 mg/day). Whether or not higher doses of venlafaxine hydrochloride extended release capsules are needed for more severely depressed patients is unknown; however, the experience with venlafaxine hydrochloride extended release capsules doses higher than 225 mg/day is very limited. (See PRECAUTIONS, General, *Use in Patients with Concomitant Illness*.)

Social Anxiety Disorder (Social Phobia): The recommended dose is 75 mg/day, administered in a single dose. There was no evidence that higher doses confer any additional benefit. (See PRECAUTIONS, Use in Patients with Concomitant Illness.)

Switching Patients from Venlafaxine Hydrochloride Tablets: Depressed patients who are currently being treated at a therapeutic dose with venlafaxine hydrochloride tablets may be switched to venlafaxine hydrochloride extended release capsules at the nearest equivalent dose (mg/day), e.g., 37.5 mg venlafaxine 2 times a day to 75 mg venlafaxine hydrochloride extended release capsules once daily. However, individual dosage adjustments may be necessary.

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

Patients with Hepatic Impairment: Given the decrease in clearance and increase in elimination half-life for both venlafaxine and ODV that is observed in patients with hepatic cirrhosis and mild and moderate hepatic impairment compared with normal subjects (see CLINICAL PHARMACOLOGY), it is recommended that the total daily dose be reduced by 50% in patients with mild to moderate hepatic impairment. Since there was much individual variability in clearance between subjects with cirrhosis, it may be necessary to reduce the dose even more than 50%, and individualization of dosing may be desirable in some patients.

Patients with Renal Impairment: Given the decrease in clearance for venlafaxine and the increase in elimination half-life for both venlafaxine and ODV that is observed in patients with renal impairment (GFR = 10 to 70 mL/min) compared with normal subjects (see CLINICAL PHARMACOLOGY), it is recommended that the total daily dose be reduced by 25% to 50%. In patients undergoing hemodialysis, it is recommended that the total daily dose be reduced by 50%. Because there was much individual variability in clearance between patients with renal impairment, individualization of dosage may be desirable in some patients.

Elderly Patients: No dose adjustment is recommended for elderly patients solely on the basis of age. As with any drug for the treatment of major depressive disorder or Social Anxiety Disorder, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

Maintenance Treatment: There is no body of evidence available from controlled trials to indicate how long patients with major depressive disorder or Social Anxiety Disorder should be treated with venlafaxine hydrochloride extended release capsules.

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacological therapy beyond response to the acute episode. In one study, in which patients responding during 8 weeks of acute treatment with venlafaxine hydrochloride extended release capsules were assigned randomly to placebo or to the same dose of venlafaxine hydrochloride extended release capsules (75, 150, or 225 mg/day, qAM) during 26 weeks of maintenance treatment as they had received during the acute stabilization phase, longer-term efficacy was demonstrated. A second longer-term study has demonstrated the efficacy of venlafaxine hydrochloride tablets in maintaining a response in patients with recurrent major depressive disorder who had responded and continued to be improved during an initial 26 weeks of treatment and were then randomly assigned to placebo or venlafaxine hydrochloride tablets for periods of up to 52 weeks on the same dose (100 to 200 mg/day, on a b.i.d. schedule) (see CLINICAL PHARMACOLOGY, Clinical Trials). Based on these limited data, it is not known whether or not the dose of venlafaxine hydrochloride tablets/venlafaxine hydrochloride extended release capsules needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

In patients with Social Anxiety Disorder, venlafaxine hydrochloride extended release has been shown to be effective in a 6-month clinical trial. The need for continuing medication in patients with Social Anxiety Disorder who improve with venlafaxine hydrochloride extended release capsules treatment should be periodically reassessed.

Discontinuing Venlafaxine Hydrochloride Extended Release Capsules: Symptoms associated with discontinuation of venlafaxine hydrochloride extended release capsules, other SNRIs, and SSRIs, 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. In clinical trials with venlafaxine hydrochloride extended release capsules, tapering was achieved by reducing the daily dose by 75 mg at one week intervals. Individualization of tapering may be necessary.

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 venlafaxine hydrochloride extended release capsules. In addition, at least 7 days should be allowed after stopping venlafaxine hydrochloride extended release capsules before starting an MAOI (see CONTRAINDICATIONS and WARNINGS).

HOW SUPPLIED Venlafaxine Hydrochloride Extended Release Capsules are available containing venlafaxine hydrochloride, USP equivalent to 37.5 mg, 75 mg or 150 mg of venlafaxine.

The 37.5 mg capsule is a hard-shell gelatin capsule with a light-blue opaque cap and a white opaque body filled with white to off-white pellets and axially printed with **MYLAN** over **5131** in black ink on both the cap and the body. They are available as follows:

NDC 0378-5131-01
bottles of 100 capsules

NDC 0378-5131-05
bottles of 500 capsules

The 75 mg capsule is a hard-shell gelatin capsule with a lavender opaque cap and a white opaque body filled with white to off-white pellets and axially printed with **MYLAN** over **5132** in black ink on both the cap and the body. They are available as follows:

NDC 0378-5132-01
bottles of 100 capsules

NDC 0378-5132-05
bottles of 500 capsules

The 150 mg capsule is a hard-shell gelatin capsule with an orange opaque cap and white opaque body filled with white to off-white pellets and axially printed with **MYLAN** over **5133** in black ink on both the cap and the body. They are available as follows:

NDC 0378-5133-01
bottles of 100 capsules

NDC 0378-5133-05
bottles of 500 capsules

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

PHARMACIST: Dispense a Medication Guide with each prescription.

Mylan®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

MARCH 2011
VNLAER:R1mc

Medication Guide
Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your or your family member's healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
   - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
   - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

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

Revised 1/2008

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

/s/

LISA H KWOK
04/12/2011

LILLIE D GOLSON
04/12/2011

TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-789

Date of Submission: July 8, 2008

Applicant's Name: Mylan Pharmaceuticals, Inc.

Established Name: Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg (base), 75 mg (base) and 150 mg (base)

Proposed Proprietary Name: None

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No, tentative approval

1. CONTAINER - 100s, and 500s

   Satisfactory in draft as of the January 15, 2007 amendment.

2. PHYSICIAN INSERT

   Satisfactory in draft as of the July 8, 2008 amendment.

3. MEDICATION GUIDE

   Satisfactory in draft as of the July 8, 2008 amendment.

Revisions needed pre approval:

CONTAINER - Please ensure that you differentiate your product strengths by using boxing, contrasting colors, and/or some other means.

Please state on the principal display panel how the Medication Guide is provided. (see 21 CFR 201.24 (d)). See statement examples below:

1. "PHARMACIST: PLEASE DISPENSE WITH ATTACHED MEDICATION GUIDE" .
2. "PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY**".**

INSERT - Please revise "Venlafaxine Extended-release" to read "Venlafaxine Hydrochloride Extended-release Capsules" throughout your labeling.

Basis of Approval:
EXCLUSIVITY:
PATENT 20-699

Number	Expiration	Use Code	Description	*Patent certification*	Labeling Impact
4535186/*PED	12-13-07 / 6-13-08			III	None
5916923/*PED	6-28-13 / 12-28-13	U-398	Tx of GAD	MOU	Carved out
6274171/*PED	3-20-17 / 9-20-17			IV	None
6403120/*PED	3-20-17 / 9-20-17	U-451	Tx of Depression	IV	None
			Tx of GAD	MOU	Carved out
		U-535	Tx of SAD	IV	None

6419958/*PED	3-20-17 / 9-20-17	U-459	Tx of Depression	IV	None
			Tx of GAD	MOU	**Carved out**
		U-535	Tx of SAD	IV	None
6444708/*PED	6-28-13 / 12-28-13	U-398	Tx of GAD	MOU	**Carved out**
6310101	6-28-13	U-46	Tx of Panic Disorder	MOU	**Carved out**

Exclusivity

Code	Reference	Expiration	Labeling Impact
I-527	LONG TERM TREATMENT OF PANIC DISORDER	11/18/08	*None*
I-538	SHORT TERM TREATMENT OF PANIC DISORDER	11/18/08	*None*
I-561	LONG TERM TREATMENT OF SOCIALANXIETY DISORDER	12/14/10	*None-* Will not market until exclusivity expires

Was this approval based upon a petition? Yes, see FTR
What is the RLD on the 356(h) form: Effexor XR Capsules
ANDA Number: 20-699
ANDA Drug Name: Venlafaxine Extended-release Capsules
ANDA Firm: Wyeth Pharmaceuticals Inc.
Date of Approval of ANDA Insert and supplement #: S-081, May 23, 2008.
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug.

NOTE TO THE CHEMIST:

FOR THE RECORD: (Portions of review from previous reviewer)

1. MODEL LABELING
The RLD is NDA 20-699 Effexor XR (venlafaxine hydrochloride) Extended Release Capsules (NDA 20-699) by Wyeth Pharmaceuticals, Inc. The model RLD labeling used for this review is NDA 20-699/S-081 approved May 23, 2008.

2. PATENT/EXCLUSIVITIES
PATENT 20-699

Number	Expiration	Use Code	Description	*Patent certification*	Labeling Impact
4535186/*PED	12-13-07 / 6-13-08			III	None
5916923/*PED	6-28-13 / 12-28-13	U-398	Tx of GAD	MOU	Carved out
6274171/*PED	3-20-17 / 9-20-17			IV	None
6403120/*PED	3-20-17 / 9-20-17	U-451	Tx of Depression	IV	None
			Tx of GAD	MOU	Carved out
		U-535	Tx of SAD	IV	None
6419958/*PED	3-20-17 / 9-20-17	U-459	Tx of Depression	IV	None
			Tx of GAD	MOU	**Carved out**
		U-535	Tx of SAD	IV	None
6444708/*PED	6-28-13 / 12-28-13	U-398	Tx of GAD	MOU	**Carved out**
6310101	6-28-13	U-46	Tx of Panic Disorder	MOU	**Carved out**

EXCLUSIVITY

Code	Reference	Expiration	Labeling Impact
I-527	LONG TERM TREATMENT OF PANIC DISORDER	11/18/08	*None*
I-538	SHORT TERM TREATMENT OF PANIC DISORDER	11/18/08	*None*
I-561	LONG TERM TREATMENT OF SOCIALANXIETY DISORDER	12/14/10	*None*

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
Morgantown, WV 26505

4. USP: Drug product not subject to a USP 30 monograph (checked 8/17/07)

5. INACTIVE INGREDIENTS
The list of inactive ingredients in the DESCRIPTION section is accurate**.**

Per Chemistry Review #1
Iron oxide is a component of the black imprinting inks and per the following calculation, meets the requirements of 21 CFR 73.1200 of not more than 5mg elemental iron per day. Since the quantity of iron oxide in [redacted] (b) (4), the quantity of iron oxide in [redacted] (b) (4) ([redacted] (b) (4) %) is used in calculating the daily intake of elemental iron. Based on a maximum daily dose of 350mg venlafaxine HCl, the maximum daily intake of elemental iron is (see Section 3.2.P.1 for further information): 9 capsules (37.5mg strength) x [redacted] (b) (4)

6. PACKAGING CONFIGURATIONS
RLD – Bottles of 15s, 30s, 90s, 100s and Blister carton of 100s
ANDA –Bottles of 100s, 500s

7. DISPENSING/STORAGE TEMPERATURE STATEMENT COMPARISION
RLD: Store at controlled room temperature, 20C to 25 C (68F to 77F). Note to authorized dispenser: Each time Effexor XR is dispensed, give the patient the attached Medication Guide.
ANDA: Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]
Pharmacist: Please dispense with Medication Guide

8. CONTAINER/CLOSURE

Fill Size	Component Description
Bottle, 100's for 37.5 mg	[redacted] (b) (4)
Bottle, 100's for 75 mg	
Bottle, 100's for 150 mg	
Bottle, 500's for 37.5 mg	
Bottle, 500's for 75 mg	
Bottle, 500's for 150 mg	

9. IMPRINTINGS:
The capsule imprinting as described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95. has been accurately described.

37.5 mg: A light blue opaque cap / white opaque body, hard-shell gelatin capsules filled with white to

off-white pellets. The capsule is axially printed with MYLAN over 5131 in black ink on both the cap and the body.

75 mg: A lavender opaque cap / white opaque body, hard-shell gelatin capsule filled with white to off-white pellets. The capsule is axially printed with MYLAN over 5132 in black ink on both the cap and the body.

150 mg: An orange opaque / white opaque body, hard-shell gelatin capsule filled with white to off-white pellets. The capsule is axially printed with MYLAN over 5133 in black ink on both the cap and the body.

10. MEDICATION GUIDE

Mylan is participating in the distribution of Medication Guides with the Hibbert Group.

Date of review:	August 13, 2008	Date of submission: July 8, 2008
Primary Reviewer:	Michelle Dillahunt	Date
Team Leader:	Lillie Golson	Date

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

/s/

Michelle Dillahunt
8/18/2008 11:13:36 AM
LABELING REVIEWER

Lillie Golson
8/18/2008 04:14:16 PM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	78-789
Date of Submissions:	January 15, 2007
Applicant's Name:	Mylan Pharmaceuticals, Inc.
Established Name:	Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg (base), 75 mg (base) and 150 mg (base)
Proposed Proprietary Name:	None

Labeling Deficiencies:

1. CONTAINER - 100s, and 500s

   Please ensure that you differentiate your product strengths by using boxing, contrasting colors, and/or some other means.

2. PHYSICIAN INSERT

   a. Please revise "Venlafaxine Extended-release" to read "Venlafaxine Hydrochloride Extended-release Capsules" throughout your labeling.

   b. Due to changes in the insert labeling for the reference listed drug, Effexor® Extended-release capsules, (NDA 20-699/S-075), approved August 1, 2007, please revise your labeling to be in accordance with the insert labeling for the reference listed drug. You should address all exclusivities and patents listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") and revise your insert labeling according. The reference listed drug's insert labeling is located on the following website, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

In addition, please make the following changes;

   c. WARNINGS, Clinical Worsening and Suicide Risk, Table 1, change '[redacted] (b) (4) to Increases Compared to Placebo" and change [redacted] (b) (4) to "Decreases Compared to Placebo".

3. MEDICATION GUIDE

   a. Please indicate how many medication guides will accompany each container size and how they will be presented.

   b. If you plan to use a tear off pad for your medication guide, please provide a sample sheet electronically in final printed format.

   c. What is the most important information I should know about….

      Revise number 1 to read; "…..young adults within the first few months of treatment."

      Revise number 3 to read; "…an antidepressant medicine is started or when the dose is changed."Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug's labeling with all differences annotated and explained.

NOTE TO THE CHEMIST:

_____

FOR THE RECORD: (Portions of review from previous reviewer)

1. MODEL LABELING

The RLD is NDA 20-699 Effexor XR (venlafaxine hydrochloride) Extended Release Capsules (NDA 20-699) by Wyeth Pharmaceuticals, Inc. The model RLD labeling used for this review is NDA 20-699/S-075 approved August 1, 2007.

Background of most recently approved RLD labeling supplements:

- NDA 20-699/S-075 approved August 1, 2007; revised prescriber labeling and Medication Guide based upon the December 13, 2006 meeting of the Psychopharmacologic Drugs and Advisory Committee.
- NDA 20-699/S-069 approved February 7, 2007: new subsection under PRECAUTIONS/General "Interstitial Lung Disease and Eosinophilic Pneumoni"
- NDA 20-699/S-072 approved 10/20/06: provide for revisions to the OVERDOSAGE-Human Experience section of labeling
- NDA 20-699/S-071 approved 9/14/06: provides for revisions to the WARNINGS-Serotonin Syndrome, PRECAUTIONS-Information for Patients, and PRECAUTIONS-Drug Interactions sections
- NDA 20-699/S-056 approved 2/24/06: provides for the following changes
  Under WARNINGS, the following new section is added:
  Mydriasis - Mydriasis has been reported in association with venlafaxine; therefore patients with raised intraocularpressure or at risk of acute narrow-angle glaucoma (angleclosure glaucoma) should be monitored (see PRECAUTIONS, Information for Patients).
  Under PRECAUTIONS, the existing subsection entitled “Mydriasis” has been removed.
  Under PRECAUTIONS/Information for Patients, the following new section is added:
  Mydriasis - Mydriasis (prolonged dilation of the pupils of the eye) has been reported with venlafaxine. Patients should be advised to notify their physician if they have a history of glaucoma or a history of increased intraocular pressure (see WARNINGS).
- NDA 20-699/S-062/S-064 approved 1/12/06: provides for the labeling addition of the terms “liver necrosis” to the OVERDOSAGE/Human Experience section
- NDA 20-699/S-059 approved 12/1/05: provides for additional safety data for changes in weight, height, and appetite occurring in pediatric patients with social anxiety disorder treated with Effexor XR.

2. PATENT/EXCLUSIVITIES

PATENT 20-699

Number	Expiration	Use Code	Description	*Patent certification*	Labeling Impact
4535186/*PED	12-13-07 / 6-13-08			III	None
5916923/*PED	6-28-13 / 12-28-13	U-398	Tx of GAD	MOU	Carved out
6274171/*PED	3-20-17 / 9-20-17			IV	None
6403120/*PED	3-20-17 / 9-20-17	U-451	Tx of Depression	IV	None
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		U-535	Tx of SAD	IV	None
6419958/*PED	3-20-17 / 9-20-17	U-459	Tx of Depression	IV	None
			Tx of GAD	MOU	**Carved out**
		U-535	Tx of SAD	IV	None
6444708/*PED	6-28-13 / 12-28-13	U-398	Tx of GAD	MOU	**Carved out**

EXCLUSIVITY

Exclusivity	Indication	Expiration Date	Labeling Impact
I-261	Treatment of Social Anxiety	February 11,	None- exclusivity has **expired**

	Disorder	2006	

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
Morgantown, WV 26505

4. USP: Drug product not subject to a USP 30 monograph (checked 8/17/07)

5. INACTIVE INGREDIENTS
The list of inactive ingredients in the DESCRIPTION section is accurate.

Per Chemistry Review #1
Iron oxide is a component of the black imprinting inks and per the following calculation, meets the requirements of 21 CFR 73.1200 of not more than 5mg elemental iron per day. Since the quantity of iron oxide in [redacted] (b) (4), the quantity of iron oxide in [redacted] (b) (4) ([redacted] (b) (4) %) is used in calculating the daily intake of elemental iron. Based on a maximum daily dose of 350mg venlafaxine HCl, the maximum daily intake of elemental iron is (see Section 3.2.P.1 for further information): 9 capsules (37.5mg strength) x [redacted] (b) (4)

6. PACKAGING CONFIGURATIONS
RLD – Bottles of 15s, 30s, 90s, 100s and Blister carton of 100s
ANDA –Bottles of 100s, 500s

7. DISPENSING/STORAGE TEMPERATURE STATEMENT COMPARISION
RLD: Store at controlled room temperature, 20C to 25 C (68F to 77F). Note to authorized dispenser: Each time Effexor XR is dispensed, give the patient the attached Medication Guide.
ANDA: Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]
Pharmacist: Please dispense with Medication Guide

8. CONTAINER/CLOSURE

Fill Size	Component Description
Bottle, 100's for 37.5 mg	[redacted] (b) (4)
Bottle, 100's for 75 mg	[redacted]
Bottle, 100's for 150 mg	[redacted]
Bottle, 500's for 37.5 mg	[redacted]
Bottle, 500's for 75 mg	[redacted]

Fill Size	Component Description
	(b) (4)
Bottle, 500's for 150 mg	

9. IMPRINTINGS:

The capsule imprinting as described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95. has been accurately described.

37.5 mg: A light blue opaque cap / white opaque body, hard-shell gelatin capsules filled with white to off-white pellets. The capsule is axially printed with MYLAN over 5131 in black ink on both the cap and the body.

75 mg: A lavender opaque cap / white opaque body, hard-shell gelatin capsule filled with white to off-white pellets. The capsule is axially printed with MYLAN over 5132 in black ink on both the cap and the body.

150 mg: An orange opaque / white opaque body, hard-shell gelatin capsule filled with white to off-white pellets. The capsule is axially printed with MYLAN over 5133 in black ink on both the cap and the body.

Date of review:	August 17, 2007	Date of submission: January 15, 2007
Primary Reviewer:	Michelle Dillahunt	Date
Team Leader:	Lillie Golson	Date

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

/s/

Michelle Dillahunt
8/22/2007 11:47:58 AM
LABELING REVIEWER

Lillie Golson
8/23/2007 02:59:56 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 074650

CHEMISTRY REVIEWS

ANDA 78-789

Venlafaxine Hydrochloride Extended-Release Capsules 37.5 mg, 75 mg, and 150 mg

Mylan Pharmaceuticals Inc.

Zhigang Sun, Ph. D.

Office of Generic Drugs/Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 78-789

2. REVIEW #: 3

3. REVIEW DATE: 07-APR-2011

4. REVIEWER: Zhigang Sun, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	15-JAN-2007
Chemistry Review #1	17-JUL-2007
Amendment (deficiency response)	06-NOV-2007
Amendement	15-FEB-2008
T-con amendment	22-MAY-2008
T-con amendment	02-JUN-2008
T-con amendment (USP<467>)	23-JUN-2008
T-con amendment (USP<467>)	01-AUG-2008
T-con amendment (USP<467>)	19-AUG-2008
T-con amendment (in-process control)	20-OCT-2008
Chemistry Review #2 (TA)	17-NOV-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (CMC changes and final approval request)	04-APR-2011
T-con amendement	07-APR-2011

7. NAME & ADDRESS OF APPLICANT:

Name: Mylan Pharmaceuticals Inc.

Address: 781 Chestnut Ridge Road
P.O.Box 4310
Morgantown, WV 26504-4310
Representative: S. Wayne Talton, VP Regulatory Affairs
781 Chestnut Ridge Road
P.O.Box 4310
Morgantown, WV 26504-4310
Telephone: (304) 599-2525
Fax: (304) 285-6407

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Venlafaxine Hydrochloride Extended-Release Capsules

9. LEGAL BASIS FOR SUBMISSION:

The basis of Mylan's proposed ANDA for Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg, 75 mg, and 150 mg, is the reference listed drug, Effexor® (Venlafaxine) XR capsule, 37.5 mg, 75 mg, and 150 mg (NDA 20-699) manufactured by Wyeth Pharmaceuticals Inc. According to information published in the list of Approved Drug Products (electronic edition), Effexor® (Venlafaxine) XR capsule, 37.5 mg, 75 mg, and 150 mg is covered by the following U.S. Patents:

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020699	004	4535186	DEC 13,2007			
020699	004	4535186*PED	JUN 13,2008			
020699	004	5916923	JUN 28,2013			U-398
020699	004	5916923*PED	DEC 28,2013			U-398
020699	004	6274171	MAR 20,2017			
020699	004	6274171*PED	SEP 20,2017			
020699	004	6403120	MAR 20,2017			U-535
020699	004	6403120	MAR 20,2017			U-451
020699	004	6403120*PED	SEP 20,2017			U-451
020699	004	6403120*PED	SEP 20,2017			U-535
020699	004	6419958	MAR 20,2017			U-459
020699	004	6419958	MAR 20,2017			U-535
020699	004	6419958*PED	SEP 20,2017			U-459
020699	004	6419958*PED	SEP 20,2017			U-535
020699	004	6444708	JUN 28,2013			U-398
020699	004	6444708*PED	DEC 28,2013			U-398

Paragraph III Patent Certification: U.S. Patent No. 4535186 with its associated pediatric exclusivity

Paragraph IV Patent Certification: U.S. Patent Nos: 6274171, 6403120, and 6419958 with their associated pediatric exclusivities

Statements pursuant to 505(j)(2)(A)(viii): US Patent Nos. 5916923 and 6444708.

The marketing exclusivities listed for this product in the Orange Book are shown as follows:

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020699	001	I-538	Nov 18, 2008
020699	001	I-537	Nov 18, 2008
020699	001	I-561	Dec 14, 2010

10. PHARMACOL. CATEGORY: Antidepressant

11. DOSAGE FORM: Extended-Release Capsule
12. STRENGTH/POTENCY: 37.5 mg, 75 mg, and 150 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

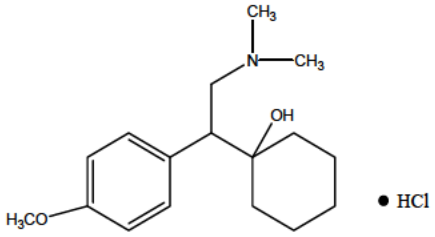
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (±)-1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride

Molecular Formula: $C_{17}H_{27}NO_2 \bullet HCl$
Molecular Weight: 313.9
CAS No.: 99300-78-4



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
17525	*II*	*Matrix Laboratories Ltd.*	*Venlafaxine HCl*	*1*	*Adequate*	*11/16/2010*	*By Ragine Maheswaran*
[redacted]				(b) (4)			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	7-APR-2011	OC
Methods Validation	Not Required		
Labeling	*Pending*		
Bioequivalence	Acceptable	16-APR-2008	Johnetta L. Farrar
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-789

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable per CMC perspective. DMF #17525 is adequate.

Labeling review is pending. All other disciplines acceptable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, Venlafaxine Hydrochloride, is a structurally novel antidepressant. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexanol hydrochloride or (±)-1-[α- [(dimethylamino)methyl]- p-methoxybenzyl] cyclohexanol hydrochloride. It is a white crystalline powder. It is very soluble in water, freely soluble in ethanol and chloroform.

Venlafaxine hydrochloride is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent. Capsules contain venlafaxine hydrochloride equivalent to 37.5 mg, 75 mg, or 150 mg venlafaxine. Inactive ingredients consist of ethylcellulose, hypromellose, polyethylene glycol, sugar spheres ((b) (4) and talc. In addition, each of the empty gelatin capsules contain the following: gelatin, sodium lauryl sulfate, and titanium dioxide and the following colorant agents:

37.5 mg – FD&C Blue No. 1, FD&C Red No. 3;
75 mg – D&C Red No. 28 and FD&C Blue No. 1;
150 mg – D&C Red No. 28, D&C Yellow No. 10 and FD&C Red No. 40.

The imprinting ink contains the following: black iron oxide, D&C Yellow No. 10 aluminum lake, FD&C Blue No. 1 aluminum lake, FD&C Blue No. 2 aluminum lake, FD&C Red No. 40 aluminum lake, propylene glycol, and shellac glaze.

B. Description of How the Drug Product is Intended to be Used

Venlafaxine Hydrochloride MR Capsules are indicated for the treatment of major depression disorder, social anxiety disorder, and panic disorder. The maximum dose was 225 mg/day.

C. Basis for Approvability or Not-Approval Recommendation

This ANDA is TA on 11/13/2008. In the 4/4/2011 amendment, the firm requested the final approval as well as several CMC changes for this ANDA. These CMC changes are acceptable. The updated DMF #17525 is adequate. Approvable is recommended per CMC perspective.

Labeling review is pending. All other disciplines acceptable.

cc: ANDA 78-789 Original
ANDA 78-789 DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/ZSun/4/7/2011
HFD-640/DSkanchy/4/8/2011
HFD-640/THinchliffe/4/8/11

F/T by

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TYPE OF LETTER: APPROVABLE pending satisfactory Labeling review.

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

/s/

ZHIGANG SUN
04/08/2011

DAVID J SKANCHY
04/08/2011

THOMAS O HINCHLIFFE
04/08/2011

ANDA 78-789

Venlafaxine Hydrochloride Extended-Release Capsules 37.5 mg, 75 mg, and 150 mg

Mylan Pharmaceuticals Inc.

Zhigang Sun, Ph. D.

Office of Generic Drugs/Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 78-789

2. REVIEW #: 2

3. REVIEW DATE: 29-APR-2008; 31-AUG-2008; 06-NOV-2008

4. REVIEWER: Zhigang Sun, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	15-JAN-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (deficiency response)	06-NOV-2007
Amendement	15-FEB-2008
T-con amendment	22-MAY-2008
T-con amendment	02-JUN-2008
T-con amendment (USP<467>)	23-JUN-2008
T-con amendment (USP<467>)	01-AUG-2008
T-con amendment (USP<467>)	19-AUG-2008
T-con amendment (in-process control)	20-OCT-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Mylan Pharmaceuticals Inc.
Address: 781 Chestnut Ridge Road
P.O.Box 4310
Morgantown, WV 26504-4310

Representative: S. Wayne Talton, VP Regulatory Affairs
781 Chestnut Ridge Road
P.O.Box 4310
Morgantown, WV 26504-4310
Telephone: (304) 599-2525
Fax: (304) 285-6407

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Venlafaxine Hydrochloride Extended-Release Capsules

9. LEGAL BASIS FOR SUBMISSION:

The basis of Mylan's proposed ANDA for Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg, 75 mg, and 150 mg, is the reference listed drug, Effexor® (Venlafaxine) XR capsule, 37.5 mg, 75 mg, and 150 mg (NDA 20-699) manufactured by Wyeth Pharmaceuticals Inc. According to information published in the list of Approved Drug Products (electronic edition), Effexor® (Venlafaxine) XR capsule, 37.5 mg, 75 mg, and 150 mg is covered by the following U.S. Patents:

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Paragraph III Patent Certification: U.S. Patent No. 4535186 with its associated pediatric exclusivity

Paragraph IV Patent Certification: U.S. Patent Nos: 6274171, 6403120, and 6419958 with their associated pediatric exclusivities

Statements pursuant to 505(j)(2)(A)(viii): US Patent Nos. 5916923 and 6444708.

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020699	001	I-561	Dec 14, 2010

10. PHARMACOL. CATEGORY: Antidepressant

11. DOSAGE FORM: Extended-Release Capsule
12. STRENGTH/POTENCY: 37.5 mg, 75 mg, and 150 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx ___ OTC

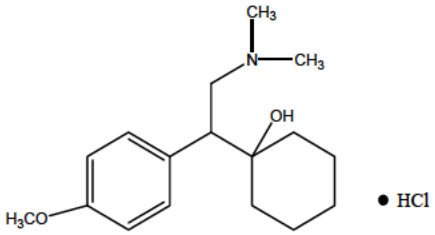
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name:	(±)-1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride
Molecular Formula:	$C_{17}H_{27}NO_2 \bullet HCl$
Molecular Weight:	313.9
CAS No.:	99300-78-4



17. RELATED/SUPPORTING DOCUMENTS:

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[redacted]				(b) (4)			

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3 – Reviewed previously and no revision since last review
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6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	21-MAY-2007	OC
Methods Validation	Not Required		
Labeling	*Acceptable*	*18-AUG-2008*	*Michelle Dillahunt*
Bioequivalence	*Acceptable*	*16-APR-2008*	*Johnetta L. Farrar*
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-789

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable per CMC perspective

Inspection of facilities is acceptable. Labeling review is acceptable. Bioequivalence review is acceptable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, Venlafaxine Hydrochloride, is a structurally novel antidepressant. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexanol hydrochloride or (±)-1-[α- [(dimethylamino)methyl]- p-methoxybenzyl] cyclohexanol hydrochloride. It is a white crystalline powder. It is very soluble in water, freely soluble in ethanol and chloroform.

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37.5 mg – FD&C Blue No. 1, FD&C Red No. 3;
75 mg – D&C Red No. 28 and FD&C Blue No. 1;
150 mg – D&C Red No. 28, D&C Yellow No. 10 and FD&C Red No. 40.

The imprinting ink contains the following: black iron oxide, D&C Yellow No. 10 aluminum lake, FD&C Blue No. 1 aluminum lake, FD&C Blue No. 2 aluminum lake, FD&C Red No. 40 aluminum lake, propylene glycol, and shellac glaze.

B. Description of How the Drug Product is Intended to be Used

Venlafaxine Hydrochloride MR Capsules are indicated for the treatment of major depression disorder, social anxiety disorder, and panic disorder. The maximum dose was 225 mg/day.

C. Basis for Approvability or Not-Approval Recommendation

Approvable per CMC perspective

Inspection of facilities is acceptable. Labeling review is acceptable. Bioequivalence review is acceptable.

cc: ANDA 78-789 Original
ANDA 78-789 DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/ZSun/11/6/2008
HFD-640/NYa/
HFD-640/THinchliffe/11/13/08

F/T by

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TYPE OF LETTER: APPROVABLE

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

/s/

Zhigang Sun
11/14/2008 10:35:40 AM
CHEMIST

Naiqi Ya
11/14/2008 03:56:40 PM
CHEMIST

Thomas Hinchliffe
11/17/2008 01:43:21 PM
CSO

ANDA 78-789

Venlafaxine Hydrochloride Extended-Release Capsules 37.5 mg, 75 mg, and 150 mg

Mylan Pharmaceuticals Inc.

Zhigang Sun, Ph. D.

Office of Generic Drugs/Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 78-789

2. REVIEW #: 1

3. REVIEW DATE: 11-JUN-2007

4. REVIEWER: Zhigang Sun, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	15-JAN-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Pharmaceuticals Inc.
Address:	781 Chestnut Ridge Road P.O.Box 4310 Morgantown, WV 26504-4310
Representative:	S. Wayne Talton, VP Regulatory Affairs 781 Chestnut Ridge Road P.O.Box 4310 Morgantown, WV 26504-4310
Telephone:	(304) 599-2525
Fax:	(304) 285-6407

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None

b) Non-Proprietary Name (USAN): Venlafaxine Hydrochloride Extended-Release Capsules

9. LEGAL BASIS FOR SUBMISSION:

The basis of Mylan's proposed ANDA for Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg, 75 mg, and 150 mg, is the reference listed drug, Effexor® (Venlafaxine) XR capsule, 37.5 mg, 75 mg, and 150 mg (NDA 20-699) manufactured by Wyeth Pharmaceuticals Inc. According to information published in the list of Approved Drug Products (electronic edition), Effexor® (Venlafaxine) XR capsule, 37.5 mg, 75 mg, and 150 mg is covered by the following U.S. Patents:

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
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020699	004	6403120	MAR 20,2017			U-451
020699	004	6403120*PED	SEP 20,2017			U-451
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Paragraph III Patent Certification: U.S. Patent No. 4535186 with its associated pediatric exclusivity

Paragraph IV Patent Certification: U.S. Patent Nos: 6274171, 6403120, and 6419958 with their associated pediatric exclusivities

Statements pursuant to 505(j)(2)(A)(viii): US Patent Nos. 5916923 and 6444708.

There is no unexpired marketing exclusivity listed for this product in the Orange Book.

10. PHARMACOL. CATEGORY: Antidepressant

11. DOSAGE FORM: Extended-Release Capsule

12. STRENGTH/POTENCY: 37.5 mg, 75 mg, and 150 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

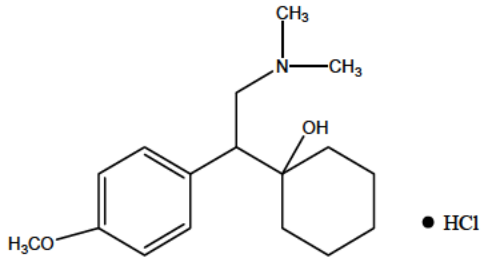
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name:	(±)-1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride
Molecular Formula:	$C_{17}H_{27}NO_2 \bullet HCl$
Molecular Weight:	313.9
CAS No.:	99300-78-4



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
17525	*II*	*Matrix Laboratories Ltd.*	*Venlafaxine HCl*	*1*	*Inadequate*	*1-JUN-2007*	*By Z. Sun*
[redacted]				(b) (4)			

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]				(b) (4)			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	21-MAY-2007	OC
Methods Validation	Not Required		
Labeling	Pending		
Bioequivalence	Pending dissolution review is pending		
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-789

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable due to minor deficiencies in the CMC sections

Inspection of facilities is acceptable. Labeling review is pending. Bioequivalence review is pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, Venlafaxine Hydrochloride, is a structurally novel antidepressant. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexanol hydrochloride or (±)-1-[α- [(dimethylamino)methyl]- p-methoxybenzyl] cyclohexanol hydrochloride. It is a white crystalline powder. It is very soluble in water, freely soluble in ethanol and chloroform.

Venlafaxine hydrochloride is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent. Capsules contain venlafaxine hydrochloride equivalent to 37.5 mg, 75 mg, or 150 mg venlafaxine. Inactive ingredients consist of ethylcellulose, hypromellose, polyethylene glycol, sugar spheres ([redacted] (b) (4) and talc. In addition, each of the empty gelatin capsules contain the following: gelatin, sodium lauryl sulfate, and titanium dioxide and the following colorant agents:

37.5 mg – FD&C Blue No. 1, FD&C Red No. 3;
75 mg – D&C Red No. 28 and FD&C Blue No. 1;
150 mg – D&C Red No. 28, D&C Yellow No. 10 and FD&C Red No. 40.

The imprinting ink contains the following: black iron oxide, D&C Yellow No. 10 aluminum lake, FD&C Blue No. 1 aluminum lake, FD&C Blue No. 2 aluminum lake, FD&C Red No. 40 aluminum lake, propylene glycol, and shellac glaze.

B. Description of How the Drug Product is Intended to be Used

Venlafaxine Hydrochloride MR Capsules are indicated for the treatment of major depression disorder, social anxiety disorder, and panic disorder. The maximum dose was 225 mg/day.

C. Basis for Approvability or Not-Approval Recommendation

Not approvable due to minor deficiencies in the CMC sections

Inspection of facilities is acceptable. Labeling review is pending. Bioequivalence review is pending.

cc: ANDA 78-789 Original
ANDA 78-789 DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/ZSun/6/11/2007
HFD-640/NYa/7/12/07
HFD-640/THinchliffe/7/12/07

F/T by TOH/7/12/07

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TYPE OF LETTER: NOT APPROVABLE - MINOR

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

/s/

Zhigang Sun
7/13/2007 02:09:32 PM
CHEMIST

Thomas Hinchliffe
7/16/2007 01:31:47 PM
CSO

Naiqi Ya
7/17/2007 10:24:28 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078789

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	078789	
Drug Product Name	Venlafaxine Hydrochloride Extended Release Capsules	
Strength(s)	Eq. to 37.5 mg, 75 mg, and 150 mg base	
Applicant Name	Mylan Pharmaceuticals	
Address	781 Chestnut Ridge Road, Morgantown, WV 26505	
Applicant's Point of Contact	S. Wayne Talton, Vice President, Regulatory Affairs	
Contact's Telephone Number	304-599-2595 ext. 6551	
Contact's Fax Number	304-285-6407	
Original Submission Date(s)	15 January, 2007	
Submission Date(s) of Amendment(s) Under Review	15 February 2008 13 April, 2011	
Reviewer	Svetlana Cherstniakova, Ph.D.	
Study Number (s)	VENL-0548	VENL-0549
Study Type (s)	Fed	Sprinkle
Strength (s)	150 mg	150 mg
Clinical Site	Kendle International Inc.	
Clinical Site Address	763 Chestnut Ridge Road, Morgantown, WV 26505	
Analytical Site	Mylan Pharmaceuticals - Bioanalytical Division	
Analytical Site Address	3711 Collins Ferry Road, Morgantown, WV 26505	
OVERALL REVIEW RESULT	**ADEQUATE**	
DSI REPORT RESULT	**ADEQUATE**	

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**DISSOLUTION**	**37.5 MG**	**ADEQUATE**
1	**DISSOLUTION**	**75 MG**	**ADEQUATE**
1	**DISSOLUTION**	**150 MG**	**ADEQUATE**
1	**FED STUDY**	**150 MG**	**ADEQUATE**
1	**FED SPRINKLE STUDY**	**150 MG**	**ADEQUATE**

Review of a Study Amendment

1 EXECUTIVE SUMMARY

This is a bioequivalence amendment for Venlafaxine Hydrochloride Extended Release Capsules, 37.5 mg, 75 mg and 150 mg in response to the FDA bioequivalence comments provided by facsimile dated April 13, 2011. The original submission, dated January 15, 2007, contained acceptable fed and fed sprinkle bioequivalence (BE) studies comparing a test product Venlafaxine Hydrochloride Extended Release Capsules, 150 mg to the corresponding reference product Effexor XR® (venlafaxine hydrochloride), eq. 150 mg base.[1] The firm has conducted acceptable comparative dissolution testing on all strengths using the FDA-recommended dissolution method.[2] On February 15, 2008, the firm acknowledged the FDA-recommended dissolution method and specifications.[3]

In the current amendment, the firm submitted the results of comparative in vitro alcohol dose dumping testing on venlafaxine hydrochloride extended release capsules and the RLD using various concentrations of ethanol in the dissolution medium. The results of in vitro alcohol dose dumping study comparing Mylan's Venlafaxine Hydrochloride Extended Release Capsules and the RLD show similar drug release (% dissolved data) at 2 hours in 40% ethanol. Therefore, Mylan's Venlafaxine ER Capsules, 37.5 mg, 75 mg and 150 mg are therapeutic equivalent to Effexor XR® Capsules, 37.5 mg, 75 mg and 150 mg. The firm's in vitro alcohol dose dumping testing is acceptable.

The application is acceptable with no deficiencies.

[1] DARRTS N 078789 REV-BIOEQ-01(General Review), 01/15/2007
[2] DARRTS N 078789 REV-BIOEQ-02(Dissolution Review), 08/22/2007
[3] DARRTS N 078789 REV-BIOEQ-01(General Review), 04/16/2008

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3 SUBMISSION SUMMARY

3.1 Review of Submission

FDA Comment:

Due to concern of dose dumping for this drug product when ingested with alcoholic beverages, the Agency currently requests that you conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium. The DBE recommends the following testing conditions:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus I (basket) at 100 rpm, with and without the alcohol (see below):

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

All strengths of the test and the corresponding reference products must be tested accordingly and data must be provided on individual unit, means, range and %CV including f2 similarity values and dissolution plots.

Firm's Response:
Mylan has conducted additional in vitro dissolution testing with alcohol. The data suggests that both Mylan's Venlafaxine Hydrochloride Extended-release Capsules and Effexor XR® show increased dissolution as a result of the incorporation of alcohol into the dissolution medium.

The in vitro alcohol dose-dumping testing data for the venlafaxine hydrochloride extended release capsules and the RLD are shown below:

Dissolution Conditions	**Apparatus:**	**1 (basket)**
	Speed of Rotation:	**100 rpm**
	Medium:	**0.1N HCl with 0% Ethanol**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	Mylan Pharmaceuticals Inc., Chemistry Research and Development Laboratories, 3711 Collins Ferry Road, Morgantown, WV, 26505	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)								Study Report Location
						15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	
N/A	4/18/11	Venlafaxine HCl Extended-release Capsules Lot R1P2473 Manufacture Date – 02/02/06	37.5 mg Capsules	12	Mean	0%	0%	0%	0%	1%	4%	9%	16%	Section 2.7
					Range	0-1%	0-1%	0-1%	0-1%	1-2%	3-5%	8-11%	15-17%	
					%CV	159.6%	151.6%	159.4%	66.0%	22.8%	14.4%	8.5%	5.3%	
N/A	4/18/11	Effexor XR® Lot E57192 Expiration Date – 01/13	37.5 mg Capsules	12	Mean	2%	2%	3%	4%	6%	8%	10%	13%	
					Range	0-3%	1-4%	1-5%	2-6%	4-8%	6-10%	8-13%	10-15%	
					%CV	44.2%	38.6%	31.4%	25.7%	21.3%	15.6%	15.3%	12.3%	
N/A	4/18/11	Venlafaxine HCl Extended-release Capsules Lot R1P2474 Manufacture Date – 02/02/06	75 mg Capsules	12	Mean	0%	0%	0%	0%	1%	4%	10%	16%	
					Range	0-0%	0-1%	0-1%	0-1%	1-2%	4-5%	9-11%	15-18%	
					%CV	121.3%	124.4%	92.4%	49.4%	23.1%	11.8%	7.2%	5.1%	
N/A	4/20/11	Effexor XR® Lot E26432 Expiration Date – 05/13	75 mg Capsules	12	Mean	0%	1%	2%	3%	5%	7%	10%	12%	
					Range	0-1%	0-1%	1-3%	2-5%	4-7%	6-10%	8-12%	10-15%	
					%CV	56.6%	47.3%	36.3%	26.1%	20.3%	16.8%	14.2%	12.6%	

Dissolution Conditions	**Apparatus:**	**1 (basket)**
	Speed of Rotation:	**100 rpm**
	Medium:	**0.1N HCl with 0% Ethanol**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	Mylan Pharmaceuticals Inc., Chemistry Research and Development Laboratories, 3711 Collins Ferry Road, Morgantown, WV, 26505	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)								Study Report Location
						15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	
N/A	4/18/11	Venlafaxine HCl Extended-release Capsules Lot R1P2475 Manufacture Date – 02/02/06	150 mg Capsules	12	Mean	0%	0%	0%	0%	2%	5%	10%	17%	Section 2.7
					Range	0-0%	0-0%	0-0%	0-1%	1-2%	4-5%	10-11%	16-17%	
					%CV	123.8%	92.3%	57.4%	25.1%	8.9%	4.4%	3.1%	1.9%	
N/A	4/18/11	Effexor XR® Lot E71086S Expiration Date – 08/12	150 mg Capsules	12	Mean	0%	1%	2%	3%	6%	8%	11%	14%	
					Range	0-1%	0-1%	1-2%	3-4%	5-7%	7-9%	10-12%	13-16%	
					%CV	61.3%	31.5%	14.1%	9.1%	8.4%	7.7%	6.5%	6.1%	

Dissolution Conditions	**Apparatus:**	**1 (basket)**
	Speed of Rotation:	**100 rpm**
	Medium:	**0.1N HCl with 5% Ethanol**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	Mylan Pharmaceuticals Inc., Chemistry Research and Development Laboratories, 3711 Collins Ferry Road, Morgantown, WV, 26505	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)								Study Report Location
						15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	
N/A	4/17/11	Venlafaxine HCl Extended-release Capsules Lot R1P2473 Manufacture Date – 02/02/06	37.5 mg Capsules	12	Mean	0%	0%	0%	1%	2%	5%	11%	18%	Section 2.7
					Range	0-1%	0-1%	0-1%	0-1%	1-3%	4-7%	10-13%	16-19%	
					%CV	113.4%	107.1%	93.0%	39.6%	25.8%	13.3%	8.0%	5.0%	
N/A	4/17/11	Effexor XR® Lot E57192 Expiration Date – 01/13	37.5 mg Capsules	12	Mean	1%	2%	2%	4%	5%	7%	9%	11%	
					Range	0-3%	1-3%	1-5%	2-6%	3-8%	4-10%	5-13%	7-15%	
					%CV	63.8%	50.2%	39.7%	32.3%	27.5%	23.9%	21.7%	18.6%	
N/A	4/17/11	Venlafaxine HCl Extended-release Capsules Lot R1P2474 Manufacture Date – 02/02/06	75 mg Capsules	12	Mean	0%	0%	0%	1%	2%	6%	13%	19%	
					Range	0-0%	0-0%	0-1%	0-1%	2-2%	5-7%	11-14%	17-20%	
					%CV	120.2%	104.2%	59.3%	25.6%	12.8%	9.4%	5.7%	4.2%	
N/A	4/21/11	Effexor XR® Lot E26432 Expiration Date – 05/13	75 mg Capsules	12	Mean	0%	1%	2%	4%	5%	7%	9%	11%	
					Range	0-1%	1-2%	1-3%	3-5%	4-7%	6-9%	7-11%	9-14%	
					%CV	43.6%	32.3%	22.3%	17.9%	14.9%	13.6%	12.8%	12.2%	

Dissolution Conditions	Apparatus:	1 (basket)
	Speed of Rotation:	100 rpm
	Medium:	0.1N HCl with 5% Ethanol
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Mylan Pharmaceuticals Inc., Chemistry Research and Development Laboratories, 3711 Collins Ferry Road, Morgantown, WV, 26505	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)								Study Report Location
						15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	
N/A	4/17/11	Venlafaxine HCl Extended-release Capsules Lot R1P2475 Manufacture Date – 02/02/06	150 mg Capsules	12	Mean	0%	0%	0%	1%	2%	6%	13%	19%	Section 2.7
					Range	0-0%	0-0%	0-1%	0-1%	2-3%	6-7%	12-14%	19-20%	
					%CV	151.2%	121.8%	79.9%	21.1%	9.1%	5.2%	3.5%	2.9%	
N/A	4/17/11	Effexor XR® Lot E71086S Expiration Date – 08/12	150 mg Capsules	12	Mean	0%	1%	2%	4%	6%	8%	11%	13%	
					Range	0-1%	1-2%	2-3%	3-5%	5-7%	7-10%	10-12%	12-15%	
					%CV	73.6%	35.1%	16.8%	11.1%	9.1%	7.7%	6.5%	5.6%	

Dissolution Conditions	**Apparatus:**	**1 (basket)**
	Speed of Rotation:	**100 rpm**
	Medium:	**0.1N HCl with 20% Ethanol**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	Mylan Pharmaceuticals Inc., Chemistry Research and Development Laboratories, 3711 Collins Ferry Road, Morgantown, WV, 26505	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)								Study Report Location
						15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	
N/A	4/16/11	Venlafaxine HCl Extended-release Capsules Lot R1P2473 Manufacture Date – 02/02/06	37.5 mg Capsules	12	Mean	0%	0%	1%	5%	16%	28%	37%	44%	Section 2.7
					Range	0-0%	0-1%	0-2%	4-6%	15-17%	27-29%	36-39%	43-46%	
					%CV	110.9%	80.5%	32.1%	12.2%	4.1%	3.2%	2.4%	2.2%	
N/A	4/17/11	Effexor XR® Lot E57192 Expiration Date – 01/13	37.5 mg Capsules	12	Mean	2%	2%	4%	6%	9%	11%	15%	19%	
					Range	0-4%	1-5%	2-7%	4-9%	7-11%	9-13%	11-17%	15-21%	
					%CV	61.3%	44.2%	25.5%	16.1%	11.7%	11.2%	11.1%	11.0%	
N/A	4/16/11	Venlafaxine HCl Extended-release Capsules Lot R1P2474 Manufacture Date – 02/02/06	75 mg Capsules	12	Mean	0%	0%	1%	4%	16%	27%	37%	44%	
					Range	0-0%	0-0%	0-1%	4-5%	14-17%	26-29%	35-39%	42-46%	
					%CV	111.6%	71.0%	30.0%	9.7%	5.0%	3.4%	3.0%	2.9%	
N/A	4/20/11	Effexor XR® Lot E26432 Expiration Date – 05/13	75 mg Capsules	12	Mean	0%	1%	3%	6%	8%	11%	15%	20%	
					Range	0-1%	1-2%	3-4%	4-7%	6-10%	8-13%	12-17%	17-23%	
					%CV	37.0%	21.0%	15.8%	16.0%	15.9%	14.6%	11.6%	8.5%	

Dissolution Conditions	**Apparatus:**	**1 (basket)**
	Speed of Rotation:	**100 rpm**
	Medium:	**0.1N HCl with 20% Ethanol**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	Mylan Pharmaceuticals Inc., Chemistry Research and Development Laboratories, 3711 Collins Ferry Road, Morgantown, WV, 26505	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)								Study Report Location
						15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	
N/A	4/17/11	Venlafaxine HCl Extended-release Capsules Lot R1P2475 Manufacture Date – 02/02/06	150 mg Capsules	12	Mean	0%	0%	1%	5%	17%	29%	39%	46%	Section 2.7
					Range	0-0%	0-0%	1-1%	4-6%	16-19%	28-31%	37-41%	44-48%	
					%CV	110.7%	57.2%	16.3%	9.1%	5.3%	3.2%	2.6%	2.3%	
N/A	4/17/11	Effexor XR® Lot E71086S Expiration Date – 08/12	150 mg Capsules	12	Mean	1%	2%	4%	7%	10%	14%	18%	25%	
					Range	0-1%	1-2%	4-5%	6-8%	8-11%	12-15%	17-20%	23-26%	
					%CV	31.2%	16.5%	9.7%	9.1%	7.9%	6.0%	4.4%	4.2%	

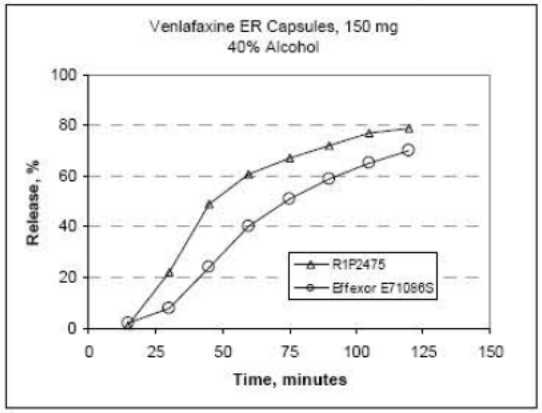
Dissolution Conditions	**Apparatus:**	**1 (basket)**
	Speed of Rotation:	**100 rpm**
	Medium:	**0.1N HCl with 40% Ethanol**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	Mylan Pharmaceuticals Inc., Chemistry Research and Development Laboratories, 3711 Collins Ferry Road, Morgantown, WV, 26505	

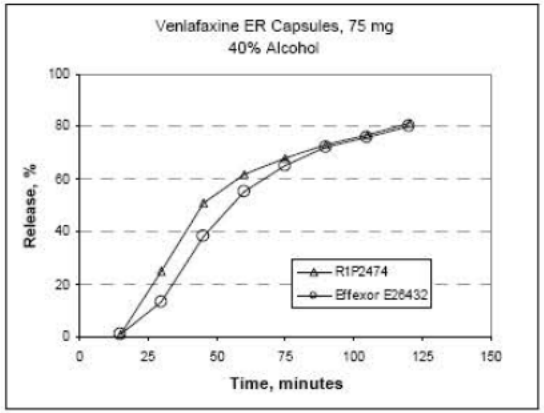
Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)								Study Report Location
						15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	
N/A	4/15/11	Venlafaxine HCl Extended-release Capsules Lot R1P2473 Manufacture Date – 02/02/06	37.5 mg Capsules	12	Mean	1%	23%	48%	59%	65%	70%	74%	77%	Section 2.7
					Range	0-2%	20-28%	45-55%	56-66%	63-72%	68-77%	71-81%	75-84%	
					%CV	36.2%	8.7%	6.0%	5.1%	4.3%	3.8%	3.7%	3.4%	
N/A	4/15/11	Effexor XR® Lot E57192 Expiration Date – 01/13	37.5 mg Capsules	12	Mean	2%	7%	21%	36%	49%	57%	63%	68%	
					Range	1-3%	5-8%	16-25%	29-40%	42-51%	51-59%	59-65%	65-70%	
					%CV	37.1%	16.5%	11.3%	9.0%	5.5%	3.8%	2.8%	2.3%	
N/A	4/15/11	Venlafaxine HCl Extended-release Capsules Lot R1P2474 Manufacture Date – 02/02/06	75 mg Capsules	12	Mean	1%	25%	51%	62%	68%	73%	77%	81%	
					Range	1-1%	22-30%	49-54%	59-64%	65-71%	70-76%	74-80%	77-83%	
					%CV	25.4%	9.3%	3.3%	2.7%	2.8%	2.6%	2.4%	2.4%	
N/A	4/20/11	Effexor XR® Lot E26432 Expiration Date – 05/13	75 mg Capsules	12	Mean	1%	13%	38%	55%	65%	72%	76%	80%	
					Range	1-3%	10-21%	34-48%	51-62%	61-72%	67-77%	71-82%	75-85%	
					%CV	33.8%	20.3%	10.4%	5.9%	4.2%	3.4%	3.0%	2.9%	

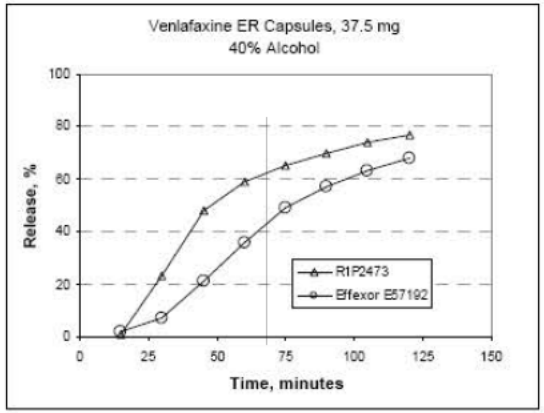
Dissolution Conditions	**Apparatus:**	**1 (basket)**
	Speed of Rotation:	**100 rpm**
	Medium:	**0.1N HCl with 40% Ethanol**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	Mylan Pharmaceuticals Inc., Chemistry Research and Development Laboratories, 3711 Collins Ferry Road, Morgantown, WV, 26505	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)								Study Report Location
						15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	
N/A	4/15/11	Venlafaxine HCl Extended-release Capsules Lot R1P2475 Manufacture Date – 02/02/06	150 mg Capsules	12	Mean	1%	22%	49%	61%	67%	72%	77%	79%	Section 2.7
					Range	1-1%	20-24%	48-51%	59-63%	66-69%	70-73%	74-81%	75-81%	
					%CV	19.8%	5.3%	1.8%	1.7%	1.4%	1.3%	2.1%	2.6%	
N/A	4/15/11	Effexor XR® Lot E71086S Expiration Date – 08/12	150 mg Capsules	12	Mean	2%	8%	24%	40%	51%	59%	65%	70%	
					Range	1-2%	7-9%	21-26%	36-43%	47-54%	56-62%	62-68%	67-72%	
					%CV	13.1%	9.6%	7.2%	5.0%	3.9%	3.2%	2.7%	2.4%	

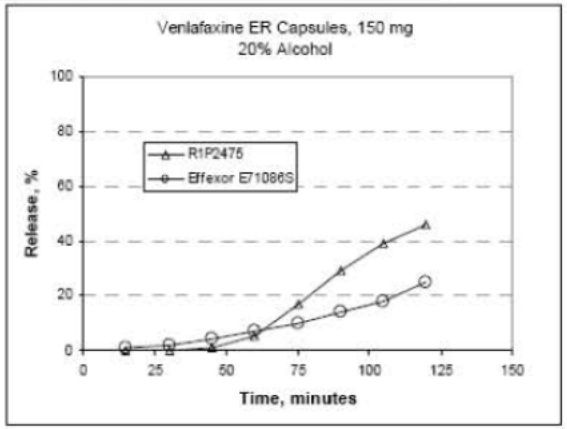
40% Alcohol in 0.1N HCl

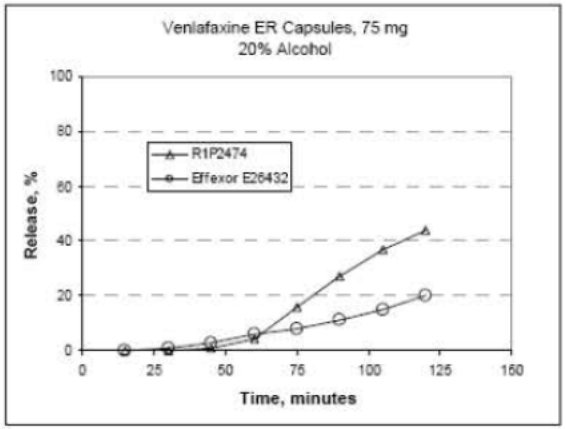


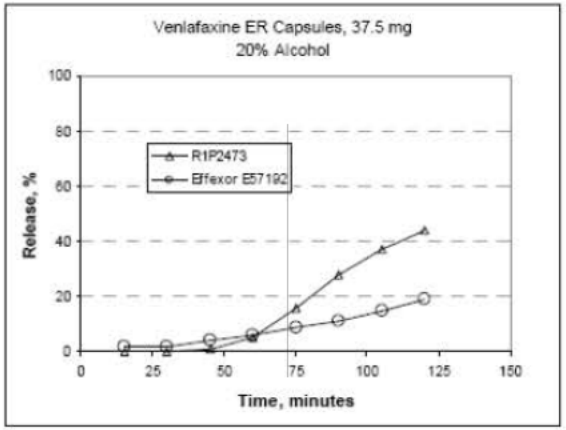




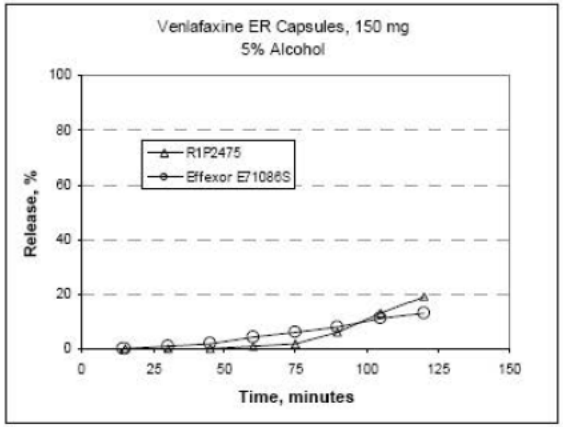
20% Alcohol in 0.1N HCl

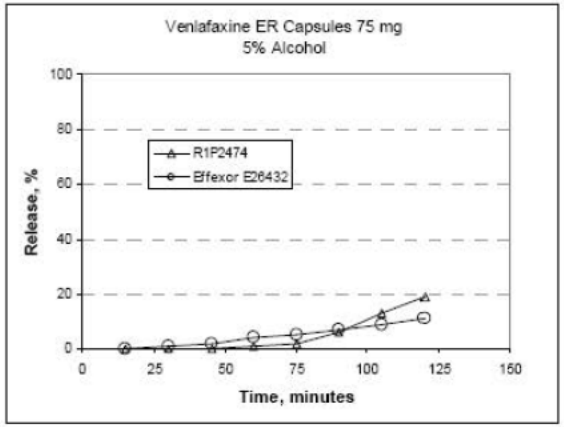


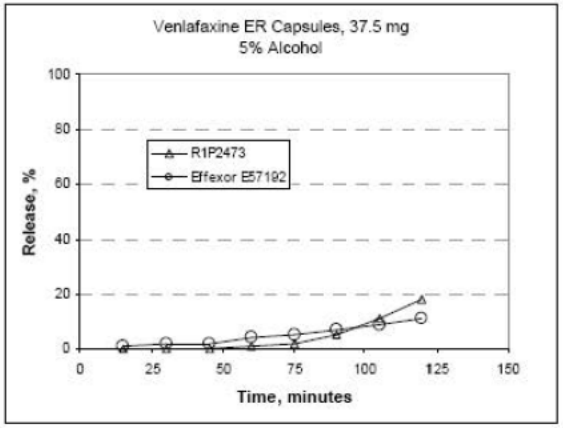




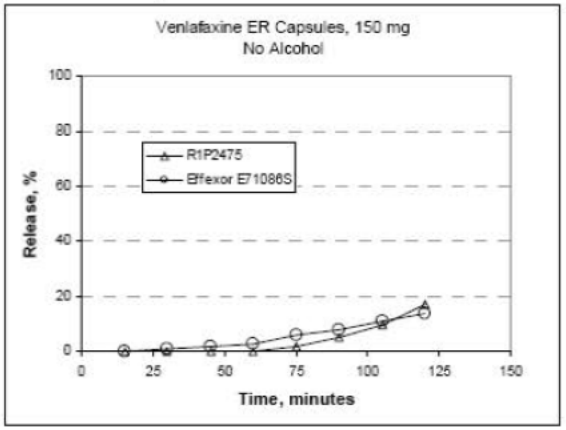
5% Alcohol in 0.1N HCl

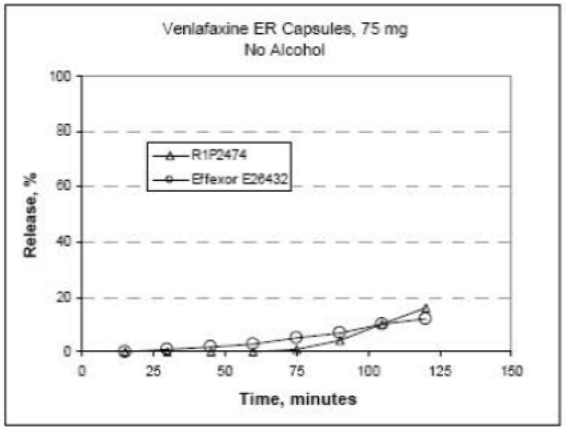


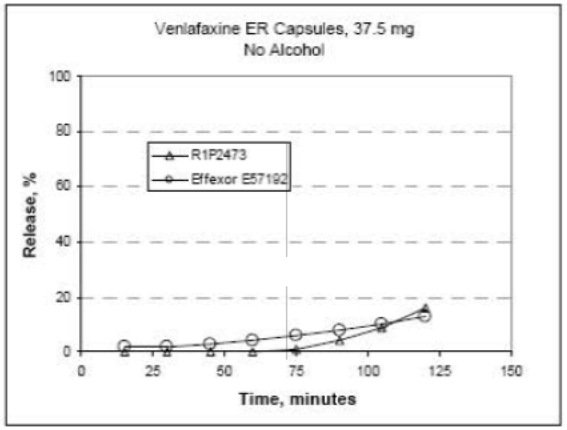




0.1N HCl







Reviewer's Comments:

Following the OGD recommendation, the firm conducted in vitro alcohol dose dumping study for all strengths in 900 mL of 0.1 N HCl in the absence and presence of various concentrations of alcohol (5, 20 and 40%). The results from the alcohol dumping study are summarized in the table below.

Summary of in vitro alcohol dose-dumping testing results in various ethanol concentrations (0%, 5%, 20% and 40%) for the Venlafaxine HCl ER capsules:

	Medium			
Strength	0.1 N HCl and 0% Ethanol	0.1 N HCl and 5% Ethanol	0.1 N HCl and 20% Ethanol	0.1 N HCl and 40% Ethanol
37.5 mg capsule	Mean % Drug Release (At 2 hours)			
Test Mean (Range, RSD)	16 15-17%, 5.3%	18 16-19%, 5.0%	**44** 43-46%, 2.2%	77 75-84%, 3.4%
Reference Mean (Range, RSD)	13 10-15%, 12.3%	11 7-15%, 18.6%	**19** 15-21%, 11.0%	68 65-70%, 2.3%
75 mg capsule	Mean % Drug Release (At 2 hours)			
Test Mean (Range, RSD)	16 15-18%, 5.1%	19 17-20%, 4.2%	**44** 42-46%, 2.9%	81 77-83%, 2.4%
Reference Mean (Range, RSD)	12 10-15%, 12.6%	11 9-14%, 12.2%	**20** 17-23%, 8.5%	80 75-85%, 2.9%
150 mg capsule	Mean % Drug Release (At 2 hours)			
Test Mean (Range, RSD)	17 16-17%, 1.9%	19 19-20%, 2.9%	**46** 44-48%, 2.3%	79 75-81%, 2.6%
Reference Mean (Range, RSD)	14 13-16%, 6.1%	13 12-15%, 5.6%	**25** 23-26%, 4.2%	70 67-72%, 2.4%

The data show the most increase of drug release (% dissolved) for the test product compared to the RLD at 2 hours in 20% ethanol i.e., 44% (Test) versus 19% (RLD) venlafaxine dissolved for 37.5 mg strength, 44% (Test) versus 20% (RLD) venlafaxine dissolved for 75 mg strength, and 46% (Test) versus 25 % (RLD) venlafaxine dissolved for 150 mg strength. At 2 hours in 20% ethanol, the test product showed 170 - 175% increase of venlafaxine release compared to the values in the absence of alcohol, while the reference product showed 40-46% increase of venlafaxine release compared to the values in the absence of alcohol.

Previously the medical team concluded, that increase of drug release (% dissolved) at 2 hours in 20% ethanol of the generic formulation of Venlafaxine Hydrochloride Extended Release Capsules compared to the Effexor XR® Capsules should not have an effect on the safety and efficacy of the test product.[4] In case of increase of drug release described above, the medical team recommended generic formulation of Venlafaxine ER Capsules should be considered therapeutic equivalent to Effexor XR® Capsules.

[4] DARRTS N 090009 CONSULT REV-BIOEQ-01(General Consult Review), 04/12/2010

The results of in vitro alcohol dose dumping study comparing Mylan's Venlafaxine Hydrochloride Extended Release Capsules and the RLD show similar drug release (% dissolved data) at 2 hours in 40% ethanol. Therefore, Mylan's Venlafaxine ER Capsules, 37.5 mg, 75 mg and 150 mg are comparable to the reference product Effexor XR® Capsules, 37.5 mg, 75 mg and 150 mg in the in vitro alcohol dose dumping testing and meet "no-alcohol dose dumping" criteria set forth in the OGD Memo titled "In vitro study to compare potential for dose-dumping in the presence of ethanol between Toprol-XL® and potential generic Metoprolol Succinate Extended-Release Tablets."[5]The firm's response is acceptable.

[5] Memo by Barbara Davit located in DARRTS N 076640 FRM-ADMIN-01(Memorandum to File), 05/16/2007

3.2 Deficiency Comments

None

3.3 Recommendations

The bioequivalence recommendations remain the same as in the bioequivalence review located at DARRTS N 078789 REV-BIOEQ-01(General Review), 04/16/2008.

The in vitro alcohol dose dumping testing conducted by Mylan on Venlafaxine Hydrochloride Extended Release Capsules, 150 mg, lot #R1P2475, 75 mg, lot # R1P2474 and 37.5 mg, lot # R1P2473 comparing to the reference product, Effexor XR® Capsules, 150 mg, lot # E71086S, 75 mg, lot # E26432 and 37.5 mg, lot # E57192, respectively, manufactured by Wyeth, is acceptable.

The Division of Bioequivalence deems Venlafaxine Hydrochloride Extended Release Capsules, manufactured by Mylan, to be bioequivalent to the reference product, Effexor XR® (venlafaxine hydrochloride) Capsules, manufactured by Wyeth.

3.4 Additional Attachments

None

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 078789

APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Venlafaxine Hydrochloride Extended Release Capsules, 37.5 mg, 75 mg and 150 mg

The Division of Bioequivalence (DBE) has completed its review and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}
Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

3.5 Outcome Page

ANDA: 078789

4 COMPLETED ASSIGNMENT FOR 78789 ID: 14094

Productivity:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Productivity***	***Subtotal***
14094	4/13/2011	Other	In-vitro dose-dumping in alcohol	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Amendment/Waiver(s)	
Study Amendment	1
Total Complexity Points	*1*

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

/s/

SVETLANA A CHERSTNIAKOVA
05/26/2011

MOHEB H MAKARY
05/26/2011

BARBARA M DAVIT
05/26/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	078789	
Drug Product Name	Venlafaxine Hydrochloride Extended Release Capsules	
Strength(s)	Eq. to 37.5 mg, 75 mg, and 150 mg base	
Applicant Name	Mylan Pharmaceuticals	
Address	781 Chestnut Ridge Road, Morgantown, WV 26505	
Applicant's Point of Contact	S. Wayne Talton, Vice President, Regulatory Affairs	
Contact's Telephone Number	304-599-2595 ext. 6551	
Contact's Fax Number	304-285-6407	
Original Submission Date(s)	15 January, 2007	
Reviewer	Svetlana Cherstniakova, Ph.D.	
Study Number (s)	VENL-0548	VENL-0549
Study Type (s)	Fed	Sprinkle
Strength (s)	150 mg	150 mg
Clinical Site	Kendle International Inc.	
Clinical Site Address	763 Chestnut Ridge Road, Morgantown, WV 26505	
Analytical Site	Mylan Pharmaceuticals - Bioanalytical Division	
Analytical Site Address	3711 Collins Ferry Road, Morgantown, WV 26505	
OUTCOME DECISION	**INADEQUATE**	

Addendum to the Review

This is an addendum for Mylan's Venlafaxine Hydrochloride Extended Release Capsules, 37.5 mg, 75 mg, and 150 mg (ANDA 078789). The purpose of the addendum is to include the following recommendations to the bioequivalence review posted in DARRTS (i.e., DARRTS N 078789 REV-BIOEQ-01(General Review), 04/16/2008).
There is an evidence that some extended-release drug products may cause "dose dump" when ingested with alcoholic beverages. Therefore, the Agency is concerned that dose-dumping may potentially result in potential risk for subjects. The current Bioequivalence Guidance on Venlafaxine Extended Release Capsules (dated December 2008) states that Agency currently requests additional in vitro dissolution testing conducted using various concentrations of ethanol in the dissolution medium (the guidance is shown below). Since the Division of Bioequivalence has completed the review of this application (04/16/2008) before issuing the Bioequivalence Guidance for Venlafaxine Hydrochloride Extended Release Capsules, the firm is requested to conduct in vitro alcohol dose dumping studies for all strengths of this drug product.

Contains Nonbinding Recommendations

Draft Guidance on Venlafaxine Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Venlafaxine Hydrochloride

Form/Route: Extended Release Capsule /Oral

Recommended studies: 2 studies

1. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover *in-vivo*
   Strength: 150 mg
   Subjects: Normal healthy males and females, general population
   Additional Comments: Due to safety concerns, bioequivalence studies under fasting conditions are not recommended.

---

2. Type of study: Fed Sprinkle
   Design: Single-dose, two-treatment, two-period crossover *in-vivo*
   Strength: 150 mg
   Subjects: Normal healthy males and females, general population
   Additional comments: Please administer the dose after sprinkling the entire contents of the capsule on a teaspoonful of applesauce in accordance with the approved labeling of the reference product under fed conditions.
   Please see comment above.

Analytes to measure: Venlafaxine, and its metabolite O-desmethylvenlafaxine, in plasma.

Bioequivalence based on (90% CI): Venlafaxine

Waiver request of in-vivo testing: 37.5 mg and 75 mg based on (i) acceptable bioequivalence studies on the 150 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least (b) (4) % of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional in vitro dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP apparatus I (basket) at 100 rpm, with and without alcohol;

Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

All strengths of the test and the corresponding reference products must be tested accordingly and data must be provided on individual unit, means, range and %CV including f2 similarity values and dissolution plots.

BIOEQUIVALENCE DEFICIENCIES

ANDA:	078789
APPLICANT:	Mylan Pharmaceuticals
DRUG PRODUCT:	Venlafaxine Hydrochloride Extended Release Capsules, Eq. to 37.5 mg, 75 mg, and 150 mg base

The Division of Bioequivalence (DBE) has completed its review and the following deficiency has been identified:

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional in vitro dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1N HCl, USP apparatus I (basket) at 100 rpm, with and without alcohol;

Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

All strengths of the test and the corresponding reference products must be tested accordingly and data must be provided on individual unit, means, range and %CV including f_2 similarity values and dissolution plots.

Please note: The DBE also requests you to complete all items in vitro study eCTD format tables for all generated dissolution profiles and submit them

electronically, both as an MS Word document and as a *.pdf file. The eCTD format tables are posted on the FDA web site (http://www.fda.gov/cder/ogd/DBE_tables.doc).

Sincerely yours,

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

OUTCOME

ANDA: 078789

I. *Completed Assignment for 78789 ID: 13749*

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
13749	1/15/2007	Other	Study Amendment	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY (ANDA 078789)

Addendum	
Study amendment (In-vitro dose-dumping in alcohol)	1
Total Complexity Points	1

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

/s/

SVETLANA A CHERSTNIAKOVA
04/13/2011

MOHEB H MAKARY
04/13/2011

BARBARA M DAVIT
04/13/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-789
Drug Product Name	Venlafaxine Hydrochloride Extended-Release Capsules
Strength(s)	37.5 mg, 75 mg, and 150 mg
Applicant Name	Mylan Pharmaceuticals
Address	781 Chestnut Ridge Road, Morgantown, WV 26505
Applicant's Point of Contact	S. Wayne Talton, Vice President, Regulatory Affairs
Contact's Telephone Number	304-599-2595 ext. 6551
Contact's Fax Number	304-285-6407
Original Submission Date(s)	15 January 2007
Submission Date(s) of Amendment(s) Under Review	06 November 2007 16 November 2007 15 February 2008 (current)
Reviewer	Johnetta L. Farrar, Ph.D.

Study Number (s)	VENL-0548	VENL-0549
Study Type (s)	Fed	Fed Sprinkle
Strength (s)	150 mg	150 mg
Clinical Site	Kendle International Inc.	
Clinical Site Address	763 Chestnut Ridge Road, Morgantown, WV 26505	
Analytical Site	Mylan Pharmaceuticals - Bioanalytical Division	
Analytical Site Address	3711 Collins Ferry Road, Morgantown, WV 26505	
OUTCOME DECISION	**ACCEPTABLE**	

I. EXECUTIVE SUMMARY

This is a review of a study amendment.

In the original application dated January 15, 2007[1], the firm submitted fed and fed sprinkle bioequivalence (BE) studies comparing the test product, Venlafaxine Hydrochloride Extended-Release Capsules, 150 mg, to the corresponding reference product, Wyeth Consumer Healthcare's Effexor® XR (venlafaxine hydrochloride) Extended-Release Capsules, 150 mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male and female subjects. The firm's fed and fed sprinkle BE studies were found to be acceptable by the Division of Bioequivalence (DBE). The results are summarized below:

[1] DFS Review, Bioequivalence Review, Biopharmaceutics, N 078789 N 000 15-Jan-2007.

Venlafaxine 1 x 150 mg, N=22, (Male =11, Female 11) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. VENL-0548					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	1616.73	1530.92	1.06	98.14	113.63
AUC∞ (hr *ng/ml)	1699.18	1642.55	1.03	95.93	111.56
Cmax (ng/ml)	106.04	96.43	1.10	101.54	119.09

Venlafaxine 1 x 150 mg, N=20, (Male = 09, Female 11) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. VENL-0549					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	1256.03	1217.64	1.03	95.54	111.37
AUC∞ (hr *ng/ml)	1339.53	1292.48	1.04	96.16	111.70
Cmax (ng/ml)	83.21	82.24	1.01	93.69	109.26

In the BE studies, the pharmacokinetic (PK) parameters of the test and reference for the active metabolite [O-desmethylvenlafaxine (ODV)] were comparable. Therefore, the metabolite data were supportive and the studies were acceptable.

The firm's Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg and 75 mg strength capsules were not deemed bioequivalent to Wyeth Consumer Healthcare's Effexor® XR (venlafaxine hydrochloride) Extended-Release Capsules, 37.5 mg and 75 mg as per 21 CFR 320.24 (b) (6). The firm's in vitro dissolution testing was incomplete pending acknowledgement and acceptance of the FDA-recommended method and specifications. Also, there was possible evidence that an additional bioequivalence study (Study No VENL-0548A) had been conducted based the bioanalytical validation data found in the bioanalytical report amendment for the Fed Study No. VENL-0548. The firm was asked to explain the bioanalytical validation data for Study No. VENL-0548A and provide additional information concerning Study No. VENL-0548A.

The firm submitted the *current* amendment to address the issues concerning Study No. VENL-0548A which included an explanation of discrepancy related to the possible re-dosing study, along with the firm's acknowledgement of the FDA-recommended dissolution method and specifications for its test product. The firm's responses in the current amendment are **acceptable**.

The DBE deems the test product, Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg and 75 mg bioequivalent to Wyeth Consumer Healthcare's Effexor®

XR (venlafaxine hydrochloride) Extended-Release Capsules, 37.5 mg and 75 mg as per 21 CFR 320.24 (b) (6).

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is now **acceptable** with no deficiencies.

II. TABLE OF CONTENTS

III. SUBMISSION SUMMARY

1.1 Drug Product Information[2]

Test Product	Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg, 75 mg, and 150 mg
Reference Product	Effexor® XR (venlafaxine hydrochloride) Extended-Release Capsules, 37.5 mg, 75 mg, and 150 mg
RLD Manufacturer	Wyeth Consumer Laboratories, Inc.
NDA No.	20-699
RLD Approval Date	20 October 1997
Indication	It is indicated for the treatment of major depressive disorder.

1.2 PK/PD Information[2,3]

Bioavailability	Venlafaxine is well absorbed and extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the only major active metabolite. On the basis of mass balance studies, at least 92% of a single oral dose of venlafaxine is absorbed. The absolute bioavailability of venlafaxine is about 45%.
Food Effect	The RLD product labeling stated that food did not affect the bioavailability of venlafaxine or its active metabolite, ODV. Time of administration (AM vs. PM) did not affect the pharmacokinetics of venlafaxine and ODV following administration of the 75 mg Effexor XR capsule. The RLD labeling also recommends that Effexor XR should be administered in a single dose with food either in the morning or in the evening at approximately the same time each day. Each capsule should be swallowed whole with fluid and not divided, crushed, chewed, or placed in water, or it may be administered by carefully opening the capsule and sprinkling the entire contents on a spoonful of applesauce. This drug/food mixture should be swallowed immediately without chewing and followed with a glass of water to ensure complete swallowing of the pellets. For these reasons, both Fed and Fed Sprinkle BE studies are currently recommended for the drug product.
T_{max}	5.5 hours for venlafaxine and 9 hours for ODV (for extended release)
Metabolism	Following absorption, venlafaxine undergoes extensive presystemic metabolism in the liver, primarily to ODV, but also to N-desmethylvenlafaxine, N, O-didesmethylvenlafaxine, and other minor metabolites. *In vitro* studies indicate that the formation of ODV is catalyzed by CYP2D6; this has been confirmed in a clinical study showing that patients with low CYP2D6 levels ("poor metabolizers")

[2] DFS Review, Bioequivalence Review, Biopharmaceutics, N 078789 N 000 15-Jan-2007.
[3] Labeling Repository: DailyMed® Search term "venlafaxine" (http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=6663). Last accessed 10 April 2008.

	had increased levels of venlafaxine and reduced levels of ODV compared to people with normal CYP2D6 ("extensive metabolizers"). The differences between the CYP2D6 poor and extensive metabolizers, however, are not expected to be clinically important because the sum of venlafaxine and ODV is similar in the two groups and venlafaxine and ODV are pharmacologically approximately equiactive and equipotent.
Excretion	Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is thus the primary route of excretion.
Half-life	elimination half-life is 5±2 hours for venlafaxine and 11±2 hours for ODV
Drug Specific Issues (if any)	The RLD labeling contains a Black Box Warning on suicidality in children, adolescents, and young adults prescribed with the drug product.

1.3 OGD Recommendations for Drug Product

1.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover *in-vivo*
	Strength:	150 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	Due to safety concerns, bioequivalence studies under fasting conditions are not recommended[4].

2.	**Type of study:**	Fed Sprinkle
	Design:	Single-dose, two-treatment, two-period crossover *in-vivo*
	Strength:	150 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	Please see comment above.

Analytes to measure (in plasma/serum/blood):	Venlafaxine, and its metabolite O-desmethylvenlafaxine (ODV), in plasma
Bioequivalence based on (90% CI):	Venlafaxine
Waiver request of *in-vivo* testing:	37.5 mg and 75 mg based on (i) acceptable bioequivalence studies on the 150 mg strength, (ii) proportional similarity of the formulations between all strengths, and (iii) acceptable *in vitro* dissolution testing of all strengths.
Source of most recent recommendations:	Current Draft BE Guidance of Venlafaxine Hydrochloride Extended-Release Capsule on the FDA's Guidance for Industry: Individual Product Bioequivalence Recommendations website, http://www fda.gov/cder/guidance/bioequivalence.

[4] FDA Draft Guidance on Venlafaxine Hydrochloride Extended-Release Capsules. Last accessed: 10 April 2008.

Summary of OGD or DBE History:

The DBE currently recommends the following for Venlafaxine Hydrochloride (HCl) Extended-Release Capsules drug products:

1. Single-dose, two-way crossover fed and fed sprinkle studies on 150 mg tablet.
2. Measurement of the parent drug and major metabolite, O-desmethylvenlafaxine.
3. The dissolution testing should be conducted in 900 mL of water using Apparatus 1 (Basket) at 100 rpm.
4. Venlafaxine HCl extended-release capsules, 37.5 mg and 75 mg, are eligible for a waiver of *in vivo* bioequivalence study requirements based on (1) acceptable bioequivalence studies on the 150 mg strength, (2) acceptable dissolution testing of all strengths, and (3) proportional similarity in the formulations of all strengths.
5. There are no approved ANDAs on the market for this product and/or any that have been tentatively approved.

According to the Electronic Orange Book (current through February 2008), there are no approved generic products for Venlafaxine HCl Extended-Release Capsules.

The following ANDAs on Venlafaxine HCl Extended-Release Capsules have been reviewed and found acceptable by the DBE:

Firm	ANDA#	Letter Date
Teva	76-565	12-10-02
Anchen	78-087	12-23-05

The following ANDAs on Venlafaxine HCl Extended-Release Capsules are currently under review in the DBE:

Firm	ANDA#	Letter Date
		(b) (4)
Impax	78-057	12-15-05

The following ANDAs on Venlafaxine HCl Extended-Release Capsules have been reviewed and found incomplete by the DBE:

Firm	ANDA#	Letter Date
		(b) (4)
Mylan (current)	78-789	01-15-07
Wockhardt	78-865	03-08-07
		(b) (4)

1.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	-
Single-dose fed	No	-
Steady-state	No	-
In vitro dissolution	No	-
Waiver requests	No	-
BCS Waivers	No	-
Clinical Endpoints	No	-
Failed Studies	No	-
Amendments	Yes	1

1.5 Pre-Study Bioanalytical Method Validation[5]

Report Location	**Venlafaxine Hydrochloride Bioanalytical Method Validation Report, Sections 5.3.1.4.1 and 5.3.1.4.2**
Analyte	Venlafaxine / O-desmethylvenlafaxine
Internal Standard (IS)	(b) (4)
Method Description	Direct Injection / Tandem MS Detection
Limit of Quantitation (ng/mL)	2 ng/mL VENL and OVEN
Average Recovery of Drug (%)	51.10% VENL and 47.57% OVEN
Average Recovery of IS (%)	25.12%
Standard Curve Concentrations (ng/mL)	2, 4, 6, 10, 20, 40, 80, 120, 160, 200
QC Concentrations (ng/mL)	2, 6, 20, 120
QC Intraday Precision Range (%)	1.85 to 7.35 VENL / 1.19 to 5.99 OVEN
QC Intraday Accuracy Range (%)	-3.75 to 1.72 VENL / -0.73 to 3.61 OVEN
QC Interday Precision Range (%)	2.49 to 7.19 VENL / 3.006 to 6.645 OVEN
QC Interday Accuracy Range (%)	-1.95 to 2.46 VENL / -0.86 to 7.76 OVEN
Bench-Top Stability (hrs)	6 hours @ room temperature VENL and OVEN
Stock Stability (days)	29 days @ 4°C VENL/OVEN working solution, 8 days @ 4°C IS working solution
Processed Stability (hrs)	52 hours @ room temperature
Freeze-Thaw Stability (cycles)	4 cycles
Long-Term Storage Stability (days)	436 days @ -70°C
Dilution Integrity	Concentration diluted 2-fold
Selectivity	No significant interfering peaks noted in blank plasma samples

[5] DFS Review, Bioequivalence Review, Biopharmaceutics, N 078789 N 000 15-Jan-2007.

1.6 In Vivo Studies[6]

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route), (Product ID)	Subjects Number (M/F), Type, Mean Age (yrs), (Range)	Mean Parameters (± SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUCL (ng/mL•hr)	AUCI (ng/mL•hr)	$T_{1/2}$ (hr)	Kel (hr^{-1})	
VENL-0548	Single-Dose Fed Bioequivalence Study of Venlafaxine Hydrochloride Extended-Release Capsules (150 mg; Mylan) and Effexor® XR Capsules (150 mg; Wyeth) in Healthy Adult Volunteers	Open-label, Single-dose, Randomized, Two-period, Two-treatment Crossover	A = Venlafaxine Hydrochloride Extended-Release 150 mg Capsule 1 x 150 mg oral route Lot# R1P2475	24 Dosed 22 Completed (M: 11, F: 11) Healthy Subjects Mean Age: 27.2 (Range: 19 to 43) Mean Weight: 156.9 (Range: 114 to 196) Mean BMI: 24.7 (Range: 19.3 to 30.2) 20 Statistically Analyzed (M: 10; F: 10)	Venlafaxine						Section 5.3.1.4.1
					117.1 ± 49.7	6.05	2091 ± 1770	2176 ± 1871	9.76	0.0781	
			B = Effexor® XR 150 mg Capsule 1 x 25 mg oral route Lot# B05403 exp: 3/2007		107.0 ± 48.8	6.55	1985 ± 1712	2114 ± 1898	11.21	0.0682	
					O-desmethylvenlafaxine						
					196.9 ± 77.7	11.20	5651 ± 1858	5828 ± 1907	12.32	0.0586	
					176.7 ± 64.07	11.40	5246 ± 1682	5444 ± 1702	13.61	0.0535	

[6] DFS Review, Bioequivalence Review, Biopharmaceutics, N 078789 N 000 15-Jan-2007.

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route), (Product ID)	Subjects Number (M/F), Type, Mean Age (yrs), (Range)	Mean Parameters (± SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUCL (ng/mL•hr)	AUCI (ng/mL•hr)	$T_{1/2}$ (hr)	Kel (hr^{-1})	
VENL-0549	Single-Dose Fed Bioequivalence Study of Venlafaxine Hydrochloride Extended-Release Capsules (150 mg; Mylan) and Effexor ® XR Capsules (150 mg; Wyeth) Administered with Applesauce in Healthy Adult Volunteers	Open-label, Single-dose, Randomized, Two-period, Two-treatment Crossover	A = Venlafaxine Hydrochloride Extended-Release 150 mg Capsule 1 x 150 mg oral route Lot# R1P2475	24 Dosed 20 Completed (M: 9, F: 11) Healthy Subjects Mean Age: 29.1 (Range: 18 to 55) Mean Weight: 163.0 (Range: 134 to 206) Mean BMI: 24.6 (Range: 20.8 to 28.7)	Venlafaxine						Section 5.3.1.4.1
					97.5 ± 58.7	6.20	1751 ± 1946	1847 ± 2039	10.07	0.0739	
			B = Effexor® XR 150 mg Capsule 1 x 25 mg oral route Lot# B05403 exp: 3/2007		92.5 ± 52.0	7.05	1678 ± 1925	1772 ± 2070	10.65	0.0707	
					O-desmethylvenlafaxine						
					183.6 ± 68.5	10.00	5398 ± 1688	5580 ± 1717	12.62	0.0576	
					177.9 ± 58.9	9.80	5198 ± 1582	5437 ± 1649	13.24	0.0540	

2. Reanalysis of Study Samples[7]

VENL-0548-Food Study Repeat Analysis Results for Venlafaxine Additional Information in Section 5.3.1.4.1 (Bioanalytical Report for VENL-0548)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual Number		% of total assays		Actual Number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0%	0%	0	0	0%	0%
Reason A	2	0	0.25%	0%	0.25%	0%	0.25%	0%
Reason B	1	1	0.13%	0.13%	0.13%	0.13%	0.13%	0.13%
Reason C	11	7	1.39%	0.88%	1.39%	0.88%	1.39%	0.88%
Total	14	8	1.77%	1.01%	1.77%	1.01%	1.77%	1.01%

VENL-0549-Fed Applesauce Study Repeat Analysis Results for Venlafaxine Additional Information in Section 5.3.1.4.2 (Bioanalytical Report for VENL-0549)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual Number		% of total assays		Actual Number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0%	0%	0	0	0%	0%
Reason A	1	0	0.14%	0%	1	0	0.14%	0%
Reason D	0	1	0%	0.14%	0	1	0%	0.14%
Total	1	1	0.14%	0.14%	1	1	0.14%	0.14%

Did use of recalculated plasma concentration data change study outcome? No.

Reviewer's Comments: Pharmacokinetic parameters were calculated for twenty-one subjects in the fed bioequivalence study (VENL-0548). The data for Subject 17 was not included in statistical analysis because the pre-dose plasma concentrations of venlafaxine in both Periods I and II for the subject were greater than 5% of the subject's maximum plasma concentration. Per the FDA's Guidance to Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Consideration (issued March 2003)[8], *"If the predose concentration is ≤ 5 percent of Cmax value in that subject, the subject's data without any adjustments can be included in all pharmacokinetic measurements and calculations. We recommend that if the predose value is > than 5 percent of Cmax, the subject be dropped from all BE study evaluations."* Based on the reviewer's statistical analysis the study outcome did not change. Subject 5 had undetectable plasma concentrations for all time points of the test treatment (Period 2) but plasma concentrations of the reference treatment were similar with the other subject's in the study. The firm initially contacted Subject 5 to investigate the reasons of undetectable plasma concentrations and/or for possible redosing. However, the subject appeared to refuse to return for redosing. The record of multiple attempts made by the firm to contact the subject were submitted in the study report. The firm subsequently analyzed the study results without this subject (n=20). The reviewer analyzed the study results with (n=21) and without

[7] DFS Review, Bioequivalence Review, Biopharmaceutics, N 078789 N 000 15-Jan-2007.
[8] Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations. March 2003.

(n=20) the inclusion of this subject. The study outcome was the same with and without the inclusion of the data for Subject 5. The fed study met the acceptable BE limits for the confidence intervals for log-transformed AUC_{0-t}, AUC_{∞} and C_{max} of venlafaxine. The fed study (VENL-0548) was **acceptable**.

Pharmacokinetic parameters for the fed sprinkle study (VENL-0549) were calculated using the data for twenty subjects. The fed sprinkle study met the acceptable BE limits for the confidence intervals for log-transformed AUC_{0-t}, AUC_{∞} and C_{max} of venlafaxine. The fed sprinkle study (VENL-0549) was **acceptable**.

In the fed study (VENL-0548) and fed sprinkle study (VENL-0549), the pharmacokinetic (PK) parameters of the test and reference for the active metabolite, O-desmethylvenlafaxine, were comparable. The metabolite data also fell within the acceptable BE limits for the 90% confidence intervals for log-transformed AUC_{0-t}, AUC_{∞} and C_{max}. Therefore, the metabolite data were supportive and the studies were **acceptable**.

1.7 Formulation

Ingredient	Amount (mg)/Capsule	Amount (%)	Amount (mg)/Capsule	Amount (%)	Amount (mg)/Capsule	Amount (%)
	37.5mg	37.5mg	75mg	75mg	150mg	150mg

(b) (4)

[redacted]

Comments:

1. All strengths of the test product are proportionally similar.
2. The amount of each of the inactive ingredients of the test product are within acceptable limits listed in the FDA's Inactive Ingredient Guidance (IIG) database.
3. There is no overage of active pharmaceutical ingredient (API).
4. The [redacted] (b) (4) are present in acceptable amounts per the Chemistry review of the ANDA[9].

1.8 In Vitro Dissolution

Dissolution Conditions	**Apparatus:**	I (basket)
	Speed of Rotation:	100 rpm
	Medium:	Water
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	2 hours: [redacted] (b) (4) %, 6 [redacted] (b) (4) 12 hours: [redacted] (b) (4) 24 hours: [redacted] (b) (4) %	
Dissolution Testing Site (Name, Address)	Mylan Pharmaceuticals 781 Chestnut Ridge Road, Morgantown, WV 26505	

[9] DFS Review, CMC REV#1 NA - MINOR, Chemist, N 078789 N 000 15-Jan-2007.

1.8.1 In Vitro Dissolution Testing Data[10]

A. Deaerated Water (900 mL), USP Apparatus I (Basket), 100 rpm (FDA-recommended method)

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)									Study Report Location
					1 hr.	2 hr.	4 hr.	6 hr.	8 hr.	10 hr.	12 hr.	14 hr.	24 hr.	
N/A	Venlafaxine HCl ER Capsules Lot R1P2473	37.5mg Capsule	**Apparatus:** 1 (basket) **Speed:** 100 rpm **Medium:** Deaerated Water, 900ml **Temperature:** 37 C± 0.5 C	12	1%	19%	47%	62%	71%	78%	83%	87%	97%	3.2.P.5.4 Batch Analysis and 5.3.1.3 In vitro - in vivo Correlation
					(b) (4)									
					RSD 48.7%	RSD 5.9%	RSD 3.6%	RSD 2.8%	RSD 2.8%	RSD 2.6%	RSD 2.6%	RSD 2.7%	RSD 2.6%	
N/A	Effexor® XR Lot A94378	37.5mg Capsule		12	4%	15%	40%	58%	68%	75%	80%	84%	94%	
					(b) (4)									
					RSD 21.2%	RSD 14.4%	RSD 6.3%	RSD 4.5%	RSD 3.9%	RSD 3.6%	RSD 3.5%	RSD 3.4%	RSD 3.0%	
N/A	Venlafaxine HCl ER Capsules Lot R1P2474	75mg Capsule		12	1%	19%	47%	61%	70%	76%	81%	85%	95%	
					(b) (4)									
					RSD 22.8%	RSD 4.0%	RSD 2.1%	RSD 1.7%	RSD 1.8%	RSD 1.7%	RSD 1.8%	RSD 1.8%	RSD 1.8%	
N/A	Effexor® XR Lot A85871	75mg Capsule		12	11%	25%	49%	64%	73%	79%	83%	87%	95%	
					(b) (4)									
					RSD 15.5%	RSD 10.4%	RSD 4.8%	RSD 3.6%	RSD 2.9%	RSD 2.6%	RSD 2.5%	RSD 2.5%	RSD 2.4%	
N/A	Venlafaxine HCl ER Capsules Lot R1P2475	150mg Capsule		12	1%	19%	48%	62%	71%	78%	83%	86%	97%	
					(b) (4)									
					RSD 14.4%	RSD 3.8%	RSD 2.8%	RSD 2.6%	RSD 2.4%	RSD 2.5%	RSD 2.3%	RSD 2.5%	RSD 2.5%	
N/A	Effexor® XR Lot B05403	150mg Capsule		12	5%	18%	45%	62%	73%	80%	85%	88%	98%	
					(b) (4)									
					RSD 7.1%	RSD 4.1%	RSD 2.7%	RSD 2.1%	RSD 1.9%	RSD 1.9%	RSD 1.8%	RSD 2.0%	RSD 2.1%	

[10] DFS Review, Bioequivalence Review, Biopharmaceutics, N 078789 N 000 15-Jan-2007.

Dissolution Testing in Additional Media

B. 0.1 N HCl (900 mL), USP Apparatus I (Basket), 100 rpm

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)										Study Report Location
					1 hr.	2 hr.	4 hr.	6 hr.	8 hr.	10 hr.	12 hr.	14 hr.	16 hr.	24 hr.	
N/A	Venlafaxine HCl ER Capsules Lot R1P2473	37.5mg Capsule	**Apparatus:** 1 (basket) **Speed:** 100 rpm **Medium:** 0.1 N HCl, 900ml **Temperature:** 37 C± 0.5 C	12	1%	17%	44%	58%	67%	72%	77%	82%	84%	93%	5.3.1.3 In vitro - in vivo Correlation
					(b) (4)										
					RSD 48.4%	RSD 5.9%	RSD 3.2%	RSD 3.3%	RSD 3.0%	RSD 4.0%	RSD 4.1%	RSD 2.6%	RSD 2.7%	RSD 2.9%	
N/A	Effexor® XR Lot A94378	37.5mg Capsule		12	4%	13%	35%	51%	61%	68%	73%	78%	81%	89%	
					(b) (4)										
					RSD 26.8%	RSD 15.8%	RSD 7.6%	RSD 5.2%	RSD 3.8%	RSD 3.1%	RSD 2.7%	RSD 2.4%	RSD 2.0%	RSD 1.8%	
N/A	Venlafaxine HCl ER Capsules Lot R1P2474	75mg Capsule		12	0%	17%	45%	58%	68%	74%	78%	82%	86%	94%	
					(b) (4)										
					RSD 26.4%	RSD 3.7%	RSD 2.1%	RSD 2.4%	RSD 2.5%	RSD 1.8%	RSD 3.3%	RSD 1.8%	RSD 3.2%	RSD 2.1%	
N/A	Effexor® XR Lot A85871	75mg Capsule		12	10%	22%	43%	57%	66%	72%	77%	80%	83%	91%	
					(b) (4)										
					RSD 6.4%	RSD 4.3%	RSD 3.5%	RSD 2.6%	RSD 2.4%	RSD 2.4%	RSD 2.4%	RSD 2.4%	RSD 2.6%	RSD 4.5%	
N/A	Venlafaxine HCl ER Capsules Lot R1P2475	150mg Capsule		12	1%	18%	45%	59%	68%	74%	79%	83%	87%	94%	
					(b) (4)										
					RSD 26 3%	RSD 2.9%	RSD 1.4%	RSD 1.2%	RSD 1.2%	RSD 1.3%	RSD 1.2%	RSD 1.2%	RSD 1.2%	RSD 1.1%	
N/A	Effexor® XR Lot B05403	150mg Capsule		12	5%	16%	38%	54%	64%	71%	76%	80%	83%	90%	
					(b) (4)										
					RSD 6.3%	RSD 5.0%	RSD 3.9%	RSD 2.9%	RSD 2.5%	RSD 2.2%	RSD 1.9%	RSD 1.8%	RSD 1.8%	RSD 1.6%	

C. pH 4.5 Acetate Buffer (900 mL), USP Apparatus I (Basket), 100 rpm

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)										Study Report Location
					1 hr.	2 hr.	4 hr.	6 hr.	8 hr.	10 hr.	12 hr.	14 hr.	16 hr.	24 hr.	
N/A	Venlafaxine HCl ER Capsules Lot R1P2473	37.5mg Capsule	**Apparatus:** 1 (basket) **Speed:** 100 rpm **Medium:** pH 4.5 acetate buffer, 900ml **Temperature:** 37 C± 0.5 C	12	1%	17%	46%	61%	70%	77%	82%	86%	90%	98%	5.3.1.3 In vitro - in vivo Correlation
					RSD 41.1%	RSD 6.1%	RSD 3.9%	RSD 3.9%	RSD 3.9%	RSD 3.8%	RSD 3.7%	RSD 3.6%	RSD 3.7%	RSD 3.6%	
N/A	Effexor® XR Lot A94378	37.5mg Capsule		12	3%	13%	36%	53%	64%	72%	77%	81%	85%	93%	
					RSD 23.7%	RSD 11.8%	RSD 6.3%	RSD 4.6%	RSD 3.9%	RSD 3.6%	RSD 3.4%	RSD 3.1%	RSD 3.1%	RSD 2.9%	
N/A	Venlafaxine HCl ER Capsules Lot R1P2474	75mg Capsule		12	0%	17%	46%	60%	69%	76%	81%	85%	88%	96%	
					RSD 42.3%	RSD 5.3%	RSD 1.9%	RSD 1.4%	RSD 1.4%	RSD 1.4%	RSD 1.4%	RSD 1.4%	RSD 1.4%	RSD 1.6%	
N/A	Effexor® XR Lot A85871	75mg Capsule		12											
					RSD 15.9%	RSD 10.5%	RSD 5.8%	RSD 4.1%	RSD 3.8%	RSD 3.5%	RSD 3.5%	RSD 3.4%	RSD 3.3%	RSD 3.4%	
N/A	Venlafaxine HCl ER Capsules Lot R1P2475	150mg Capsule		12	1%	18%	47%	61%	71%	77%	82%	87%	90%	97%	
					RSD 15.7%	RSD 3.8%	RSD 2.3%	RSD 2.3%	RSD 2.2%	RSD 2.3%	RSD 2.2%	RSD 2.2%	RSD 2.2%	RSD 2.6%	
N/A	Effexor® XR Lot B05403	150mg Capsule		12	5%	16%	39%	56%	67%	74%	79%	83%	86%	93%	
					RSD 8.0%	RSD 6.1%	RSD 3.5%	RSD 2.2%	RSD 1.7%	RSD 1.5%	RSD 1.4%	RSD 1.2%	RSD 1.3%	RSD 1.4%	

(b) (4)

D. pH 6.8 Phosphate Buffer (900 mL), USP Apparatus I (Basket), 100 rpm

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)										Study Report Location
					1 hr.	2 hr.	4 hr.	6 hr.	8 hr.	10 hr.	12 hr.	14 hr.	16 hr.	24 hr.	
N/A	Venlafaxine HCl ER Capsules Lot R1P2473	37.5mg Capsule	**Apparatus:** 1 (basket) **Speed:** 100 rpm **Medium:** pH 6.8 phosphate buffer, 900ml **Temperature:** 37 C± 0.5 C	12	1%	18%	46%	60%	69%	75%	80%	84%	87%	94%	5.3.1.3 In vitro - in vivo Correlation
					RSD 34.8%	RSD 4.4%	RSD 2.7%	RSD 2.2%	RSD 2.1%	RSD 2.1%	RSD 2.1%	RSD 2.1%	RSD 2.1%	RSD 2.3%	
N/A	Effexor® XR Lot A94378	37.5mg Capsule		12	4%	15%	39%	55%	66%	72%	77%	81%	84%	92%	
					RSD 20.8%	RSD 8.7%	RSD 4.5%	RSD 3.3%	RSD 2.9%	RSD 2.7%	RSD 2.6%	RSD 2.5%	RSD 2.5%	RSD 2.4%	
N/A	Venlafaxine HCl ER Capsules Lot R1P2474	75mg Capsule		12	1%	17%	45%	59%	68%	74%	79%	83%	86%	93%	
					RSD 29.7%	RSD 4.2%	RSD 2.0%	RSD 1.8%	RSD 1.6%	RSD 1.7%	RSD 1.7%	RSD 1.8%	RSD 1.7%	RSD 2.0%	
N/A	Effexor® XR Lot A85871	75mg Capsule		12	11%	25%	48%	62%	71%	77%	81%	85%	87%	94%	
					RSD 16.4%	RSD 8.7%	RSD 5.0%	RSD 4.0%	RSD 3.0%	RSD 3.3%	RSD 3.3%	RSD 3.2%	RSD 3.4%	RSD 3.5%	
N/A	Venlafaxine HCl ER Capsules Lot R1P2475	150mg Capsule		12	1%	18%	46%	61%	70%	76%	81%	85%	88%	95%	
					RSD 23.0%	RSD 3.0%	RSD 1.8%	RSD 1.9%	RSD 1.9%	RSD 1.9%	RSD 1.8%	RSD 2.0%	RSD 2.0%	RSD 2.1%	
N/A	Effexor® XR Lot B05403	150mg Capsule		12	5%	17%	42%	59%	69%	76%	80%	84%	87%	94%	
					RSD 8.2%	RSD 5.9%	RSD 3.7%	RSD 2.8%	RSD 2.2%	RSD 2.3%	RSD 2.2%	RSD 2.1%	RSD 2.1%	RSD 2.2%	

(b) (4)

1.9 Firm's Current Responses to the DBE's Deficiency Comments

DBE's Previous Deficiency Comment No. 1:

Your proposed specifications of (b) (4) [redacted] (b) (4) for the 2, 4, 8, 12, and 24 hour sampling time points, respectively, based on the submitted stability (stored sample) data are not acceptable. As per the Division of Bioequivalence (DBE) practice, the dissolution specifications are established based on the dissolution data on 12 units of the biolot (fresh, not stored lot) that has been used in acceptable bioequivalence studies. The DBE does not revise the dissolution specifications on the basis of the dissolution testing data on the stored lots. In order to justify your proposed specifications, please submit additional dissolution data of three fresh production lots, to determine if a revision of the dissolution specification is warranted. Alternatively, please acknowledge the FDA-recommended dissolution method and specifications given below:

Medium:	Water
Volume:	900 mL
USP Apparatus:	Type I (basket)
Rotation (rpm):	100 rpm
Specifications:	2 hr: (b) (4) [redacted] 4 hrs: (b) (4) [redacted] 8 hrs: (b) (4) [redacted] 12 hrs: (b) (4) [redacted] 24 hrs: (b) (4) [redacted]

Firm's Current Response No. 1:

"Mylan acknowledges our acceptance of the following interim dissolution method and specification as recommended by the Division of Bioequivalence:

Medium:	Water
Volume:	900 mL
USP Apparatus:	Type I (basket)
Rotation (rpm):	100 rpm
Specifications:	2 hr: (b) (4) [redacted] 4 hrs: (b) (4) [redacted] 8 hrs: (b) (4) [redacted] 12 hrs: (b) (4) [redacted] 24 hrs: (b) (4) [redacted]

Prior to final ANDA approval, Mylan may provide additional dissolution data from production batches to determine if an adjustment to the tolerances is warranted. Any request for an adjustment in the dissolution specifications will be submitted as a Bioequivalence Amendment.

The interim dissolution method and specifications have been incorporated into Mylan's stability and quality control programs. Revised finished product specifications, which apply at release and stability, are provided in Attachment B.

Please note that the revised documentation provided herein is also being submitted concurrently in a Chemistry Amendment under separate cover."

Reviewer's Comment:

The DBE previously reviewed the firm's dissolution testing using the FDA recommended method [900 mL of water (37°C) using USP Apparatus I (basket) at 100 rpm]. The firm was asked to acknowledge the FDA-recommended specifications [(b) (4) in 2 hours; 4 hrs: (b) (4) 8 hrs: (b) (4) 12 hrs: (b) (4) 24 hrs: (b) (4) for its test product. In this amendment dated 15 February 2008, the firm accepted the FDA-recommended specifications. Therefore, the firm's response to this deficiency is **acceptable**.

DBE's Previous Deficiency Comment No. 2:

There was evidence that an additional bioequivalence study was conducted as Study No. VENL-0548A based on some within-study bioanalytical validation data submitted in the amendment dated November 6, 2007 (Attachment E, pages 67-68) for the Fed Study No. VENL-0548, as well as based on the existence of the SOP Nos. D-400-07 ("Reassay or Reinjection of Clinical Samples", issued October 19, 2006) and D-416-05 ("Reassay of Whole Subjects", issued October 19, 2007). You have submitted a protocol amendment for the Fed Study VENL-0548 to include a Redose Study which was to be identified as Study No. VENL-0548A. However, there was no other data or report submitted for Study No. VENL-0548A. You have also indicated in the Fed Study report that Subject 5 was difficult to contact for redosing, and this subject was dropped from your final analysis of the Fed Study results. Please provide explanation for the existence of the bioanalytical validation data for Study No. VENL-0548A as submitted in the amendment dated November 6, 2007, and please confirm if the Redose Study No. VENL-0548A was ever carried out.

Firm's Current Response No. 2:

> *"At the time Mylan submitted our ANDA for Venlafaxine Hydrochloride Extended-Release Capsules, Kendle International, Inc., the CRO Mylan contracted to conduct the VENL-0548 study, was in the process of contacting Subject 5, the subject whom did not have any observed plasma concentrations during Period 2 of the VENL-0548 study, to schedule a re-dosing of the test and reference products. However, it was not until November 4, 2006, that Subject 5 also only agreed to the administration of a single dose of study medication. Thus, this investigation was limited to a single period. An additional three (3) subjects were enrolled from the original VENL-0548 study for control purposes. The results of this redose study (VENL-0548A) found Subject 5 to have plasma concentrations and primary pharmacokinetic parameters (CPEAK, AUCL, and AUCI) for both venlafaxine and O-desmethylvenlafaxine in the range of the other subjects observed plasma concentrations and primary pharmacokinetic parameters in the original study (VENL-0548). In addition, the control subjects (Subjects 1, 6, and 11) re-dose primary pharmacokinetic parameters were very comparable to their originally observed values from VENL-0548. Thus, these re-dose results fully support the removal of Subject 5's pharmacokinetic data from the original dataset due to an aberrant pharmacokinetic response. The original*

bioequivalence study (VENL-0548) demonstrates that Mylan's Venlafaxine Hydrochloride Extended-Release Capsules, 150 mg are bioequivalent to Wyeth's Effexor® XR 150 mg capsules following a single, oral 150mg (1x150mg) dose administered under fed conditions. The complete report for this re-dose study (VENL-0548A) is provided in Attachment C."

Reviewer's Comment:

Per the previous bioequivalence review of ANDA 78-789[11], "*Pharmacokinetic parameters were calculated for twenty-one subjects. Subject 17 was not analyzed statistically due to pre-dose plasma concentrations for both Periods I and II being greater than 5% of the subject's maximum plasma concentration. Subject 5 had undetectable plasma concentrations for all time points of the Test treatment (Period 2) but plasma concentrations of the Reference treatment within the range of those of other study subjects. The firm initially contacted Subject 5 to investigate the reasons of undetectable plasma concentrations and/or for possible redosing. However, the subject appeared to refuse to return for redosing. The record of multiple contacts of the subject made by the firm was submitted in the study report. The firm subsequently analyzed the study results without this subject (n=20). However, the reviewer analyzed the study results with this subject included (n=21)*[12]*. The study outcome was the same with and without Subject 5. The fed study met the confidence interval acceptance criteria for log-transformed* AUC_{0-t}, AUC_{∞} *and* C_{max} *of venlafaxine. The fed study is acceptable."* A summary of the re-dosing study (VENL-0548A) is provided in this review, section 1.10 below, for information and clarification purposes only. The information for the re-dosing study (VENL-0548A) as submitted is acceptable. The DBE has no further question concerning the re-dosing or original fed study. The fed BE study is now considered **acceptable.**

[11] DFS Review, Bioequivalence Review, Biopharmaceutics, N 078789 N 000 15-Jan-2007.

[12] Data for subject number five (Period II, Treatment A) was set to "0" during statistical analysis for all sampling time points.

1.10 Individual Study Reviews

1.10.1 Single-dose Fed (Re-Dosing) Bioequivalence Study

1.10.1.1 Study Design

Table 3 Study Information

Study Number	VENL-0548A
Study Title	Single-Dose Fed Bioequivalence Study of Venlafaxine Hydrochloride Extended-Release Capsules (150 mg; Mylan) and Effexor® XR Capsules (150 mg; Wyeth) in Healthy Adult Volunteers (Re-Dose)
Clinical Site (Name & Address)	Kendle International, Inc. 763 Chestnut Ridge Road Morgantown, WV 26505
Principal Investigator	Dorian Williams, MD
Dosing Dates	Period I: 04 November 2006 – 07 November 2006
Analytical Site (Name & Address)	Mylan Pharmaceuticals – Bioanalytical Division 3711 Collins Ferry Road Morgantown, WV 26505
Analytical Director	Patrick T. Vallano, Ph.D.
Analysis Dates	21 February 2007 – 22 February 2007
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	110 days

Table 4. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Venlafaxine HCl Extended-Release Capsules, 150 mg	Effexor XR® Capsules, 150 mg
Manufacturer	Mylan Pharmaceuticals, Inc.	Wyeth Pharmaceuticals, Inc.
Batch/Lot No.	R1P2475	B05403
Manufacture Date	02 February 2006	
Expiration Date		March 2007
Strength	150 mg	150 mg
Dosage Form	Extended-release capsule	Extended-release capsule
Bio-Batch Size	(b) (4) capsules	
Production Batch Size	capsules	
Potency (Assay)	99.8%	100.6%
Content Uniformity (mean, %CV)	99.2 (CV 1.0%)	
Dose Administered	1 x 150 mg	1 x 150 mg
Route of Administration	Orally	Orally

Table 5. Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Four (4) volunteers were enrolled in the study. All four (4) subjects completed the study and their collected samples analyzed.
No. of Sequences	1
No. of Periods	1
No. of Treatments	2
No. of Groups	1
Washout Period	At least 7 days
Randomization Scheme	Treatment A: 01, 05, 11 Treatment B: 06
Blood Sampling Times	Predose (within 45 minutes prior to dosing), and at 0.5, 1.0, 2.0, 4.0, 5.0, 6.0, 7.0, 8.0. 9.0, 10, 12. 14, 16, 24, 36, 48, and 72 hours postdose.
Blood Volume Collected/Sample	1 x 6 mL of blood collected in sodium heparin tubes
Blood Sample Processing/Storage	Samples were collected and centrifuged at 3000 RPM and 4°C for 10 minutes. The samples were then returned to an ice bath. The plasma was then transferred into the appropriately labeled polypropylene tubes, with each sample being divided into 2 aliquots. The samples were then frozen at -70°C ± 15°C until shipment for sample analysis.
IRB Approval	Yes – 15 September 2006
Informed Consent	Yes - 15 September 2006. Note: A new informed consent was obtained from each subject before entering the study.
Length of Fasting	Food was not permitted from at least 10 hours prior to dosing until breakfast the day of dosing, On the day prior to dosing, dinner was consumed 13.5 hours prior to dosing. After a supervised overnight fast subjects received a standardized breakfast 30 minutes prior to dosing, and the breakfast was consumed within 15 minutes.
Length of Confinement	Subjects were housed at least 16 hours prior to and at least until 24 hours after post-dosing and were allowed to return to the clinic for blood draws scheduled after 24 hours.
Safety Monitoring	For safety monitoring, vital signs (including systolic and diastolic blood pressures, pulse, respiration rates, and temperature) were measured within 60 minutes prior to dosing and prior to the pre-dose blood sample collection.
Standard FDA Meal Used?	Yes

Comments on Study Design:

The study design consisted of only one period per the availability of the subjects participating in redosing. This design is not **acceptable** for the purpose of the redosing study. However, as stated in the Reviewer's Comments, the redose data as submitted are for information only and not used toward determination of bioequivalence, as the study

outcome did not change with or without the inclusion of the subject in question, Subject No. 5.

Comments on Pharmacokinetic and Statistical Analysis:

Based on the data submitted in the current amendment for the re-dosing study (VENL-0548A), Subject 5 had plasma concentrations and calculated primary pharmacokinetic parameters (AUC_{0-t}, AUC_{∞} and C_{max}) for both venlafaxine and O-desmethylvenlafaxine in the same range as the subjects (N=20) in the original fed study (VENL-0548). Based on the results of one re-dosing period, it is possible that Subject 5 had "aberrant" concentration and PK parameter values (test treatment) in Period II of the original fed BE study. The primary pharmacokinetic parameters of venlafaxine for the control subjects for one re-dosing period appeared comparable to their originally observed values in the fed BE study No. VENL-0548, as shown below. However, since the re-dosing study was incomplete (with only one period included in the re-dosing study), the data for the study VENL-0548A are for information only.

Subject	Cmax (ng/mL)	AUC0-t (ng*hr/mL)	AUC∞ (ng*hr/mL)
Subject 1, Treatment A (original fed study)	237.4	8595.0	9150.8
Subject 1, Treatment A (re-dose study)	241.6	8783.9	9515.0
Subject 5, Treatment A (original fed study)	**0.00**	**0.00**	**0.00**
Subject 5, Treatment A (re-dose study)	106.7	1388.4	1463.8
Subject 6, Treatment B (original fed study)	122.6	2609.3	2773.3
Subject 6, Treatment B (re-dose study)	121.7	2327.6	2461.5
Subject 11, Treatment A (original fed study)	92.1	1571.9	1595.0
Subject 11, Treatment A (re-dose study)	99.7	1459.7	1532.0

Treatment A = Test
Treatment B = Reference

Summary and Conclusions, Single-Dose *Redose* Fed Bioequivalence Study:

The redose fed study (VENL-0548A) is for information only. The original fed BE study (VENL-0548), as analyzed with and without the inclusion of Subject 5, is **acceptable**.

1.11 Comments for Other OGD Disciplines

Discipline	Comment
--	None

1.12 Waiver Request(s)

Strengths for which waivers are requested	37.5 mg and 75 mg
Proportional to strength tested *in vivo*?	Yes
Is dissolution acceptable?	**ACCEPTABLE**
Waivers granted?	**YES**
If not then why?	**N/A**

V. RECOMMENDATIONS

1. The Division of Bioequivalence (DBE) **accepts** the fed bioequivalence (BE) study No. VENL-0548 conducted by Mylan Pharmaceuticals on its Venlafaxine Hydrochloride Extended-Release Capsules, 150 mg, lot # R1P2475, comparing it to Wyeth Consumer Healthcare's Effexor® XR (venlafaxine hydrochloride) Extended-Release Capsules, 150 mg, lot # B05403.

2. The DBE **accepts** the fed sprinkle BE study No. VENL-0549 conducted by Mylan Pharmaceuticals on its Venlafaxine Hydrochloride Extended-Release Capsules, 150 mg, lot # R1P2475, comparing it to Wyeth Consumer Healthcare's Effexor® XR (venlafaxine hydrochloride) Extended-Release Capsules, 150 mg,lot # B05403.

3. The DBE **accepts** the re-dosing fed BE study No. VENL-0548A for information only.

4. The firm's *in vitro* dissolution testing is **acceptable**. The dissolution testing should be conducted in 900 mL of Water at 37ºC ± 0.5ºC using Apparatus I (Basket) at 100 rpm. The test product should meet the following specifications:

   2 hour: (b) (4)
   4 hours: (b) (4)
   8 hours: (b) (4)
   12 hours: (b) (4)
   24 hours: (b) (4)

5. The dissolution testing conducted by Mylan on its Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg and 75 mg, is acceptable. The firm has conducted acceptable in vivo bioequivalence testing comparing its Venlafaxine Hydrochloride Extended-Release Capsules, 150 mg, with Wyeth Consumer Healthcare's Effexor® XR (venlafaxine hydrochloride) Extended-Release Capsules, 150 mg. The formulations for the 37.5 mg and 75 mg strengths are proportionally similar to the 150 mg strength of the test product which underwent bioequivalence testing. The DBE finds Mylan Pharmaceuticals' Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg and 75 mg, to be acceptable as per Section 21 CFR § 320.24 (b) (6).

6. The DBE deems the test product, Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg, 75 mg, and 150 mg, manufactured by Mylan Pharmaceuticals, bioequivalent to Effexor® XR (venlafaxine hydrochloride) Extended-Release Capsules, 37.5, 75 mg, and 150 mg, respectively, manufactured by Wyeth Consumer Healthcare.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-789

APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg, 75 mg, and 150 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has no further questions at this time.

We acknowledge that you will conduct dissolution testing on your Venlafaxine Hydrochloride Extended-Release Capsules using the following FDA-recommended dissolution method and specifications:

Medium:	Water
Volume:	900 mL
USP Apparatus:	Type I (Basket)
Rotation (rpm):	100 rpm
Specifications:	2 hr: (b) (4) 4 hrs: (b) (4) 8 hrs: (b) (4) 12 hrs: (b) (4) 24 hrs: (b) (4)

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

VI. OUTCOME PAGE

ANDA: 78-789

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
5117	2/15/2008	Other	Study Amendment	1	1
				Bean Total:	1

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

/s/

Johnetta Farrar
4/15/2008 01:49:13 PM
BIOPHARMACEUTICS

April Braddy
4/16/2008 08:26:51 AM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
4/16/2008 08:45:56 AM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-789	
Drug Product Name	Venlafaxine Hydrochloride Extended-release Capsules	
Strength(s)	37.5 mg, 75 mg, and 150 mg	
Applicant Name	Mylan Pharmaceuticals	
Address	781 Chestnut Ridge Road, Morgantown, WV 26505	
Applicant's Point of Contact	S. Wayne Talton, Vice President, Regulatory Affairs	
Contact's Telephone Number	304-599-2595 ext. 6551	
Contact's Fax Number	304-285-6407	
Original Submission Date(s)	15 January 2007	
Submission Date(s) of Amendment(s) Under Review	06 November 2007 16 November 2007	
Reviewer	Johnetta L. Farrar, Ph.D.	
Study Number (s)	VENL-0548	VENL-0549
Study Type (s)	Fed	Fed Sprinkle
Strength (s)	150 mg	150 mg
Clinical Site	Kendle International Inc.	
Clinical Site Address	763 Chestnut Ridge Road, Morgantown, WV 26505	
Analytical Site	Mylan Pharmaceuticals - Bioanalytical Division	
Analytical Site Address	3711 Collins Ferry Road, Morgantown, WV 26505	
OUTCOME DECISION	**INCOMPLETE**	

1 EXECUTIVE SUMMARY

This application contains the results of fed and fed sprinkle bioequivalence (BE) studies comparing the test product, Mylan Pharmaceutical's Venlafaxine Hydrochloride Extended-Release Capsules, 150 mg, to the corresponding reference product, Wyeth Consumer Healthcare's Effexor® XR Capsules, 150 mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy subjects. The firm's fed and fed sprinkle BE studies are acceptable. The results are summarized in the tables below.

Venlafaxine Hydrochloride Extended-Release 150 mg Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study VENL-0548 - Venlafaxine				
Parameter	**Test**	**Reference**	**Ratio***	**90% C.I.****
AUCL	1643	1555	1.06	98% - 114%
AUCI	1725	1668	1.03	96% - 112%
C_{max}	106.7	97.0	1.10	101% - 119%

Venlafaxine Hydrochloride Extended-Release 150 mg Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Applesauce Sprinkle Fed Bioequivalence Study VENL-0549 - Venlafaxine				
Parameter	**Test**	**Reference**	**Ratio***	**90% C.I.****
AUCL	1259	1219	1.03	95% - 110%
AUCI	1350	1297	1.03	96% - 111%
C_{max}	83.7	81.9	1.01	94% - 109%

*Ratio (A/B) = $e^{[\text{LSMEAN of LNA} - \text{LSMEAN of LNB}]}$
**Used Natural Log Transformed Parameter

In the BE studies, the pharmacokinetic (PK) parameters of the test and reference for the active metabolite, O-desmethylvenlafaxine, were comparable. Therefore the metabolite data are supportive and the studies are acceptable.

There was evidence that an additional bioequivalence study was conducted as Study No VENL-0548A based on bioanalytical validation data found in the bioanalytical report amendment for the Fed Study No. VENL-0548. The firm is asked to explain the bioanalytical validation data for Study No. VENL-0548A and provide additional information concerning Study No. VENL-0548A.

The firm has conducted acceptable comparative dissolution testing on all strengths using the FDA-recommended dissolution method (DFS). The DBE recommended dissolution specifications based on the submitted dissolution data which met the recommended specifications at L1 level. However, in a recent dissolution amendment, the firm did not accept the FDA-proposed specifications and proposed different specifications instead. The firm's latest proposed specifications are wider than the FDA-recommended specifications and without acceptable justification. The firm is asked to submit additional dissolution data for three fresh production batches to justify its proposed specifications. The dissolution testing is incomplete pending additional dissolution data, or alternatively, the firm's acceptance of the FDA-recommended specifications.

The DBE does not grant the waiver request(s) for *in vivo* BE study requirements for the lower strengths, 37.5 mg and 75 mg, pending acceptable and complete dissolution testing of all strengths.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is incomplete.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg, 75 mg and 150 mg
Reference Product	Effexor XR® Capsules,37.5 mg, 75 mg and 150 mg
RLD Manufacturer	Wyeth Consumer Laboratories, Inc.
NDA No.	20-699
RLD Approval Date	20 October 1997
Indication	Effexor XR (venlafaxine hydrochloride) extended-release capsule is indicated for the treatment of major depressive disorder.

3.2 PK/PD Information[1]

Bioavailability	Venlafaxine is well absorbed and extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the only major active metabolite. On the basis of mass balance studies, at least 92% of a single oral dose of venlafaxine is absorbed. The absolute bioavailability of venlafaxine is about 45%.
Food Effect	The RLD product labeling stated that food did not affect the bioavailability of venlafaxine or its active metabolite, ODV. Time of administration (AM vs. PM) did not affect the pharmacokinetics of venlafaxine and ODV following administration of the 75 mg Effexor XR capsule. The RLD labeling also recommends that Effexor XR should be administered in a single dose with food either in the morning or in the evening at approximately the same time each day. Each capsule should be swallowed whole with fluid and not divided, crushed, chewed, or placed in water, or it may be administered by carefully opening the capsule and sprinkling the entire contents on a spoonful of applesauce. This drug/food mixture should be swallowed immediately without chewing and followed with a glass of water to ensure complete swallowing of the pellets. For these reasons, both Fed and Fed Sprinkle BE studies are currently recommended for the drug product.
T_{max}	5.5 hours for venlafaxine and 9 hours for ODV (for extended release)
Metabolism	Following absorption, venlafaxine undergoes extensive presystemic metabolism in the liver, primarily to ODV, but also to N-desmethylvenlafaxine, N, O-didesmethylvenlafaxine, and other minor metabolites. *In vitro* studies indicate that the formation of ODV is catalyzed by CYP2D6; this has been confirmed in a clinical study showing that patients with low CYP2D6 levels ("poor metabolizers") had increased levels of venlafaxine and reduced levels of ODV compared to people with normal CYP2D6 ("extensive metabolizers"). The differences between the CYP2D6

[1] PDR® Electronic Library (http://www.thomsonhc.com/pdrel/librarian)

	poor and extensive metabolizers, however, are not expected to be clinically important because the sum of venlafaxine and ODV is similar in the two groups and venlafaxine and ODV are pharmacologically approximately equiactive and equipotent.
Excretion	Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is thus the primary route of excretion.
Half-life	elimination half-life is 5±2 hours for venlafaxine and 11±2 hours for ODV
Drug Specific Issues (if any)	The RLD labeling contains a Black Box Warning on suicidality in children, adolescents, and young adults prescribed with the drug product.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fed and fed sprinkle

1.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover *in-vivo*
	Strength:	150 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	Due to safety concerns, bioequivalence studies under fasting conditions are not recommended[2].

2.	**Type of study:**	Fed Sprinkle
	Design:	Single-dose, two-treatment, two-period crossover *in-vivo*
	Strength:	150 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	Please see comment above.

Analytes to measure (in plasma/serum/blood):	Venlafaxine, and its metabolite O-desmethylvenlafaxine (ODV), in plasma
Bioequivalence based on (90% CI):	Venlafaxine
Waiver request of *in-vivo* testing:	37.5 mg and 75 mg based on (i) acceptable bioequivalence studies on the 100 mg strength, (ii) proportional similarity of the formulations between all strengths, and (iii) acceptable *in vitro* dissolution testing of all strengths.
Source of most recent recommendations:	Current Draft BE Guidance of Venlafaxine Hydrochloride Extended-Release Capsule on the FDA website.

[2] FDA Draft Guidance on Venlafaxine Hydrochloride Extended-Release Capsules

Summary of OGD or DBE History:

The DBE currently recommends the following for Venlafaxine HCl Extended-Release Capsule drug products:

1. Single-dose, two-way crossover fed and fed sprinkle studies on 150 mg tablet.
2. Measurement of the parent drug and major metabolite, O-desmethylvenlafaxine.
3. The dissolution testing should be conducted in 900 mL of water using Apparatus 1 (Basket) at 100 rpm.
4. Venlafaxine HCl extended-release capsules, 37.5 mg and 75 mg, are eligible for a waiver of *in vivo* bioequivalence study requirements based on (1) acceptable bioequivalence studies on the 150 mg strength, (2) acceptable dissolution testing of all strengths, and (3) proportional similarity in the formulations of all strengths.

The following ANDAs on Venlafaxine HCl Extended-Release capsules have been reviewed and found acceptable by the DBE:

Firm	ANDA#	Letter Date
Teva	76-565	12-10-02
Anchen	78-087	12-23-05

The following ANDAs on Venlafaxine HCl Extended-Release capsules are currently under review in the DBE:

Firm	ANDA#	Letter Date
		(b) (4)
		(b) (4)
Mylan (current)	78-789	01-15-07
Wockhardt	78-865	03-08-07
		(b) (4)

The following ANDAs on Venlafaxine HCl Extended-Release capsules have been reviewed and found incomplete by the DBE:

Firm	ANDA#	Letter Date
		(b) (4)
Impax	78-057	12-15-05

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fed	Yes	1
Single-dose fed sprinkle	Yes	1
Steady-state	No	-
***In vitro* dissolution**	Yes	3
Waiver requests	Yes	2
BCS Waivers	No	-
Clinical Endpoints	No	-
Failed Studies	No	-
Amendments	Yes	2

3.5 Pre-Study Bioanalytical Method Validation

Report Location	Venlafaxine Hydrochloride Bioanalytical Method Validation Report, Sections 5.3.1.4.1 and 5.3.1.4.2
Analyte	Venlafaxine / O-desmethylvenlafaxine
Internal Standard (IS)	(b) (4)
Method Description	Direct Injection / Tandem MS Detection
Limit of Quantitation (ng/mL)	2 ng/mL VENL and OVEN
Average Recovery of Drug (%)	51.10% VENL and 47.57% OVEN
Average Recovery of IS (%)	25.12%
Standard Curve Concentrations (ng/mL)	2, 4, 6, 10, 20, 40, 80, 120, 160, 200
QC Concentrations (ng/mL)	2, 6, 20, 120
QC Intraday Precision Range (%)	1.85 to 7.35 VENL / 1.19 to 5.99 OVEN
QC Intraday Accuracy Range (%)	-3.75 to 1.72 VENL / -0.73 to 3.61 OVEN
QC Interday Precision Range (%)	2.49 to 7.19 VENL / 3.006 to 6.645 OVEN
QC Interday Accuracy Range (%)	-1.95 to 2.46 VENL / -0.86 to 7.76 OVEN
Bench-Top Stability (hrs)	6 hours @ room temperature VENL and OVEN
Stock Stability (days)	29 days @ 4°C VENL/OVEN working solution, 8 days @ 4°C IS working solution
Processed Stability (hrs)	52 hours @ room temperature
Freeze-Thaw Stability (cycles)	4 cycles
Long-Term Storage Stability (days)	436 days @ -70°C
Dilution Integrity	Concentration diluted 2-fold
Selectivity	No significant interfering peaks noted in blank plasma samples

SOPs submitted	Yes
Bioanalytical method is acceptable	Acceptable

Comments on the Pre-Study Method Validation:

Acceptable.

3.6 *In Vivo* Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route), (Product ID)	Subjects Number (M/F), Type, Mean Age (yrs), (Range)	Mean Parameters (± SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUCL (ng/mL•hr)	AUCI (ng/mL•hr)	$T_{1/2}$ (hr)	Kel (hr^{-1})	
VENL-0548	Single-Dose Fed Bioequivalence Study of Venlafaxine Hydrochloride Extended-Release Capsules (150 mg; Mylan) and Effexor® XR Capsules (150 mg; Wyeth) in Healthy Adult Volunteers	Open-label, Single-dose, Randomized, Two-period, Two-treatment Crossover	A = Venlafaxine Hydrochloride Extended-Release 150 mg Capsule 1 x 150 mg oral route Lot# R1P2475	24 Dosed 22 Completed (M: 11, F: 11) Healthy Subjects Mean Age: 27.2 (Range: 19 to 43) Mean Weight: 156.9 (Range: 114 to 196) Mean BMI: 24.7 (Range: 19.3 to 30.2) 20 Statistically Analyzed (M: 10; F: 10)	Venlafaxine						Section 5.3.1.4.1
					117.1 ± 49.7	6.05	2091 ± 1770	2176 ± 1871	9.76	0.0781	
			B = Effexor® XR 150 mg Capsule 1 x 25 mg oral route Lot# B05403 exp: 3/2007		107.0 ± 48.8	6.55	1985 ± 1712	2114 ± 1898	11.21	0.0682	
					O-desmethylvenlafaxine						
					196.9 ± 77.7	11.20	5651 ± 1858	5828 ± 1907	12.32	0.0586	
					176.7 ± 64.07	11.40	5246 ± 1682	5444 ± 1702	13.61	0.0535	

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route), (Product ID)	Subjects Number (M/F), Type, Mean Age (yrs), (Range)	Mean Parameters (± SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUCL (ng/mL•hr)	AUCI (ng/mL•hr)	$T_{1/2}$ (hr)	Kel (hr^{-1})	
VENL-0549	Single-Dose Fed Bioequivalence Study of Venlafaxine Hydrochloride Extended-Release Capsules (150 mg; Mylan) and Effexor ® XR Capsules (150 mg; Wyeth) Administered with Applesauce in Healthy Adult Volunteers	Open-label, Single-dose, Randomized, Two-period, Two-treatment Crossover	A = Venlafaxine Hydrochloride Extended-Release 150 mg Capsule 1 x 150 mg oral route Lot# R1P2475	24 Dosed 20 Completed (M: 9, F: 11) Healthy Subjects Mean Age: 29.1 (Range: 18 to 55) Mean Weight: 163.0 (Range: 134 to 206) Mean BMI: 24.6 (Range: 20.8 to 28.7)	Venlafaxine						Section 5.3.1.4.1
					97.5 ± 58.7	6.20	1751 ± 1946	1847 ± 2039	10.07	0.0739	
			B = Effexor® XR 150 mg Capsule 1 x 25 mg oral route Lot# B05403 exp: 3/2007		92.5 ± 52.0	7.05	1678 ± 1925	1772 ± 2070	10.65	0.0707	
					O-desmethylvenlafaxine						
					183.6 ± 68.5	10.00	5398 ± 1688	5580 ± 1717	12.62	0.0576	
					177.9 ± 58.9	9.80	5198 ± 1582	5437 ± 1649	13.24	0.0540	

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Venlafaxine Dose: 1 x 150 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (VENL-0548)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/mL)	1616.73	1530.92	1.06	98.14	113.63
AUC∞ (ng*hr/mL)	1699.18	1642.55	1.03	95.93	111.56
C_{max} (ng/mL)	106.04	96.43	1.10	101.54	119.09

Venlafaxine Dose: 1 x 150 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Sprinkle Bioequivalence Study (VENL-0549)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/mL)	1256.03	1228.84	1.02	94.08	111.05
AUC∞ (ng*hr/mL)	1339.53	1300.50	1.03	94.91	111.78
C_{max} (ng/mL)	83.21	82.05	1.01	93.18	110.35

Table 3. Reanalysis of Study Samples

VENL-0548-Food Study Repeat Analysis Results for Venlafaxine Additional Information in Section 5.3.1.4.1 (Bioanalytical Report for VENL-0548)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual Number		% of total assays		Actual Number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0%	0%	0	0	0%	0%
Reason A	2	0	0.25%	0%	0.25%	0%	0.25%	0%
Reason B	1	1	0.13%	0.13%	0.13%	0.13%	0.13%	0.13%
Reason C	11	7	1.39%	0.88%	1.39%	0.88%	1.39%	0.88%
Total	14	8	1.77%	1.01%	1.77%	1.01%	1.77%	1.01%

VENL-0549-Fed Applesauce Study Repeat Analysis Results for Venlafaxine Additional Information in Section 5.3.1.4.2 (Bioanalytical Report for VENL-0549)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual Number		% of total assays		Actual Number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0%	0%	0	0	0%	0%
Reason A	1	0	0.14%	0%	1	0	0.14%	0%
Reason D	0	1	0%	0.14%	0	1	0%	0.14%
Total	1	1	0.14%	0.14%	1	1	0.14%	0.14%

Reason A = Analytical error
Reason B = Measurable concentration in subject zero samples
Reason C = Sample Outside limits of curve range (BLQ)
Reason D = Sample lost during assay procedure

Did use of recalculated plasma concentration data change study outcome?

No.

Comments from the Reviewer:

Since subject 17 had predose drug concentrations greater than 5% of the Cmax, the subject was dropped from the study statistical analysis. The study outcome from the reviewer's analysis was not different from that of the firm's analysis.

3.7 Formulation

Location in appendix	Section 4.2, Page 42
If a tablet, is the RLD scored?	**N/A**
If a tablet, is the test product biobatch scored	**N/A**
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	**N/A**

Comments from the Reviewer:

1. All strengths of the test product are proportionally similar.
2. Each inactive ingredient of the test product also falls within acceptable limits listed in the Inactive Ingredient Guidance (IIG).
3. There is no overage of active pharmaceutical ingredient (API).
4. The (b) (4) are present in acceptable amounts per the Chemistry review of the ANDA (DFS).

3.8 *In Vitro* Dissolution

Location of DBE Dissolution Review	DFS
Source of Method (USP, FDA or Firm)	FDA
Medium	Water
Volume	900 mL
USP Apparatus type	Apparatus I (basket)
Rotation	100 rpm
DBE-recommended specifications (based on submitted data)	2 hour: (b) (4) 4 hour: (b) (4) 8 hour: (b) (4) 12 hour: (b) (4) 24 hour: (b) (4)
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	Yes
If no, reason why F2 not calculated	N/A
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	N/A

F2 metric, biostudy strengths compared to other strength(s)			
Biostudy Strength	**Other Strength**	**F2 metric for test**	**F2 metric for RLD**
150 mg	37.5 mg	98.02	66.94
150 mg	75 mg	88.07	67.47

The firm proposed dissolution specifications in the original submission were too wide and not optimal (i.e., 2 hours: NMT (b) (4)%; 6 hours: (b) (4); 12 hours: (b) (4)%; 24 hours: NLT (b) (4)%). The DBE recommended dissolution specifications based on the submitted dissolution data which met the recommended specifications at L1 level (see above). However, in a recent dissolution amendment, the firm did not accept the FDA-

proposed specifications and proposed different specifications instead. The firm's latest proposed specifications are still wider than the FDA-recommended specifications and without acceptable justification (i.e., 2 hours: (b) (4) 6 hours: (b) (4)%; 8 hours: (b) (4) (b) (4)%; 12 hours: (b) (4)%; 24 hours: (b) (4) The firm submitted stability data in support of the newly proposed specifications. The DBE generally does not set dissolution specifications based on stability data of stored lots. Therefore, the firm is asked to submit additional dissolution data for three fresh production batches to justify its proposed specifications. The dissolution testing is incomplete pending additional dissolution data, or alternatively, the firm's acceptance of the FDA-recommended specifications.

3.9 Waiver Request(s)

Strengths for which waivers are requested	37.5 mg and 75 mg
Proportional to strength tested *in vivo*?	Yes
Is dissolution acceptable?	Incomplete
Waivers granted?	**No.**
If not then why?	**Pending acceptable and complete dissolution testing.**

3.10 Deficiency Comments

1. The firm's recent proposed specifications for the 2, 4, 8, 12, and 24 hour sampling time points of (b) (4) (b) (4) (b) (4) (b) (4) and (b) (4) (respectively) based on the submitted stability (stored) data are not acceptable. As per the Division of Bioequivalence (DBE) practice, the dissolution specifications are established based on the dissolution data on 12 units of the biolot (**fresh, not stored**) that has been used in acceptable bioequivalence studies. The DBE does not revise the dissolution specifications on the basis of the dissolution testing data on the stored lots. In order to justify their proposed specification, the firm should submit additional dissolution data of three **fresh** production lots, to determine if a revision of the dissolution specification is warranted. Alternatively, the firm should acknowledge the FDA-recommended dissolution method and specifications given below:

Medium:	Water
Volume:	900 mL
USP Apparatus:	Type 1 (basket)
Rotation (rpm):	100 rpm
Specifications:	2 hr: (b) (4) 4 hrs: (b) (4) 8 hrs: (b) (4) 12 hrs: (b) (4) 24 hrs: (b) (4)

2. There was evidence that an additional bioequivalence study was conducted as Study No. VENL-0548A based on some within-study bioanalytical validation data submitted in the amendment dated November 6, 2007 (Attachment E, pages 67-68) for the Fed Study No. VENL-0548, as well as based on the existence of the SOP Nos. D-400-07 ("Reassay or Reinjection of Clinical Samples", issued October 19, 2006) and D-416-05 ("Reassay of Whole Subjects", issued October 19, 2007) . The firm has submitted a protocol amendment for the Fed Study VENL-0548 to include a *Redose Study* which was to be identified as Study No. VENL-0548A. However, there was no other data or report submitted for Study No. VENL-0548A. The firm has also indicated in the Fed Study report that Subject 5 was difficult to contact for redosing, and this subject was dropped from the firm's analysis of the Fed Study results. The firm is now asked to explain the existence of the bioanalytical validation data for Study No. VENL-0548A, and to confirm if the Redose Study No. VENL-0548A was ever carried out.

3.11 Recommendations

1. The Division of Bioequivalence **accepts** the fed BE study No. VENL-0548 conducted by Mylan Pharmaceuticals on its Venlafaxine Hydrochloride Extended-Release Capsules, 150 mg, lot # R1P2475, comparing it to Wyeth Consumer Healthcare's Effexor® XR 150 mg Capsules, lot # B05403.

2. The Division of Bioequivalence **accepts** the fed sprinkle BE study No. VENL-0549 conducted by Mylan Pharmaceuticals on its Venlafaxine Hydrochloride Extended-Release Capsules, 150 mg, lot # R1P2475, comparing it to Wyeth Consumer Healthcare's Effexor® XR 150 mg Capsules, lot # B05403.

3. There was evidence that an additional bioequivalence study was conducted as Study No VENL-0548A based on bioanalytical validation data found in the bioanalytical report amendment for the Fed Study No. VENL-0548. The firm is asked to explain the bioanalytical validation data for Study No. VENL-0548A and provide additional information concerning Study No. VENL-0548A.

4. The firm's *in vitro* dissolution testing is **incomplete** pending its acceptance and acknowledgment of the FDA-recommended method and specifications. The dissolution testing should be conducted in 900 mL of Water at 37ºC ± 0.5ºC using Apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

   2 hour: (b) (4)
   4 hours: (b) (4)
   8 hours: (b) (4)
   12 hours: (b) (4)
   24 hours: (b) (4)

The firm's recent proposed specifications for the 2, 4, 8, 12, and 24 hour sampling time points of (b) (4) (b) (4) (b) (4) (b) (4) and (b) (4) (respectively) based on the submitted stability (stored) data are not acceptable. As per the Division of Bioequivalence (DBE) practice, the dissolution specifications are established based on the dissolution data on 12 units of the biolot (**fresh, not stored**) that has been used in acceptable bioequivalence studies. The DBE does not revise the dissolution specifications on the basis of the dissolution testing data on the stored lots. In order to justify their proposed specification, the firm should submit additional dissolution data of three **fresh** production lots, to determine if a revision of the dissolution specification is warranted. Alternatively, the firm should acknowledge the FDA-recommended dissolution method and specifications above.

4. At this time, the Division of Bioequivalence (DBE) does not consider the waiver requests for the lower strengths, 37.5 mg and 75 mg, of the test product pending acceptable and complete dissolution testing of all strengths.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
--	None

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fed Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	VENL-0548
Study Title	Single-Dose Fed Bioequivalence Study of Venlafaxine Hydrochloride Extended-Release Capsules (150 mg; Mylan) and Effexor® XR Capsules (150 mg; Wyeth) in Healthy Adult Volunteers
Clinical Site (Name & Address)	Kendle International, Inc. 763 Chestnut Ridge Road Morgantown, WV 26505
Principal Investigator	Dorian Williams, MD
Dosing Dates	Period I: 21 July 2006 – 25 July 2006 Period II: 28 July 2006 – 1 August 2006
Analytical Site (Name & Address)	Mylan Pharmaceuticals – Bioanalytical Division 3711 Collins Ferry Road Morgantown, WV 26505
Analytical Director	Patrick T. Vallano, Ph.D.
Analysis Dates	7 August 2006 – 15 August 2006
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	24 days at -70°C

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Venlafaxine HCl Extended-Release Capsules, 150 mg	Effexor XR® Capsules, 150 mg
Manufacturer	Mylan Pharmaceuticals, Inc.	Wyeth Pharmaceuticals, Inc.
Batch/Lot No.	R1P2475	B05403
Manufacture Date	02 February 2006	
Expiration Date		March 2007
Strength	150 mg	150 mg
Dosage Form	Extended-release capsule	Extended-release capsule
Bio-Batch Size	(b) (4) capsules	
Production Batch Size	(b) (4) capsules	
Potency (Assay)	99.8%	100.6%
Content Uniformity (mean, %CV)	99.2 (CV 1.0%)	
Dose Administered	1 x 150 mg	1 x 150 mg
Route of Administration	Orally	Orally

Table 6. Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Twenty-four (24) non-tobacco using, adult, male and female healthy volunteers between the ages of 19 and 43 were enrolled in the study. Twenty-two subjects completed both periods I and II of the study.
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	At least 7 days
Randomization Scheme	Sequence 1 = A B :02, 04, 06, 09, 10, 12, 13, 15, 17, 19, 22, 24 Sequence 2 = B A: 01, 03, 05, 07, 08, 11, 14, 16, 18, 20, 21, 23
Blood Sampling Times	Predose (within 45 minutes prior to dosing), and at 0.5, 1.0, 2.0, 4.0, 5.0, 6.0, 7.0, 8.0. 9.0, 10, 12. 14, 16, 24, 36, 48, and 72 hours postdose.
Blood Volume Collected/Sample	1 x 6 mL of blood collected in sodium heparin tubes
Blood Sample Processing/Storage	Samples were collected and centrifuged at 3000 RPM and 4°C for 10 minutes. The samples were then returned to an ice bath. The plasma was then transferred into the appropriately labeled polypropylene tubes, with each sample being divided into 2 aliquots. The samples were then frozen at -70°C ± 15°C until shipment for sample analysis.
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	Food was not permitted from at least 10 hours prior to dosing until breakfast the day of dosing, On the day prior to dosing, dinner was consumed 13.5 hours prior to dosing. After a supervised overnight fast subjects received a standardized breakfast 30 minutes prior to dosing, and the breakfast was consumed within 15 minutes.
Length of Confinement	Subjects were housed at least 16 hours prior to and at least until 24 hours after post-dosing and were allowed to return to the clinic for blood draws scheduled after 24 hours.
Safety Monitoring	For safety monitoring, vital signs (including systolic and diastolic blood pressures, pulse, respiration rates, and temperature) were measured within 60 minutes prior to dosing and prior to the pre-dose blood sample collection.
Standard FDA Meal Used?	Yes

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

	FED BIOEQUIVALENCE STUDY VENL-0548		FED WITH APPLESAUCE BIOEQUIVALENCE STUDY VENL-0549	
	TREATMENT GROUPS			
	TEST N=22	REFERENCE N=22	TEST N=20	REFERENCE N=20
AGE				
Mean ± SD	27.2 ± 6.5	27.2 ± 6.5	29.1 ± 10.6	29.1 ± 10.6
Range	19-43	19-43	18-55	18-55
Groups				
<18	0	0	0	0
18-40	21 (95%)	21 (95%)	17 (85%)	17 (85%)
41-64	1 (5%)	1 (5%)	3 (15%)	3 (15%)
65-75	0	0	0	0
>75	0	0	0	0
SEX				
Female	11 (50%)	11 (50%)	11 (55%)	11 (55%)
Male	11 (50%)	11 (50%)	9 (45%)	9 (45%)
RACE				
Asian	0	0	0	0
Black	4 (18%)	4 (18%)	2 (10%)	2 (10%)
Caucasian	16 (73%)	16 (73%)	18 (90%)	18 (90%)
Other	2 (9%)	2 (9%)		
ETHNICITY				
Hispanic or Latino	3 (14%)	3 (14%)	4 (20%)	4 (20%)
Not Hispanic or Latino	19 (86%)	19 (86%)	16 (80%)	16 (80%)
Other Factors				

Table 8. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
04	Dropped by sponsor during Period I due to adverse event (vomiting). Received treatment A (Test)	I	No
18	Dropped by sponsor during Period I due to administration of concomitant medication. Received treatment B (Reference)	I	No

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System/Adverse Event [1]	Reported Incidence by Treatment Groups			
	Fed Bioequivalence Study VENL-0548 *		Fed with Applesauce Bioequivalence Study VENL-0549	
	TEST N = 23 [2] n=% [3]	REFERENCE N = 23 [2] n=% [3]	TEST N = 23 [2] n=% [3]	REFERENCE N = 21 [2] n=% [3]
Nervous System Disorders				
Headache	7 (30%)	4 (17%)	1 (4%)	1 (5%)
Dizziness	1 (4%)	2 (9%)	3 (13%)	2 (10%)
Restlessness	1 (4%)	1 (4%)	0	0
Shakiness	0	0	1 (4%)	2 (10%)
Lightheadedness	0	1 (4%)	0	0
Drowsiness	3 (13%)	2 (9%)	0	0
Insomnia	1 (4%)	0	0	0
Lethargic	0	0	1 (4%)	0
Gastrointestinal Disorders				
Nausea	8 (35%)	6 (26%)	6 (26%)	7 (33%)
Vomiting	1 (4%)	0	2 (9%)	1 (5%)
Dry Mouth	0	0	1 (4%)	2 (10%)
Bad Taste	1 (4%)	0	0	0
Psychiatric Disorders				
Anxiety	1 (4%)	1 (4%)	0	0
Nervousness	1 (4%)	1 (4%)	1 (4%)	0
Emotional Disorder	1 (4%)	0	0	0
Metabolism and Nutrition Disorders				
Decreased Appetite	2 (9%)	1 (4%)	1 (4%)	0
General Disorders and Administrative Site Disorders				
Skin Clammy	1 (4%)	0	0	0
Hot Flash	1 (4%)	0	0	0
Skin and Subcutaneous Disorders				
Rash (Near Left Eye)	1 (4%)	0	0	0
Itchiness (Near Left Eye)	1 (4%)	0	0	0

Body System/Adverse Event [1]	Reported Incidence by Treatment Groups			
	Fed Bioequivalence Study VENL-0548 *		Fed with Applesauce Bioequivalence Study VENL-0549	
	TEST N = 23 [2] n=% [3]	REFERENCE N = 23 [2] n=% [3]	TEST N = 23 [2] n=% [3]	REFERENCE N = 21 [2] n=% [3]
Eye Disorders				
Blurred Vision	0	1 (4%)	0	0
Musculoskeletal and Connective Tissue Disorders				
Aching in Limb	0	0	1 (4%)	0
Back Pain	0	0	1 (4%)	0
Wrist Pain (Left)	0	0	1 (4%)	0
Wrist Swelling (Left)	0	0	1 (4%)	0
Cramp (Leg)	0	1 (4%)	0	0
Ankles Swelling	0	1 (4%)	0	0
Cardiac Disorders				
Heart Fluttering	0	1 (4%)	0	0
Respirtatory, Thoracic, and Mediastinal Disorders				
Yawning	0	0	0	1 (5%)
Shortness of Breath	0	0	0	1 (5%)
Investigations				
Blood Iron Decreased	1 (4%)	0	0	0
AST Levels Elevated	0	0	0	1 (5%)
Total Subjects Reporting at Least One Adverse Event	13 (57%)	12 (52%)	13 (57%)	10 (48%)

(1) MedDRA Version 8.0
(2) N = Number of subjects dosed for each treatment
(3) n = Number of subjects reporting at least one incidence of respective adverse event; (%)=percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100% (n/N%)
** One subject experienced an adverse event of headache prior to Period I dosing, and another subject had swelling and redness of left foot prior to dosing in Period I.*

Table 10. Protocol Deviations, Fed Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sample collection deviation (Period I, +0:48, 2%)	12	
Blood sample collection deviation (Period II, +0:3, 1%)	21	
Blood sample collection deviation (Period II, +0:12, 0.4%)		15
Blood sample collection deviation (Period II, +0:20, 0.5%)		12
Concomitant medication within 7 days of start of study: vitamin – Subject MDR7943		
Vital sign collection inadvertently collected outside allowable protocol window at study hour 4	21	
Vital sign collection inadvertently collected outside allowable protocol window at study hour 12		15
Vital sign collection inadvertently collected outside allowable protocol window at study hour 48		23

Comments on Dropouts/Adverse Events/Protocol Deviations:

- Primary protocol deviations that occurred during the study consisted of blood sample collection deviations at various time points. The sample collection time deviations were not significant (± 5%).

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fed Bioequivalence Study

Venlafaxine										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	2.0	4.0	6.0	10.0	40.0	80.0	160.0	240.0	320.0	400.0
Inter day Precision (%CV)	1.93	3.48	2.35	1.31	2.35	1.47	1.61	1.68	1.83	1.56
Inter day Accuracy (%Actual)	101.2	100.3	95.62	98.18	97.00	99.85	100.5	101.8	102.0	103.0
Linearity	0.9978 – 0.9996									
Linearity Range (ng/mL)	2.0 – 400.0									
Sensitivity/LOQ (ng/mL)	2.0									

Parameter	**Quality Control Samples**		
Concentration (ng/mL)	6.000	40.00	240.00
Inter day Precision (%CV)	7.7	3.05	1.74
Inter day Accuracy (%Actual)	100.95	99.6	100.46

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable.

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
D-400-06[1]	07 December 2005	Reassay or Reinjection of Clinical Samples
D-400-07[2]	19 October 2006	Reassay or Reinjection of Clinical Samples
D-416-04[1]	18 May 2006	Reassay of Whole Subjects
D-416-05[2]	19 October 2006	Reassay of Whole Subjects

[1]VENL-0548 & VENL-0549
[2]VENL-0548A, no miscellaneous repeats or whole subjects were performed.

Comments: In table 12 (above) as well as in the bioanalytical report amendment (bioequivalence amendment dated 06 November 2007, Attachment E, pages 67-68), the firm refers to study VENL-0548A. However, there was no mentioning of this study elsewhere in the submission. The firm is asked to identify and/or provide additional information concerning the study# VENL-0548A.

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

Repeat assay study values were acceptable for the reasons of "analytical error", "measurable concentration in subject zero samples", "sample outside limits of curve range (BLQ)", and "sample lost during assay procedure".

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

Fed Bioequivalence Study, Study No. VENL-0548									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *ng/ml)	2049.46	85.69	390.01	8594.97	1989.99	85.05	396.45	8314.18	1.03
AUC∞ (hr *ng/ml)	2143.82	88.09	556.64	9308.64	2119.84	89.73	540.90	9466.03	1.01
Cmax (ng/ml)	111.06	48.74	0.00	237.40	106.64	45.49	40.16	219.40	1.04
T_{max}* (hr)	6.00	.	5.00	72.00	6.00	.	6.00	9.00	1.00
Kel (hr^{-1})	0.08	30.94	0.03	0.14	0.07	22.74	0.03	0.10	1.08
T1/2 (hr)	10.12	33.30	5.00	20.53	10.65	32.56	6.98	23.64	0.95

* T_{max} values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Venlafaxine Hydrochloride Extended-Release 150 mg Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Food Bioequivalence Study VENL-0548 - venlafaxine				
Parameter	**Test**	**Reference**	**Ratio***	**90% C.I.****
AUCL	1643	1555	1.06	98% - 114%
AUCI	1725	1668	1.03	96% - 112%
C_{max}	106.7	97.0	1.10	101% - 119%

Venlafaxine Hydrochloride Extended-Release 150 mg Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Food Bioequivalence Study VENL-0548 – o-desmethylvenlafaxine				
Parameter	**Test**	**Reference**	**Ratio***	**90% C.I.****
AUCL	5252	4879	1.08	105% - 110%
AUCI	5429	5102	1.06	104% - 109%
C_{max}	176.2	159.2	1.11	106% - 115%

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Venlafaxine 1 x 150 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. VENL-0548					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	1616.73	1530.92	1.06	98.14	113.63
AUC∞ (hr *ng/ml)	1699.18	1642.55	1.03	95.93	111.56
Cmax (ng/ml)	106.04	96.43	1.10	101.54	119.09

Table 17. Additional Study Information, Fed Study No. VENL-0548

Root mean square error, AUC0-t	0.1368	
Root mean square error, AUC∞	0.1409	
Root mean square error, C_{max}	0.1488	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	21	21
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		

measurable drug concentrations at 0 hr	1	1
first measurable drug concentration as Cmax	No	No
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	20	0.95	0.70	0.99
Reference	21	0.94	0.73	0.99

Comments on Pharmacokinetic and Statistical Analysis:

In the Fed Study, the pharmacokinetic (PK) parameters of the test and reference for the active metabolite, O-desmethylvenlafaxine, were comparable. The metabolite data also falls within the 90% confidence interval; therefore the metabolite data are supportive and the study is acceptable.

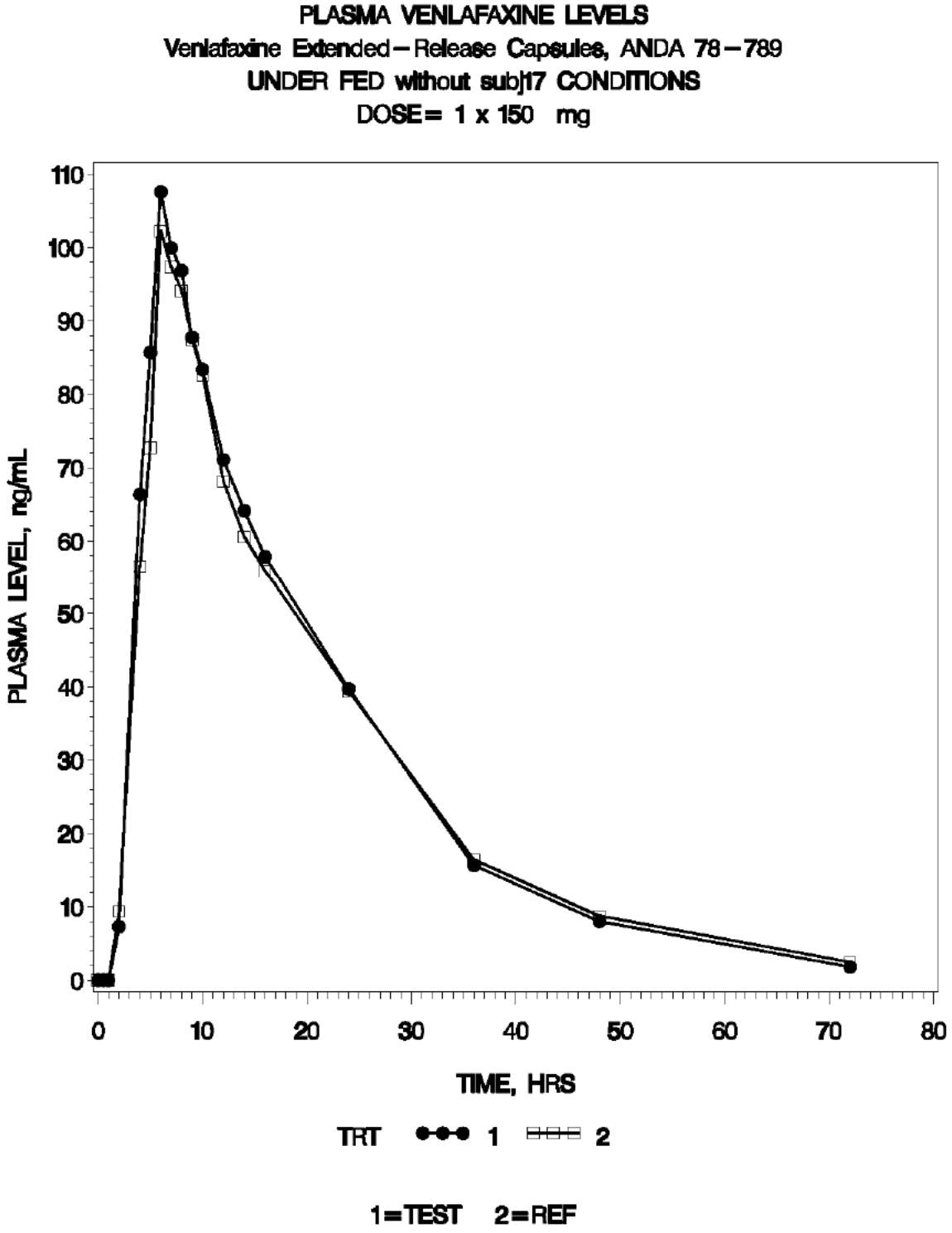
Summary and Conclusions, Single-Dose Fed Bioequivalence Study:

Pharmacokinetic parameters were calculated for twenty-one subjects. Subject 17 was not analyzed statistically due to pre-dose plasma concentrations for both Periods I and II being greater than 5% of the subject's maximum plasma concentration. Subject 5 had undetectable plasma concentrations for all time points of the Test treatment (Period 2) but plasma concentrations of the Reference treatment within the range of those of other study subjects. The firm initially contacted Subject 5 to investigate the reasons of undetectable plasma concentrations and/or for possible redosing. However, the subject appeared to refuse to return for redosing. The record of multiple contacts of the subject made by the firm was submitted in the study report. The firm subsequently analyzed the study results without this subject (n=20). However, the reviewer analyzed the study results with this subject included (n=21). The study outcome was the same with and without Subject 5. The fed study met the confidence interval acceptance criteria for log-transformed AUC_{0-t}, AUC_{∞} and C_{max} of venlafaxine. The fed study is acceptable.

Table 18. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Venlafaxine					
Time (hr)	Test (n=21)		Reference (n=21)		T/R Ratio
	Mean (units)	% CV	Mean (units)	% CV	
0.00	0.00	.	0.00	.	.
0.50	0.00	.	0.00	.	.
1.00	0.00	.	0.00	.	.
2.00	7.30	118.22	9.39	79.96	0.78
4.00	66.34	66.32	56.53	53.21	1.17
5.00	85.70	56.25	72.77	44.89	1.18
6.00	107.58	49.67	102.24	43.61	1.05
7.00	99.92	51.59	97.32	44.04	1.03
8.00	96.82	54.51	94.09	47.00	1.03
9.00	87.72	55.41	87.48	52.20	1.00
10.00	83.34	59.11	82.59	53.89	1.01
12.00	71.07	67.66	68.15	65.19	1.04
14.00	64.13	75.29	60.56	70.11	1.06
16.00	57.81	80.41	55.84	75.29	1.04
24.00	39.68	102.77	39.40	93.76	1.01
36.00	15.67	151.58	16.42	149.07	0.95
48.00	8.01	190.75	8.75	185.53	0.91
72.00	1.81	294.51	2.47	298.35	0.73

Figure 1. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.1.2 Single-dose Fed Sprinkle Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	VENL-0549
Study Title	Single-Dose Fed Bioequivalence Study of Venlafaxine Hydrochloride Extended-Release Capsules (150 mg; Mylan) to Effexor® XR Capsules (150 mg; Wyeth) Administered with Applesauce in Healthy Adult Volunteers
Clinical Site (Name & Address)	Kendle International, Inc. 763 Chestnut Ridge Road Morgantown, WV 26505
Principal Investigator	Dorian Williams, MD
Dosing Dates	Period I: 22 July 2006 Period II: 29 July 2006
Analytical Site (Name & Address)	Mylan Pharmaceuticals – Bioanalytical Division 3711 Collins Ferry Road Morgantown, WV 26505
Analytical Director	Patrick T. Vallano, Ph.D.
Analysis Dates	09 August 2006 - 15 August 2006
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	20 days @ -70°C

Table 20. Product Information

Product	Test	Reference
Treatment ID	A	B
Product Name	Venlafaxine HCl Extended-Release Capsules, 150 mg	Effexor XR® Capsules, 150 mg
Manufacturer	Mylan Pharmaceuticals, Inc.	Wyeth Pharmaceuticals, Inc.
Batch/Lot No.	R1P2475	B05403
Manufacture Date	02 February 2006	
Expiration Date		March 2007
Strength	150 mg	150 mg
Dosage Form	Extended-release capsule	Extended-release capsule
Bio-Batch Size	(b) (4) capsules	
Production Batch Size	(b) (4) capsules	
Potency (Assay)	99.8%	100.6%
Content Uniformity (mean, %CV)	99.2 (CV 1.0%)	
Dose Administered	1 x 150 mg	1 x 150 mg
Route of Administration	Orally	Orally

Table 21. Study Design, Single-Dose Fed Sprinkle Bioequivalence Study

No. of Subjects	Twenty-four (24) non-tobacco using, adult, male and female healthy volunteers between the ages of 18 and 55 were enrolled in the study. Twenty subjects completed both periods I and II of the study.
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	At least 7 days
Randomization Scheme	Sequence 1 – AB: 3, 4, 6, 7, 9, 11, 14, 16, 17, 22, 23, 24 Sequence 2 – BA: 1, 2, 5, 8, 10, 12, 13, 15, 18, 19, 20, 21
Blood Sampling Times	Predose (within 45 minutes prior to dosing), and at 0.5, 1.0, 2.0, 4.0, 5.0, 6.0, 7.0, 8.0. 9.0, 10, 12. 14, 16, 24, 36, 48, and 72 hours postdose.
Blood Volume Collected/Sample	1 x 6 mL of blood collected in sodium heparin tubes
Blood Sample Processing/Storage	Samples were collected and centrifuged at 3000 RPM and 4°C for 10 minutes. The samples were then returned to an ice bath. The plasma was then transferred into the appropriately labeled polypropylene tubes, with each sample being divided into 2 aliquots. The samples were then frozen at -70°C ± 15°C until shipment for sample analysis.
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting Before Meal	Food was not permitted from at least 10 hours prior to dosing until breakfast the day of dosing, Subjects received dinner the evening prior to dosing. After a supervised overnight fast subjects received a standardized breakfast 30 minutes prior to dosing, and the breakfast was consumed within 30 minutes.
Length of Confinement	Subjects were housed at least 16 hours prior to and at least until 24 hours after post-dosing and were allowed to return to the clinic for blood draws scheduled after 24 hours.
Safety Monitoring	For safety monitoring, vital signs (including systolic and diastolic blood pressures, pulse, respiration rates, and temperature) were measured within 60 minutes prior to dosing and prior to the pre-dose blood sample collection.
Standard FDA Meal Used?	Yes

Comments on Study Design:

The study design is acceptable.

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

	FED BIOEQUIVALENCE STUDY VENL-0548		FED WITH APPLESAUCE BIOEQUIVALENCE STUDY VENL-0549	
	TREATMENT GROUPS			
	TEST N=22	REFERENCE N=22	TEST N=20	REFERENCE N=20
AGE				
Mean ± SD	27.2 ± 6.5	27.2 ± 6.5	29.1 ± 10.6	29.1 ± 10.6
Range	19-43	19-43	18-55	18-55
Groups				
<18	0	0	0	0
18-40	21 (95%)	21 (95%)	17 (85%)	17 (85%)
41-64	1 (5%)	1 (5%)	3 (15%)	3 (15%)
65-75	0	0	0	0
>75	0	0	0	0
SEX				
Female	11 (50%)	11 (50%)	11 (55%)	11 (55%)
Male	11 (50%)	11 (50%)	9 (45%)	9 (45%)
RACE				
Asian	0	0	0	0
Black	4 (18%)	4 (18%)	2 (10%)	2 (10%)
Caucasian	16 (73%)	16 (73%)	18 (90%)	18 (90%)
Other	2 (9%)	2 (9%)		
ETHNICITY				
Hispanic or Latino	3 (14%)	3 (14%)	4 (20%)	4 (20%)
Not Hispanic or Latino	19 (86%)	19 (86%)	16 (80%)	16 (80%)
Other Factors				

Body System/Adverse Event [1]	Reported Incidence by Treatment Groups			
	Fed Bioequivalence Study VENL-0548 *		Fed with Applesauce Bioequivalence Study VENL-0549	
	TEST N = 23 [2] n=% [3]	REFERENCE N = 23 [2] n=% [3]	TEST N = 23 [2] n=% [3]	REFERENCE N = 21 [2] n=% [3]
Eye Disorders				
Blurred Vision	0	1 (4%)	0	0
Musculoskeletal and Connective Tissue Disorders				
Aching in Limb	0	0	1 (4%)	0
Back Pain	0	0	1 (4%)	0
Wrist Pain (Left)	0	0	1 (4%)	0
Wrist Swelling (Left)	0	0	1 (4%)	0
Cramp (Leg)	0	1 (4%)	0	0
Ankles Swelling	0	1 (4%)	0	0
Cardiac Disorders				
Heart Fluttering	0	1 (4%)	0	0
Respirtatory, Thoracic, and Mediastinal Disorders				
Yawning	0	0	0	1 (5%)
Shortness of Breath	0	0	0	1 (5%)
Investigations				
Blood Iron Decreased	1 (4%)	0	0	0
AST Levels Elevated	0	0	0	1 (5%)
Total Subjects Reporting at Least One Adverse Event	13 (57%)	12 (52%)	13 (57%)	10 (48%)

Table 23. Dropout Information, Fed Sprinkle Bioequivalence Study

Subject No.	Reason	Period	Replaced?
4	Dropped by Medical Investigator for an adverse event (back pain) requiring non-study related medication during Period I. Received Treatment A (Test).	1	No
6	Discontinued by Sponsor during Period I due to an adverse event (vomiting). Received Treatment A (Test).	1	No
11	Discontinued by Sponsor during Period I due to an adverse event (vomiting). Received Treatment A (Test).	1	No
18	Withdrew consent during Period I. Received Treatment B (Reference).	I	No

Table 24. Study Adverse Events, Fed Sprinkle Bioequivalence Study

Body System/Adverse Event [1]	Reported Incidence by Treatment Groups			
	Fed Bioequivalence Study VENL-0548 *		Fed with Applesauce Bioequivalence Study VENL-0549	
	TEST N = 23 [2] n=% [3]	REFERENCE N = 23 [2] n=% [3]	TEST N = 23 [2] n=% [3]	REFERENCE N = 21 [2] n=% [3]
Nervous System Disorders				
Headache	7 (30%)	4 (17%)	1 (4%)	1 (5%)
Dizziness	1 (4%)	2 (9%)	3 (13%)	2 (10%)
Restlessness	1 (4%)	1 (4%)	0	0
Shakiness	0	0	1 (4%)	2 (10%)
Lightheadedness	0	1 (4%)	0	0
Drowsiness	3 (13%)	2 (9%)	0	0
Insomnia	1 (4%)	0	0	0
Lethargic	0	0	1 (4%)	0
Gastrointestinal Disorders				
Nausea	8 (35%)	6 (26%)	6 (26%)	7 (33%)
Vomiting	1 (4%)	0	2 (9%)	1 (5%)
Dry Mouth	0	0	1 (4%)	2 (10%)
Bad Taste	1 (4%)	0	0	0
Psychiatric Disorders				
Anxiety	1 (4%)	1 (4%)	0	0
Nervousness	1 (4%)	1 (4%)	1 (4%)	0
Emotional Disorder	1 (4%)	0	0	0
Metabolism and Nutrition Disorders				
Decreased Appetite	2 (9%)	1 (4%)	1 (4%)	0
General Disorders and Administrative Site Disorders				
Skin Clammy	1 (4%)	0	0	0
Hot Flash	1 (4%)	0	0	0
Skin and Subcutaneous Disorders				
Rash (Near Left Eye)	1 (4%)	0	0	0
Itchiness (Near Left Eye)	1 (4%)	0	0	0

Table 25. Protocol Deviations, Fed Sprinkle Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sample collection deviation (Period I, no specimen collection)	9	
Blood sample collection deviation (Period I, +0:24, 0.8%)	16	
Blood sample collection deviation (Period II, no specimen collection)	5	
Blood sample collection deviation (Period I, no specimen collection)		19
Blood sample collection deviation (Period II, +5:58, 8%)		16

Comments on Adverse Events/Protocol Deviations:

- Primary protocol deviations that occurred during the study consisted of blood sample collection deviations at various time points. The sample collection time deviations were not significant (± 5%) or are not expected to alter the study outcome.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Sprinkle Bioequivalence Study

Venlafaxine										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	2.0	4.0	6.0	10.0	40.0	80.0	160.0	240.0	320.0	400.0
Inter day Precision (%CV)	1.49	2.48	1.78	1.46	1.06	1.19	1.00	1.19	1.51	1.63
Inter day Accuracy (%Actual)	102.1	99.27	97.62	95.75	96.05	101.25	100.5	102.33	103.16	102.03
Linearity	0.9974 – 0.9994									
Linearity Range (ng/mL)	2.000 ng/mL – 400.0 ng/mL									
Sensitivity/LOQ (ng/mL)	2.000 ng/mL									

Parameter	**Quality Control Samples**		
Concentration (ng/mL)	6.000	40.00	240.00
Inter day Precision (%CV)	6.47	2.36	1.73
Inter day Accuracy (%Actual)	102.20	98.18	100.83

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable.

Table 27. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
D-400-06[1]	07 December 2005	Reassay or Reinjection of Clinical Samples
D-400-07[2]	19 October 2006	Reassay or Reinjection of Clinical Samples
D-416-04[1]	18 May 2006	Reassay of Whole Subjects
D-416-05[2]	19 October 2006	Reassay of Whole Subjects

[1]VENL-0548 & VENL-0549
[2]VENL-0548A, no miscellaneous repeats or whole subjects were performed.

Comments: In table 27 (above) as well as in the bioanalytical report amendment (bioequivalence amendment dated 06 November 2007, page 67-68), the firm refers to

study VENL-0548A. However, there was no mentioning of this study elsewhere in the submission.

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

Repeat assay study values were acceptable for the reasons of "analytical error", "measurable concentration in subject zero samples", "sample outside limits of curve range (BLQ)", and "sample lost during assay procedure".

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 33 and Figure 2

Fed Sprinkle Bioequivalence Study, Study No. VENL-0549									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *ng/ml)	1762.11	110.50	454.58	9218.87	1744.18	112.03	545.42	9147.73	1.01
AUC∞ (hr *ng/ml)	1850.66	109.89	515.71	9707.85	1835.08	114.49	611.33	9897.76	1.01
C_{max} (ng/ml)	97.50	60.24	35.42	268.90	95.26	54.41	40.25	260.40	1.02
T_{max}* (hr)	6.00	.	4.00	16.00	6.00	.	5.00	24.00	1.00
Kel (hr^{-1})	0.07	22.63	0.05	0.11	0.07	20.52	0.04	0.10	1.03
T1/2 (hr)	9.85	23.14	6.39	14.65	10.11	23.48	7.11	17.23	0.97

* T_{max} values are presented as median, range

Table 30. Geometric Means and 90% Confidence Intervals - Firm Calculated

Venlafaxine Hydrochloride Extended-Release 150 mg Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Applesauce Bioequivalence Study VENL-0549 - venlafaxine				
Parameter	**Test**	**Reference**	**Ratio***	**90% C.I.****
AUCL	1259	1219	1.03	95% - 110%
AUCI	1350	1297	1.03	96% - 111%
C_{max}	83.7	81.9	1.01	94% - 109%

Venlafaxine Hydrochloride Extended-Release 150 mg Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Applesauce Bioequivalence Study VENL-0549 – o-desmethylvenlafaxine				
Parameter	**Test**	**Reference**	**Ratio***	**90% C.I.****
AUCL	5079	4929	1.03	99% - 106%
AUCI	5262	5159	1.02	99% - 105%
C_{max}	168.6	165.8	1.02	97% - 107%

Table 31. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Venlafaxine 150 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. VENL-0549					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	1256.03	1217.64	1.03	95.54	111.37
AUC∞ (hr *ng/ml)	1339.53	1292.48	1.04	96.16	111.70
Cmax (ng/ml)	83.21	82.24	1.01	93.69	109.26

Table 32. Additional Study Information

Root mean square error, AUC0-t	0.1391	
Root mean square error, AUC∞	0.1359	
Root mean square error, Cmax	0.1395	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	20	20
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	None	None
first measurable drug concentration as C_{max}	None	None
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	20	0.94	0.74	0.99
Reference	20	0.95	0.81	0.99

Comments on Pharmacokinetic and Statistical Analysis:

In the Fed Sprinkle Study, the pharmacokinetic (PK) parameters of the test and reference for the active metabolite, O-desmethylvenlafaxine, were comparable. The metabolite data also falls within the 90% confidence interval; therefore the metabolite data are supportive and the study is acceptable.

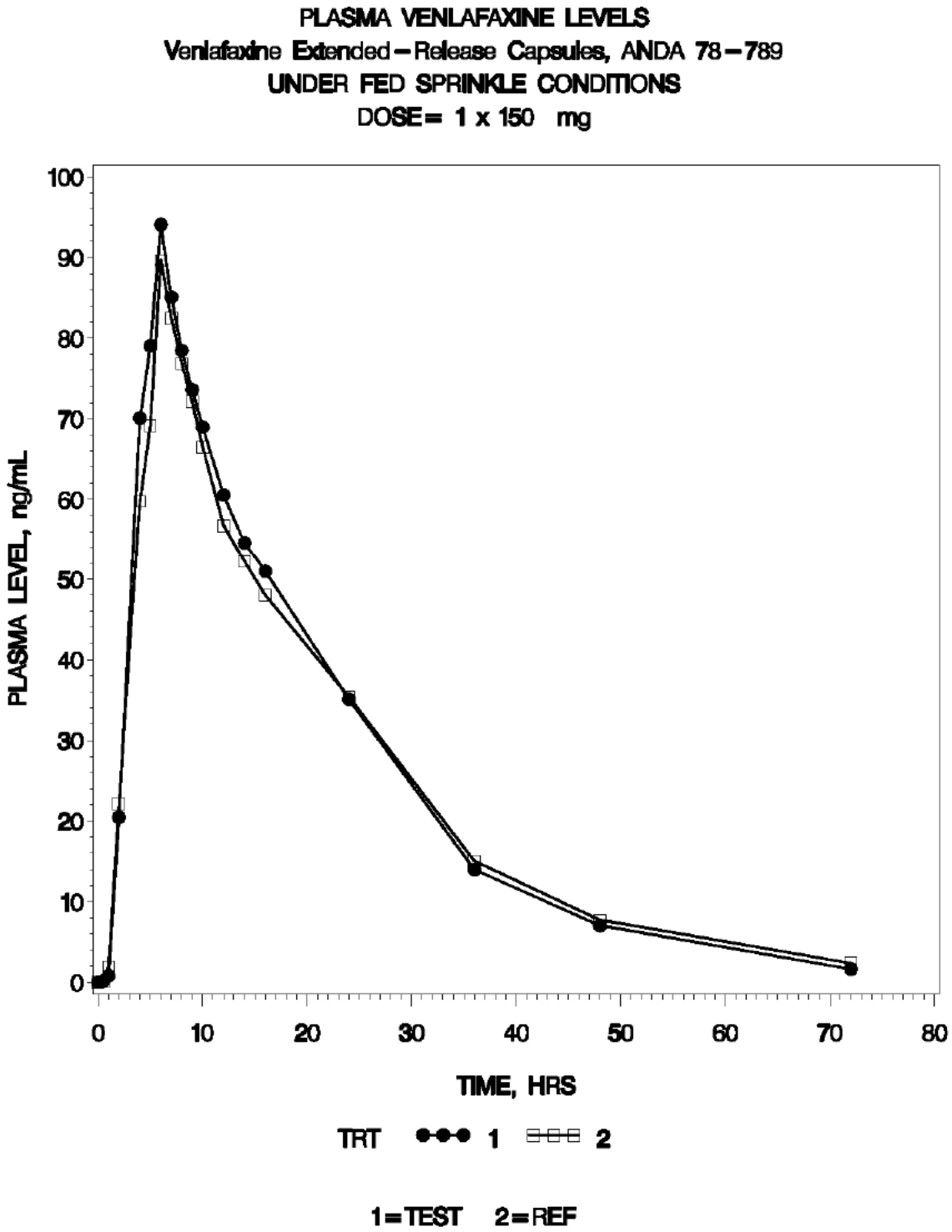
Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

Pharmacokinetic parameters were calculated for twenty subjects under Test treatment and twenty subjects under Reference treatment. The fed sprinkle study met the confidence interval acceptance criteria for log-transformed AUC_{0-t}, AUC_{∞} and C_{max} of venlafaxine. The fed sprinkle study is acceptable.

Table 33. Mean Plasma Concentrations, Single-Dose Fed Sprinkle Bioequivalence Study

	Test (n=20)		Reference (n=20)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.50	0.17	447.21	0.11	447.21	1.49
1.00	0.80	255.61	2.00	115.47	0.40
2.00	20.45	72.40	21.65	61.03	0.94
4.00	70.07	42.37	58.06	38.98	1.21
5.00	79.02	53.24	67.05	43.77	1.18
6.00	94.06	56.11	87.16	43.32	1.08
7.00	85.06	60.02	80.10	49.62	1.06
8.00	78.45	65.95	74.49	55.09	1.05
9.00	73.59	69.79	69.84	59.68	1.05
10.00	68.94	77.38	64.37	66.84	1.07
12.00	60.53	90.34	54.88	75.94	1.10
14.00	54.58	99.21	50.37	87.94	1.08
16.00	50.95	111.61	46.18	110.51	1.10
24.00	35.06	140.88	33.92	163.84	1.03
36.00	13.96	183.48	14.28	192.68	0.98
48.00	7.03	207.00	7.33	226.96	0.96
72.00	1.63	318.67	2.23	308.87	0.73

Figure 2. Mean Plasma Concentrations, Single-Dose Fed Sprinkle Bioequivalence Study



4.2 Formulation Data

Ingredient	Function	37.5mg	75mg	150mg
[redacted]				

(b) (4)

(b) (4)

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	Formulation acceptable.

Comments:

1. All strengths of the test product are proportionally similar.
2. Each inactive ingredient of the test product also falls within acceptable limits listed in the Inactive Ingredient Guidance (IIG).
3. There is no overage of active pharmaceutical ingredient (API).
4. The [redacted] (b) (4) are present in acceptable amounts per the Chemistry review of the ANDA (DFS) below.

All of the excipients used in Mylan's Venlafaxine Hydrochloride Extended-release Capsules, 37.5mg, 75mg and 150mg are within the limits for an oral route of administration as listed in the Inactive Ingredient Database. A comparison is summarized in the table below. The proposed inactive ingredients do not affect the safety of the proposed drug product and the requirements outlined in 21CFR314.95 (a) (ii) have been satisfied.

Ingredient	Amount per unit of Venlafaxine HCl ER Capsules, 37.5mg (mg)	Amount per unit of Venlafaxine HCl ER Capsules, 75mg (mg)	Amount per unit of Venlafaxine HCl ER Capsules, 150mg (mg)	Maximum Level[1] listed in the FDA *Inactive Ingredient Database for Approved Drug Products*

(b) (4)

[redacted]

(b) (4)

4.3 Dissolution Data

Dissolution Review Path	DFS

Table 34. Dissolution Data

Dissolution Conditions	Apparatus:	I (basket)
	Speed of Rotation:	100 rpm
	Medium:	Water
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	(b) (4)	
Dissolution Testing Site (Name, Address)	Mylan Pharmaceuticals 781 Chestnut Ridge Road, Morgantown, WV 26505	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times					Study Report Location
						2 hr.	4 hr.	8 hr.	12 hr.	24 hr.	
VENL-0548		Venlafaxine Hydrochloride Extended-Release Capsules Batch: R1P2475 Manufacturing Date: 02-Feb-2006	150 mg Capsule	12	Mean	19%	48%	71%	83%	97%	3.2.P.5.4 Batch Analysis And 5.3.1.3 *In vitro* - *In vivo* Correlation
					Range	(b) (4)					
					%CV	3.8%	2.8%	2.4%	2.3%	2.5%	
VENL-0548		Effexor® XR Capsule Batch: B05403 Expiry Date: 03/07	150 mg Capsule	12	Mean	18%	45%	73%	85%	98%	
					Range	(b) (4)					
					%CV	4.1%	2.7%	1.9%	1.8%	2.1%	

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)									Study Report Location
					1 hr.	2 hr.	4 hr.	6 hr.	8 hr.	10 hr.	12 hr.	14 hr.	24 hr.	
N/A	Venlafaxine HCl ER Capsules Lot R1P2473	37.5mg Capsule	**Apparatus:** 1 (basket) **Speed:** 100 rpm **Medium:** Deaerated Water, 900ml **Temperature:** 37° C± 0.5°C	12	1%	19%	47%	62%	71%	78%	83%	87%	97%	3.2.P.5.4 Batch Analysis and 5.3.1.3 In vitro - in vivo Correlation
					RSD 48.7%	RSD 5.9%	RSD 3.6%	RSD 2.8%	RSD 2.8%	RSD 2.6%	RSD 2.6%	RSD 2.7%	RSD 2.6%	
N/A	Effexor® XR Lot A94378	37.5mg Capsule		12	4%	15%	40%	58%	68%	75%	80%	84%	94%	
					RSD 21.2%	RSD 14.4%	RSD 6.3%	RSD 4.5%	RSD 3.9%	RSD 3.6%	RSD 3.5%	RSD 3.4%	RSD 3.0%	
N/A	Venlafaxine HCl ER Capsules Lot R1P2474	75mg Capsule		12	1%	19%	47%	61%	70%	76%	81%	85%	95%	
					RSD 22.8%	RSD 4.0%	RSD 2.1%	RSD 1.7%	RSD 1.8%	RSD 1.7%	RSD 1.8%	RSD 1.8%	RSD 1.8%	
N/A	Effexor® XR Lot A85871	75mg Capsule		12	11%	25%	49%	64%	73%	79%	83%	87%	95%	
					RSD 15.5%	RSD 10.4%	RSD 4.8%	RSD 3.6%	RSD 2.9%	RSD 2.6%	RSD 2.5%	RSD 2.5%	RSD 2.4%	
N/A	Venlafaxine HCl ER Capsules Lot R1P2475	150mg Capsule		12	1%	19%	48%	62%	71%	78%	83%	86%	97%	
					RSD 14.4%	RSD 3.8%	RSD 2.8%	RSD 2.6%	RSD 2.4%	RSD 2.5%	RSD 2.3%	RSD 2.5%	RSD 2.5%	
N/A	Effexor® XR Lot B05403	150mg Capsule		12	5%	18%	45%	62%	73%	80%	85%	88%	98%	
					RSD 7.1%	RSD 4.1%	RSD 2.7%	RSD 2.1%	RSD 1.9%	RSD 1.9%	RSD 1.8%	RSD 2.0%	RSD 2.1%	

(b) (4)

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)										Study Report Location
					1 hr.	2 hr.	4 hr.	6 hr.	8 hr.	10 hr.	12 hr.	14 hr.	16 hr.	24 hr.	
N/A	Venlafaxine HCl ER Capsules Lot R1P2473	37.5mg Capsule	**Apparatus:** 1 (basket) **Speed:** 100 rpm **Medium:** 0.1 N HCl, 900ml **Temperature:** 37° C± 0.5°C	12	1%	17%	44%	58%	67%	72%	77%	82%	84%	93%	5.3.1.3 In vitro - in vivo Correlation
					RSD 48.4%	RSD 5.9%	RSD 3.2%	RSD 3.3%	RSD 3.0%	RSD 4.0%	RSD 4.1%	RSD 2.6%	RSD 2.7%	RSD 2.9%	
N/A	Effexor® XR Lot A94378	37.5mg Capsule		12	4%	13%	35%	51%	61%	68%	73%	78%	81%	89%	
					RSD 26.8%	RSD 15.8%	RSD 7.6%	RSD 5.2%	RSD 3.8%	RSD 3.1%	RSD 2.7%	RSD 2.4%	RSD 2.0%	RSD 1.8%	
N/A	Venlafaxine HCl ER Capsules Lot R1P2474	75mg Capsule		12	0%	17%	45%	58%	68%	74%	78%	82%	86%	94%	
					RSD 26.4%	RSD 3.7%	RSD 2.1%	RSD 2.4%	RSD 2.5%	RSD 1.8%	RSD 3.3%	RSD 1.8%	RSD 3.2%	RSD 2.1%	
N/A	Effexor® XR Lot A85871	75mg Capsule		12	10%	22%	43%	57%	66%	72%	77%	80%	83%	91%	
					RSD 6.4%	RSD 4.3%	RSD 3.5%	RSD 2.6%	RSD 2.4%	RSD 2.4%	RSD 2.4%	RSD 2.4%	RSD 2.6%	RSD 4.5%	
N/A	Venlafaxine HCl ER Capsules Lot R1P2475	150mg Capsule		12	1%	18%	45%	59%	68%	74%	79%	83%	87%	94%	
					RSD 26.3%	RSD 2.9%	RSD 1.4%	RSD 1.2%	RSD 1.2%	RSD 1.3%	RSD 1.2%	RSD 1.2%	RSD 1.2%	RSD 1.1%	
N/A	Effexor® XR Lot B05403	150mg Capsule		12	5%	16%	38%	54%	64%	71%	76%	80%	83%	90%	
					RSD 6.3%	RSD 5.0%	RSD 3.9%	RSD 2.9%	RSD 2.5%	RSD 2.2%	RSD 1.9%	RSD 1.8%	RSD 1.8%	RSD 1.6%	

(b) (4)

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)										Study Report Location
					1 hr.	2 hr.	4 hr.	6 hr.	8 hr.	10 hr.	12 hr.	14 hr.	16 hr.	24 hr.	
N/A	Venlafaxine HCl ER Capsules Lot R1P2473	37.5mg Capsule	**Apparatus:** 1 (basket) **Speed:** 100 rpm **Medium:** pH 4.5 acetate buffer, 900ml **Temperature:** 37° C± 0.5°C	12	1%	17%	46%	61%	70%	77%	82%	86%	90%	98%	5.3.1.3 In vitro - in vivo Correlation
					RSD 41.1%	RSD 6.1%	RSD 3.9%	RSD 3.9%	RSD 3.9%	RSD 3.8%	RSD 3.7%	RSD 3.6%	RSD 3.7%	RSD 3.6%	
N/A	Effexor® XR Lot A94378	37.5mg Capsule		12	3%	13%	36%	53%	64%	72%	77%	81%	85%	93%	
					RSD 23.7%	RSD 11.8%	RSD 6.3%	RSD 4.6%	RSD 3.9%	RSD 3.6%	RSD 3.4%	RSD 3.1%	RSD 3.1%	RSD 2.9%	
N/A	Venlafaxine HCl ER Capsules Lot R1P2474	75mg Capsule		12	0%	17%	46%	60%	69%	76%	81%	85%	88%	96%	
					RSD 42.3%	RSD 5.3%	RSD 1.9%	RSD 1.4%	RSD 1.4%	RSD 1.4%	RSD 1.4%	RSD 1.4%	RSD 1.4%	RSD 1.6%	
N/A	Effexor® XR Lot A85871	75mg Capsule		12	10%	22%	45%	60%	69%	75%	80%	83%	86%	93%	
					RSD 15.9%	RSD 10.5%	RSD 5.8%	RSD 4.1%	RSD 3.8%	RSD 3.5%	RSD 3.5%	RSD 3.4%	RSD 3.3%	RSD 3.4%	
N/A	Venlafaxine HCl ER Capsules Lot R1P2475	150mg Capsule		12	1%	18%	47%	61%	71%	77%	82%	87%	90%	97%	
					RSD 15.7%	RSD 3.8%	RSD 2.3%	RSD 2.3%	RSD 2.2%	RSD 2.3%	RSD 2.2%	RSD 2.2%	RSD 2.2%	RSD 2.6%	
N/A	Effexor® XR Lot B05403	150mg Capsule		12	5%	16%	39%	56%	67%	74%	79%	83%	86%	93%	
					RSD 8.0%	RSD 6.1%	RSD 3.5%	RSD 2.2%	RSD 1.7%	RSD 1.5%	RSD 1.4%	RSD 1.2%	RSD 1.3%	RSD 1.4%	

(b) (4)

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)										Study Report Location
					1 hr.	2 hr.	4 hr.	6 hr.	8 hr.	10 hr.	12 hr.	14 hr.	16 hr.	24 hr.	
N/A	Venlafaxine HCl ER Capsules Lot R1P2473	37.5mg Capsule	**Apparatus:** 1 (basket) **Speed:** 100 rpm **Medium:** pH 6.8 phosphate buffer, 900ml **Temperature:** 37° C± 0.5°C	12	1%	18%	46%	60%	69%	75%	80%	84%	87%	94%	5.3.1.3 In vitro - in vivo Correlation
					RSD 34.8%	RSD 4.4%	RSD 2.7%	RSD 2.2%	RSD 2.1%	RSD 2.1%	RSD 2.1%	RSD 2.1%	RSD 2.1%	RSD 2.3%	
N/A	Effexor® XR Lot A94378	37.5mg Capsule		12	4%	15%	39%	55%	66%	72%	77%	81%	84%	92%	
					RSD 20.8%	RSD 8.7%	RSD 4.5%	RSD 3.3%	RSD 2.9%	RSD 2.7%	RSD 2.6%	RSD 2.5%	RSD 2.5%	RSD 2.4%	
N/A	Venlafaxine HCl ER Capsules Lot R1P2474	75mg Capsule		12	1%	17%	45%	59%	68%	74%	79%	83%	86%	93%	
					RSD 29.7%	RSD 4.2%	RSD 2.0%	RSD 1.8%	RSD 1.6%	RSD 1.7%	RSD 1.7%	RSD 1.8%	RSD 1.7%	RSD 2.0%	
N/A	Effexor® XR Lot A85871	75mg Capsule		12	11%	25%	48%	62%	71%	77%	81%	85%	87%	94%	
					RSD 16.4%	RSD 8.7%	RSD 5.0%	RSD 4.0%	RSD 3.0%	RSD 3.3%	RSD 3.3%	RSD 3.2%	RSD 3.4%	RSD 3.5%	
N/A	Venlafaxine HCl ER Capsules Lot R1P2475	150mg Capsule		12	1%	18%	46%	61%	70%	76%	81%	85%	88%	95%	
					RSD 23.0%	RSD 3.0%	RSD 1.8%	RSD 1.9%	RSD 1.9%	RSD 1.9%	RSD 1.8%	RSD 2.0%	RSD 2.0%	RSD 2.1%	
N/A	Effexor® XR Lot B05403	150mg Capsule		12	5%	17%	42%	59%	69%	76%	80%	84%	87%	94%	
					RSD 8.2%	RSD 5.9%	RSD 3.7%	RSD 2.8%	RSD 2.2%	RSD 2.3%	RSD 2.2%	RSD 2.1%	RSD 2.1%	RSD 2.2%	

(b) (4)

4.4 SAS Output

(b) (4)

15 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI) IMMEDIATELY FOLLOWING THIS PAGE

4.5 Additional Attachments – Dissolution Consult

Hi Jim,
After looking at the data for Venlafaxine, I would recommend the following specs for this product:
2 hr: (b) (4) 4 hr: (b) (4) 8 hr: (b) (4) 12 hr: (b) (4) 24 hr: (b) (4)
Similar to Moheb's suggested specs except we grant them a < (b) (4) % spec at 2 hours (for a little more breathing room).
This is just a recommendation. Please consult your TL as well.
Thanks,
Paul
-----Original Message-----
From: Osterhout, James
Sent: Friday, July 27, 2007 11:29 AM
To: Seo, Paul
Subject: RE: 78789 - Diss - AC?
OK,
Moheb suggested the following spec FYI.
Jim
2 hr: (b) (4) %, 4 hr: (b) (4) 8 hr: (b) (4) 12 hr: (b) (4) 24 hr: (b) (4)
LCDR James L. Osterhout
FDA/CDER/OGD
Metropark North 1 (MPN I)
7520 Standish Place
Rockville, Maryland 20855
Room: 1338
P: 240-276-8779
-----Original Message-----
11
From: Seo, Paul
Sent: Friday, July 27, 2007 10:12 AM
To: Osterhout, James
Cc: Seo, Paul
Subject: RE: 78789 - Diss - AC?
Hi Jim,
Same deal here. Need to see the individual disso data. Since its MR, need to be more careful and seeing all the data helps.
You can leave the data on my chair and I'll let you know Mon morning.
Thanks,
Paul
-----Original Message-----
From: Osterhout, James
Sent: Thu 7/26/2007 11:39 PM
To: Makary, Moheb H; Seo, Paul

Subject: 78789 - Diss - AC?
Here is another one Paul. My thoughts are to accept the firm's proposed specifications as they are close. But we can also suggest specs at the FDA time points.
<<78789D1206.doc>> <<78789Data.xls>>
LCDR James L. Osterhout
FDA/CDER/OGD
Metropark North 1 (MPN I)
752O Standish Place
Rockville, Maryland 20855
Room: 1338
P: 240-276-8779

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-789

APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Venlafaxine Hydrochloride Extended-Release Capsules, 150 mg, 75 mg and 37.5 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your proposed specifications of [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4) % and [redacted] (b) (4) for the 2, 4, 8, 12, and 24 hour sampling time points,respectively, based on the submitted stability (stored sample) data are not acceptable. As per the Division of Bioequivalence (DBE) practice, the dissolution specifications are established based on the dissolution data on 12 units of the biolot (fresh, not stored lot) that has been used in acceptable bioequivalence studies. The DBE does not revise the dissolution specifications on the basis of the dissolution testing data on the stored lots. In order to justify your proposed specifications, please submit additional dissolution data of three fresh production lots, to determine if a revision of the dissolution specification is warranted. Alternatively, please acknowledge the FDA-recommended dissolution method and specifications given below:

Medium:	Water
Volume:	900 mL
USP Apparatus:	Type 1 (basket)
Rotation (rpm):	100 rpm
Specifications:	2 hr: (b) (4) 4 hrs: (b) (4) 8 hrs: (b) (4) 12 hrs: (b) (4) 24 hrs: (b) (4)

2. There was evidence that an additional bioequivalence study was conducted as Study No. VENL-0548A based on some within-study bioanalytical validation data submitted in the amendment dated November 6, 2007 (Attachment E, pages 67-68) for the Fed Study No. VENL-0548, as well as based on the existence of the SOP Nos. D-400-07 ("Reassay or Reinjection of Clinical Samples", issued October 19, 2006) and D-416-05 ("Reassay of Whole Subjects", issued October 19, 2007). You have submitted a protocol amendment for the Fed Study VENL-0548 to include a *Redose Study* which was to be identified as Study No. VENL-0548A. However, there was no other data or report submitted for Study No. VENL-0548A. You have also indicated in the Fed Study report that Subject 5 was difficult to contact for redosing, and this subject was dropped from your final analysis of the Fed Study results. Please provide explanation for the existence of the bioanalytical validation data for Study No. VENL-0548A as submitted in the amendment dated November 6, 2007, and please confirm if the Redose Study No. VENL-0548A was ever carried out.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.6 Outcome Page

ANDA: 78-789

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
999	1/15/2007	Bioequivalence Study	Fed Study	1	1
999	1/15/2007	Bioequivalence Study	Sprinkle Study	1	1
999	1/15/2007	Other	Dissolution Waiver	1	1
999	1/15/2007	Other	Dissolution Waiver	1	1
999	11/6/2007	Other	Study Amendment	0	0
999	11/16/2007	Other	Study Amendment	0	0
				Bean Total:	4

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

/s/

Johnetta Farrar
12/7/2007 03:38:58 PM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
12/7/2007 03:41:51 PM
BIOPHARMACEUTICS

Barbara Davit
12/10/2007 10:22:41 AM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	78789	
Drug Product Name	Venlafaxine Hydrochloride Extended-release Capsules	
Strength (s)	37.5 mg, 75 mg, and 150 mg	
Applicant Name	Mylan Pharmaceuticals	
Address	781 Chestnut Ridge Road, Morgantown, WV 26505	
Applicant's Point of Contact	S. Wayne Talton	
Contact's Phone Number	304-599-2595	
Contact's Fax Number	304-285-6407	
Submission Date(s)	15 January 2007	
First Generic	No	
Reviewer	James L. Osterhout	
Study Number (s)	VENL-0548	VENL-0549
Study Type (s)	Fed	Fed Sprinkle
Strength (s)	150 mg	150 mg
Clinical Site	Kendle International Inc.	
Clinical Address	763 Chestnut Ridge Road, Morgantown, WV 26505	
Analytical Site	Mylan Pharmaceuticals - Bioanalytical Division	
Analytical Address	3711 Collins Ferry Road, Morgantown, WV 26505	

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only. The RLD is Effexor® XR, 150 mg from Wyeth Pharmaceuticals.

There is no USP method for this product but there is an FDA-recommended method. The firm also conducted comparative *in vitro* dissolution testing in three (3) different media (1) 0.1N HCl, (2) acetate buffer, pH 4.5, and (3) phosphate buffer, pH 6.8. The other dissolution parameters remained the same. The data showed no evidence of dose dumping. The firm's dissolution testing data with the FDA-recommended method [USP Apparatus I (basket) at 100 rpm in 900 mL water] is acceptable. The firm proposed specifications for its test product that were not the same as the FDA recommended specifications. Therefore, based on the submitted data, the FDA-recommends the following specifications:

2 hr: (b) (4) 4 hr: (b) (4) 8 hr: (b) (4) 12 hr: (b) (4) 24 hr: (b) (4)

The firm should acknowledge and accept the FDA-recommended method and specifications. The DBE will review the fasted and fed BE studies and waiver requests at a later date.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☒	☐	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☐	☒	☐
Is FDA method in the public dissolution database (on the web)			☒	☐	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
Are all eight electronic summary biotables present			☒	☐	☐
Are electronic summary biotables in pdf format			☒	☐	☐

Comments:

The firm performed a Fed Study and a Sprinkle Study in applesauce. The firm measured venlafexine and o-desmethylvenlafaxine and calculated 90% CI data for both analytes. The BE Summary tables 1-8 are in the EDR. The SAS files are valid.

II. DISSOLUTION DATA

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	Apparatus:	I (basket)
	Speed of Rotation:	100 rpm
	Medium:	Water
	Volume:	900 mL
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications	(b) (4)	
Dissolution Testing Site (Name, Address)	Mylan Pharmaceuticals 781 Chestnut Ridge Road, Morgantown, WV 26505	
Study Report Location	5.3.1.3 - In vitro - in vivo Correlation	

Comments on Dissolution Data:

FDA-recommended specifications (From the OGD Internal Database):
(b) (4)

There is no evidence of dose dumping in the test product in the 0.1N HCl media, pH 4.5 acetate buffer media, and the pH 6.8 phosphate media. The Test Product exhibited a comparable variability to that of the Reference Product for all media types at all time points. The data pass the F2 curve similarity test (Test vs. Reference) for all media tested. Furthermore, the 90% CI are well within the 80-125% range for both the fed and sprinkle studies for all parameters are acceptable.

The firm's dissolution testing data with the FDA-recommended method are acceptable. The firm proposed dissolution specifications for its test product as follows:
(b) (4)

Based on the submitted data, the DBE recommends the following dissolution specifications (see Dissolution Consult):
2 hr: (b) (4) 4 hr: (b) (4) 8 hr: (b) (4) 12 hr: (b) (4) 24 hr: (b) (4)

SEE BELOW FOR DISSOLUTION AND F2 DATA

F2 Values			
	37.5 mg	**75 mg**	**150 mg**
1N HCl	64.06	68.69	68.62
pH 4.5 Acetate Buffer	60.93	68.92	67.24
pH 6.8 Phosphate Buffer	70.53	65.39	80.55

	METHOD:	FDA			
	Apparatus:	I (basket)			
	Speed:	100 rpm			
	Media	water			
	Volume:	900mL			
ANDA #	78789	150 mg			
Test 1	Test				
Test 2	Reference				
		Time	Test	Reference	(R-T)2
n=	7	1	1	5	16
F2=	79.80	2	19	18	1
		4	48	45	9
		6	62	62	0
		8	71	73	4
		10	78	80	4
		12	83	85	4

	METHOD:	FDA			
	Apparatus:	I (basket)			
	Speed:	100 rpm			
	Media	water			
	Volume:	900mL			
ANDA #	78789	75 mg			
Test 1	Test				
Test 2	Reference				
		Time	Test	Reference	(R-T)2
n=	8	1	1	11	100
F2=	66.02	2	19	25	36
		4	47	49	4
		6	61	64	9
		8	70	73	9
		10	76	79	9
		12	81	83	4
		14	85	87	4

	METHOD:	FDA	**Time**	**Test**	**Reference**	**(R-T)2**
	Apparatus:	I (basket)	1	1	4	9
	Speed:	100 rpm	2	19	15	16
	Media	water	4	47	40	49
	Volume:	900mL	6	62	58	16
			8	71	68	9
ANDA #	78789	37.5 mg	10	78	75	9
Test 1	Test		12	83	80	9
Test 2	Reference		14	87	84	9
			24	97	94	9
n=	9					
F2=	69.90					

Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)								
				1 hr.	2 hr.	4 hr.	6 hr.	8 hr.	10 hr.	12 hr.	14 hr.	24 hr.
Venlafaxine HCl ER Capsules Lot R1P2473	37.5mg Capsule	Apparatus: 1 (basket) Speed: 100 rpm Medium: Deaerated Water, 900ml Temperature: 37º C± 0.5ºC	12	48.7%	19% (b) (4) 5.9%	47% 3.6%	62% 2.8%	71% 2.8%	78% 2.6%	83% 2.6%	RSD 2.7%	RSD 2.6%
Effexor® XR Lot A94378	37.5mg Capsule		12	4% (b) (4) RSD 21.2%	15% (b) (4) RSD 14.4%	40% RSD 6.3%	58% RSD 4.5%	68% RSD 3.9%	75% RSD 3.6%	80% RSD 3.5%	84% (b) (4) RSD 3.4%	94% (b) (4) RSD 3.0%
Venlafaxine HCl ER Capsules Lot R1P2474	75mg Capsule		12	1% (b) (4) RSD 22.8%	19% (b) (4) RSD 4.0%	47% RSD 2.1%	61% RSD 1.7%	70% RSD 1.8%	76% RSD 1.7%	81% RSD 1.8%	85% (b) (4) RSD 1.8%	95% (b) (4) % RSD 1.8%
Effexor® XR Lot A85871	75mg Capsule		12	11% (b) (4) % RSD 15.5%	25% (b) (4) RSD 10.4%	49% RSD 4.8%	64% RSD 3.6%	73% RSD 2.9%	79% RSD 2.6%	83% RSD 2.5%	87% (b) (4) RSD 2.5%	95% (b) (4) RSD 2.4%
Venlafaxine HCl ER Capsules Lot R1P2475	150mg Capsule		12	1% (b) (4) RSD 14.4%	19% (b) (4) RSD 3.8%	48% RSD 2.8%	62% RSD 2.6%	71% RSD 2.4%	78% RSD 2.5%	83% RSD 2.3%	86% (b) (4) RSD 2.5%	97% (b) (4) RSD 2.5%
Effexor® XR Lot B05403	150mg Capsule		12	5% (b) (4) RSD 7.1%	18% (b) (4) RSD 4.1%	45% RSD 2.7%	62% RSD 2.1%	73% RSD 1.9%	80% RSD 1.9%	85% RSD 1.8%	88% (b) (4) RSD 2.0%	98% RSD 2.1%

Product ID /Batch No.	Dosage Form	Conditions	No. of Dosage	Collection Times Mean % Dissolved (Range)									
				1 hr.	2 hr.	4 hr.	6 hr.	8 hr.	10 hr.	12 hr.	14 hr.	16 hr.	24 hr.
Venlafaxine HCl ER Cap Lot R1P2473	37.5mg Capsule	Apparatus: 1 (basket) Speed: 100 rpm Medium: 0.1 N HCl, 900ml Temperature: 37º C± 0.5ºC	12	1% (b) (4) RSD 48.4%	17% (b) (4) RSD 5.9%	44% RSD 3.2%	58% RSD 3.3%	67% RSD 3.0%	72% RSD 4.0%	77% RSD 4.1%	82% RSD 2.6%	84% (b) (4) RSD 2.7%	93% (b) (4) RSD 2.9%
Effexor® XR Lot A94378	37.5mg Capsule		12	4% (b) (4) RSD 26.8%	13% (b) (4) RSD 15.8%	35% RSD 7.6%	51% RSD 5.2%	61% RSD 3.8%	68% RSD 3.1%	73% RSD 2.7%	78% RSD 2.4%	81% (b) (4) RSD 2.0%	89% (b) (4) RSD 1.8%
Venlafaxine HCl ER Cap Lot R1P2474	75mg Capsule		12	0% (b) (4) RSD 26.4%	17% (b) (4) RSD 3.7%	45% RSD 2.1%	58% RSD 2.4%	68% RSD 2.5%	74% RSD 1.8%	78% RSD 3.3%	82% RSD 1.8%	86% (b) (4) RSD 3.2%	94% (b) (4) RSD 2.1%
Effexor® XR Lot A85871	75mg Capsule		12	10% (b) (4) RSD 6.4%	22% RSD 4.3%	43% RSD 3.5%	57% RSD 2.6%	66% RSD 2.4%	72% RSD 2.4%	77% RSD 2.4%	80% (b) (4) RSD 2.4%	83% (b) (4) % RSD 2.6%	91% (b) (4) RSD 4.5%
Venlafaxine HCl ER Cap Lot R1P2475	150mg Capsule		12	1% (b) (4) RSD 26.3%	18% (b) (4) RSD 2.9%	45% RSD 1.4%	59% RSD 1.2%	68% RSD 1.2%	74% RSD 1.3%	79% RSD 1.2%	83% (b) (4) RSD 1.2%	87% (b) (4) RSD 1.2%	94% (b) (4) RSD 1.1%
Effexor® XR Lot B05403	150mg Capsule		12	5% (b) (4) RSD 6.3%	16% (b) (4) RSD 5.0%	38% RSD 3.9%	54% RSD 2.9%	64% RSD 2.5%	71% RSD 2.2%	76% RSD 1.9%	80% (b) (4) RSD 1.8%	83% (b) (4) RSD 1.8%	90% (b) (4) RSD 1.6%

Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)									
				1 hr.	2 hr.	4 hr.	6 hr.	8 hr.	10 hr.	12 hr.	14 hr.	16 hr.	24 hr.
Venlafaxine HCl ER Cap Lot R1P2473	37.5mg Capsule	Apparatus: 1 (basket) Speed: 100 rpm Medium: pH 4.5 acetate buffer, 900ml Temperature: 37º C± 0.5ºC	12	1% (b) (4) RSD 41.1%	17% (b) (4) RSD 6.1%	46% (b) (4) RSD 3.9%	61% (b) (4) RSD 3.9%	70% (b) (4) RSD 3.9%	77% (b) (4) RSD 3.8%	82% (b) (4) RSD 3.7%	86% (b) (4) RSD 3.6%	90% (b) (4) RSD 3.7%	98% (b) (4) RSD 3.6%
Effexor® XR Lot A94378	37.5mg Capsule		12	3% (b) (4) RSD 23.7%	13% (b) (4) RSD 11.8%	36% (b) (4) RSD 6.3%	53% (b) (4) RSD 4.6%	64% (b) (4) RSD 3.9%	72% (b) (4) RSD 3.6%	77% (b) (4) RSD 3.4%	81% (b) (4) RSD 3.1%	85% (b) RSD 3.1%	93% (b) (4) RSD 2.9%
Venlafaxine HCl ER Cap Lot R1P2474	75mg Capsule		12	0% (b) (4) RSD 42.3%	17% (b) (4) RSD 5.3%	46% (b) (4) RSD 1.9%	60% (b) (4) RSD 1.4%	69% (b) (4) RSD 1.4%	76% (b) (4) RSD 1.4%	81% (b) (4) RSD 1.4%	85% (b) (4) RSD 1.4%	88% (b) (4) RSD 1.4%	96% (b) (4) RSD 1.6%
Effexor® XR Lot A85871	75mg Capsule		12	10% (b) (4) RSD 15.9%	22% (b) (4) RSD 10.5%	45% (b) (4) RSD 5.8%	60% (b) (4) RSD 4.1%	69% (b) (4) RSD 3.8%	75% (b) (4) RSD 3.5%	80% (b) (4) RSD 3.5%	83% (b) (4) RSD 3.4%	86% (b) (4) RSD 3.3%	93% (b) (4) RSD 3.4%
Venlafaxine HCl ER Cap Lot R1P2475	150mg Capsule		12	1% (b) (4) RSD 15.7%	18% (b) (4) RSD 3.8%	47% (b) (4) RSD 2.3%	61% (b) (4) RSD 2.3%	71% (b) (4) RSD 2.2%	77% (b) (4) RSD 2.3%	82% (b) (4) RSD 2.2%	87% (b) (4) RSD 2.2%	90% (b) (4) % RSD 2.2%	97% (b) (4) RSD 2.6%
Effexor® XR Lot B05403	150mg Capsule		12	5% (b) (4) RSD 8.0%	16% (b) (4) RSD 6.1%	39% (b) (4) RSD 3.5%	56% (b) (4) RSD 2.2%	67% (b) (4) RSD 1.7%	74% (b) (4) RSD 1.5%	79% (b) (4) RSD 1.4%	83% (b) (4) RSD 1.2%	86% (b) (4) RSD 1.3%	93% (b) (4) RSD 1.4%

Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)									
				1 hr.	2 hr.	4 hr.	6 hr.	8 hr.	10 hr.	12 hr.	14 hr.	16 hr.	24 hr.
Venlafaxine HCl ER Cap Lot R1P2473	37.5mg Capsule	Apparatus: 1 (basket) Speed: 100 rpm Medium: pH 6.8 phosphate buffer, 900ml Temperature: 37º C± 0.5ºC	12	1% (b) (4) RSD 34.8%	18% (b) (4) RSD 4.4%	46% (b) (4) RSD 2.7%	60% (b) (4) RSD 2.2%	69% (b) (4) RSD 2.1%	75% (b) (4) RSD 2.1%	80% (b) (4) RSD 2.1%	84% (b) (4) RSD 2.1%	87% (b) (4) RSD 2.1%	94% (b) (4) RSD 2.3%
Effexor® XR Lot A94378	37.5mg Capsule		12	4% (b) (4) RSD 20.8%	15% (b) (4) RSD 8.7%	39% (b) (4) RSD 4.5%	55% (b) (4) RSD 3.3%	66% (b) (4) RSD 2.9%	72% (b) (4) RSD 2.7%	77% (b) (4) RSD 2.6%	81% (b) (4) RSD 2.5%	84% (b) (4) RSD 2.5%	92% (b) (4) RSD 2.4%
Venlafaxine HCl ER Cap Lot R1P2474	75mg Capsule		12	1% (b) (4) RSD 29.7%	17% (b) (4) RSD 4.2%	45% (b) (4) RSD 2.0%	59% (b) (4) RSD 1.8%	68% (b) (4) RSD 1.6%	74% (b) (4) RSD 1.7%	79% (b) (4) RSD 1.7%	83% (b) (4) RSD 1.8%	86% (b) (4) RSD 1.7%	93% (b) (4) RSD 2.0%
Effexor® XR Lot A85871	75mg Capsule		12	11% (b) (4) RSD 16.4%	25% (b) (4) RSD 8.7%	48% (b) (4) RSD 5.0%	62% (b) (4) RSD 4.0%	71% (b) (4) RSD 3.0%	77% (b) (4) RSD 3.3%	81% (b) (4) RSD 3.3%	85% (b) (4) RSD 3.2%	87% (b) (4) RSD 3.4%	94% (b) (4) RSD 3.5%
Venlafaxine HCl ER Cap Lot R1P2475	150mg Capsule		12	1% (b) (4) RSD 23.0%	18% (b) (4) RSD 3.0%	46% (b) (4) RSD 1.8%	61% (b) (4) RSD 1.9%	70% (b) (4) RSD 1.9%	76% (b) (4) RSD 1.9%	81% (b) (4) RSD 1.8%	85% (b) (4) RSD 2.0%	88% (b) (4) RSD 2.0%	95% (b) (4) RSD 2.1%
Effexor® XR Lot B05403	150mg Capsule		12	5% (b) (4) RSD 8.2%	17% (b) (4) RSD 5.9%	42% (b) (4) RSD 3.7%	59% (b) (4) RSD 2.8%	69% (b) (4) RSD 2.2%	76% (b) (4) RSD 2.3%	80% (b) (4) RSD 2.2%	84% (b) (4) RSD 2.1%	87% (b) (4) RSD 2.1%	94% (b) (4) RSD 2.2%

III. DISSOLUTION CONSULT

Hi Jim,

After looking at the data for Venlafaxine, I would recommend the following specs for this product:
2 hr: (b) (4) 4 hr: (b) (4) 8 hr: (b) (4) 12 hr: (b) (4) 24 hr: (b) (4)
Similar to Moheb's suggested specs except we grant them a (b) (4)% spec at 2 hours (for a little more breathing room).

This is just a recommendation. Please consult your TL as well.

Thanks,
Paul

-----Original Message-----
From: Osterhout, James
Sent: Friday, July 27, 2007 11:29 AM
To: Seo, Paul
Subject: RE: 78789 - Diss - AC?

OK,
Moheb suggested the following spec FYI.
Jim

2 hr (b) (4)%, 4 hr: (b) (4) 8 hr: (b) (4) 12 hr: (b) (4) 24 hr: (b) (4)

LCDR James L. Osterhout
FDA/CDER/OGD
Metropark North 1 (MPN I)
7520 Standish Place
Rockville, Maryland 20855
Room: 1338
P: 240-276-8779

-----Original Message-----

From: Seo, Paul
Sent: Friday, July 27, 2007 10:12 AM
To: Osterhout, James
Cc: Seo, Paul
Subject: RE: 78789 - Diss - AC?

Hi Jim,

Same deal here. Need to see the individual disso data. Since its MR, need to be more careful and seeing all the data helps.

You can leave the data on my chair and I'll let you know Mon morning.

Thanks,
Paul

-----Original Message-----
From: Osterhout, James
Sent: Thu 7/26/2007 11:39 PM
To: Makary, Moheb H; Seo, Paul
Subject: 78789 - Diss - AC?

Here is another one Paul. My thoughts are to accept the firm's proposed specifications as they are close. But we can also suggest specs at the FDA time points.

<<78789D1206.doc>> <<78789Data.xls>>

LCDR James L. Osterhout
FDA/CDER/OGD
Metropark North 1 (MPN I)
7520 Standish Place
Rockville, Maryland 20855
Room: 1338
P: 240-276-8779

IV. COMMENTS

The firm's dissolution testing data with the FDA-recommended method are acceptable. However, the firm proposed dissolution specifications are not acceptable. The firm conducted dissolution testing on multiple media types as requested for a modified release product. Based on the submitted data, the DBE recommends the following dissolution specifications using the FDA-recommended dissolution method:

2 hr: (b) (4) 4 hr: (b) (4) 8 hr: (b) (4) 12 hr: (b) (4) 24 hr: (b) (4)

V. DEFICIENCY COMMENTS

1. Based on the submitted data, the DBE recommends the following dissolution specifications:

   2 hr: (b) (4) 4 hr: (b) (4) 8 hr: (b) (4) 12 hr: (b) (4) 24 hr: (b) (4)

   The firm should acknowledge the FDA-recommended dissolution method and specifications.

VI. RECOMMENDATIONS

1. The firm's dissolution testing data with the FDA-recommended dissolution method are acceptable. However, The firm needs to acknowledge the FDA-recommended method and the current proposed specifications given below:

   USP Apparatus I (basket) at 100 rpm in 900 mL water with the following specifications applicable to all strengths:

   2 hr: (b) (4) 4 hr: (b) (4) 8 hr: (b) (4) 12 hr: (b) (4) 24 hr: (b) (4)

2. The Division of Bioequivalence has developed new data summary tables in a concise format consistent with the Common Technical Document (CTD). Please provide complete tables and send them with the rest of the bioequivalence submission. The tables are available in Word and PDF format under the title "Model Bioequivalence Data Summary Tables" in our website at http://www.fda.gov/cder/ogd/index.htm. To improve the efficiency of the Division, these tables should be provided in all pending and future ANDA submissions.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78789

APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg, 75 mg, and 150 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiencies have been identified:

1. Your proposed dissolution specifications are not acceptable. Based on the data you submitted, please acknowledge your acceptance of the FDA-recommended dissolution method and specifications given below:

USP Apparatus I (basket) at 100 rpm in 900 mL water with the following specifications applicable to all strengths:

2 hours: (b) (4) 4 hours: (b) (4) 8 hours: (b) (4)
12 hours: (b) (4) 24 hours: (b) (4)

2. The Division of Bioequivalence has developed new data summary tables in a concise format consistent with the Common Technical Document (CTD). Please provide complete tables and send them with the rest of the bioequivalence submission. The tables are available in Word and PDF format under the title "Model Bioequivalence Data Summary Tables" in our website at http://www.fda.gov/cder/ogd/index.htm. To improve the efficiency of the Division, these tables should be provided in all pending and future ANDA submissions.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

VII. OUTCOME

ANDA 78789

[NOTE: The firm needs to acknowledge their acceptance of the FDA-recommended method and specifications. The fasting and fed BE studies and waiver request are pending review]

1.	**Dissolution (Dissolution Data)**	Strength:	37.5 mg, 75 mg, and 150 mg
	(DIS)	Outcome:	**IC**
	Submission Date(s)	15 January 2007	

BIOEQUIVALENCE OUTCOME DECISIONS:	AC – Acceptable IC – Incomplete UN – Unacceptable WC – Without Credit

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

/s/

James L. Osterhout
8/21/2007 12:23:58 AM
BIOPHARMACEUTICS

Moheb H. Makary
8/21/2007 06:53:15 AM
BIOPHARMACEUTICS

Barbara Davit
8/22/2007 09:43:44 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078789

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ROUTING SHEET

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: IV	Team: 42	PM: Thomas Hinchliffe

Electronic ANDA: Yes ☒ No ☐

ANDA #:078789
Firm Name:Mylan
ANDA Name:Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg (base), 75 mg (base), and 150 mg (base)
RLD Name:Effexor XR Extended Release Capsules (NDA 020699) Wyeth Pharmaceuticals, Inc.

Electronic AP Routing Summary Located:
V:\Chemistry Division IV\Team 42\Electronic AP Summaries

AP/TA Letter Located:
V:\Chemistry Division IV\Team 42\Final Version For DARRTS

Project Manager Evaluation: **Date: 4/5/11 Initials:** TOH

☒ Previously reviewed and tentatively approved --- Date 11/13/2008
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date 01/16/2007	Date of Application 01/15/2007	Date Acceptable for Filing 01/16/2007
Patent Certification (type) 4/MOU	Date Patent/Excl. expires multiple	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒ **DMF#:** _____ (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☐ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☒ Acceptable ☐ OAI *EES Date Acceptable: 4/7/11* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☒ Comment:
Date of Acceptable Quality (Chemistry) 4/8/11 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 05/26/2011 Bio reviews in DARRTS: Yes ☐ No ☐ (Volume location:)
Date of Acceptable Labeling 04/12/2011 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) _____

Methods Val. Samples Pending: Yes ☐ No ☒; Commitment Rcvd. from Firm: Yes ☒ No ☐

Post Marketing Agreement (PMA): Yes ☒ No ☐ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☒ No ☐ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 5/27/11 REMS Required: Yes ☐ No ☐ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support, Date emailed: 4/5/11

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 4/11/11

☒ Division

☐ 1st Generic Review

☐ Bob West / Peter Rickman
☐ Keith Webber

☐ Filed AP Routing Summary in DARRTs	☐ Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 4/6/2011**
Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☒ No ☐ Has case been settled: Yes ☒ No ☐ Date settled: Is applicant eligible for 180 day	RLD = Effexor XR NDA# 20-699 Date Checked Granted Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒	
Type of Letter: ☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP ☐ OTHER:	
Comments:ANDA TAeds on 11/13/2008. At the time the TA was issued, the reason for TA was an unexpired 30 month stay of approval. This stay of approval expired on 11/30/2009. After 11/20/2009 Mylan was blocked from Full Approval by TEVA's eligiblity for 180 day exclusivity-this exclusivity expired on 12/28/2010. Request for final approval submitted by Mylan on 4/4/2011. The cover letter of this amendment indicates that Mylan is requesting approval on 6/1/2011. The 4/4/2011 amendment also contains a Dismissal Order for CA 07 CV 91 which was entered on 12/21/2009-the order indicates that the CA was dismissed with prejudice. Mylan did not provide a copy of the license agreement entered into by Mylan and Wyeth but based upon their requested approval date it appears that the license agreement is similar to that agreed upon by other ANDA applicants (e.g. Torrent). Since the CA was dismissed and ther is no longer any blocking 180 day exclusivity there is no patent/legal issue to the issuance of a Full Approval at this time. That being said, the OGD has made an internal decision to delay approving ANDAs for these drug product until 6/1/2011 in compliance with the applicant's request and so as not to potentially upset Wyeth.	

2. ***Labeling Endorsement***

Reviewer, :
Date_____
Initials_____

Labeling Team Leader, :
Date 6/1/11
Initials rlw/for

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☐n/a

Comments:

From: Golson, Lillie D
Sent: Friday, May 27, 2011 2:42 PM
To: Hinchliffe, Thomas; Golson, Lillie D
Subject: FW: ANDA For your AP/TA review and Endorsement

Hi Tom,

Please endorse the AP routing form on behalf of Lisa and me.

Thanks

From: Kwok, Lisa
Sent: Friday, May 27, 2011 9:18 AM
To: Hinchliffe, Thomas
Cc: Golson, Lillie D
Subject: RE: ANDA For your AP/TA review and Endorsement

Hi Tom,

The Labeling AP Summary signed by Lillie Golson on 4/12/11 is still acceptable.

Thanks,
Lisa

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date 25Apr2011**
OGD Regulatory Counsel **InitialsDTR**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:changes to AP letter saved to V drive.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 4/12/2011**
Chemistry Div. **IV (Iser)** **InitialsRLI**
Comments:CMC OK, Acting Director

5. ***First Generic Evaluation*** **First Generics Only**
Frank Holcombe **Date 6/1/11**
Assoc. Dir. For Chemistry **Initials rlw/for**
Comments: (First generic drug review)
N/A. Multiple ANDAs have been approved for this drug product.

OGD Office Management Evaluation

6. Peter Rickman **Date 6/1/11**
Director, DLPS **Initials rlw/for**
Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes ☐ No ☐
Petition: Yes☐ No☐
Comments: This ANDA was granted tentative approval on November 13, 2008. final approval was blocked at that time by the 30-month stay associated with the ongoing patent litigation and 180-day generic drug exclusivity for this drug product that was subsequently awarded to Teva. Both the 30-month stay and Teva's 180-day exclusivity have expired. Based upon a settlement agreement with Wyeth, Mylan is requesting final approval of this ANDA effective June 1, 2011.

Final-printed labeling found acceptable for approval 4/12/11, as endorsed 5/27/11. No REMS is required.

CMC found acceptable for approval (Chemistry Review #3) 4/8/11.

Bioequivalence - Mylan was requested to submit the results of in-vitro dissolution testing for each capsule strength in order to evaluate the alcohol "dose-dumping" characteristics of the product v. that of the RLD. This request is part of the current BE guidance for this drug product was was not requested at the time of the tentative approval. Mylan's alcohol "dose-dumping" data were reviewed and found acceptable 5/26/11.

7. Robert L. West **Date 6/1/11**
Deputy Director, OGD **Initials RLWest**
Para.IV Patent Cert: Yes☒ No☐
Pending Legal Action: Yes☐ No☒
Petition: Yes☐ No☒
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 4/7/11 (Verified 6/1/11). No "OAI" Alerts noted.

Refer to the regulatory and legal history as summarized above by M.Shimer. Based upon the licensing agreement with Wyeth, Mylan's ANDA is eligible for final approval effective June 1, 2011.

Mylan's ANDA meets the current regulatory and scientific requirements for approval.

Approval is recommended.

8. ***OGD Director Evaluation***
Keith Webber
Deputy Director, OPS
Comments: RLWest for Keith Webber, Ph.D. 6/1/11.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments:

9. Project Manager
Date 6/1/11
Initials TOH

Check Communication and Routing Summary into DARRTS

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

/s/

THOMAS O HINCHLIFFE
06/01/2011

Mylan®
Pharmaceuticals

781 Chestnut Ridge Road
Morgantown, WV 26505 USA
Phone 304.599.2595
Web www.mylan.com

May 6, 2011

PATENT AMENDMENT

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 078789
SEQUENCE NUMBER: 0004
(Amendment to Section 1.3.5 – Patent Information)

Dear Dr. Webber:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. Reference is also made to our Minor Amendment – Request for Final Approval that was submitted April 4, 2011.

The Patent Amendment provided in Section 1.3.5.1 provides a copy of the correspondence from Pfizer notifying the Agency of the licensing agreement with Mylan.

All files in this amendment have been scanned utilizing Norton antivirus software and are free of known viruses. All correspondence regarding this amendment should be directed to the attention of the undersigned at (304) 599-2595, ext. 6551 and/or via facsimile at (304) 285-6407.

Sincerely,

<Please see following page for signature manifestation.>

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

cc: Wyeth Pharmaceuticals

SIGNATURE MANIFESTATION

Document Name : venl-er-cvr-0004

Document Title : Cover Letter - 0004 - Patent Amendment - 20110506

Document Version : 0.2; CURRENT; Most-Recent; In Approval

Date	Signed By	Reason for Signing
06-May-2011 09:26 AM EDT	Wayne Talton	Approve

Mylan®
Pharmaceuticals

781 Chestnut Ridge Road
Morgantown, WV 26505 USA
Phone 304.599.2595
Web www.mylan.com

May 6, 2011

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, 37.5 MG, 75 MG AND 150 MG

ANDA # 078789

PATENT AMENDMENT

Dear Dr. Webber:

Reference is made to the abbreviated new drug application ("ANDA") identified above submitted by Mylan Pharmaceuticals Inc. ("Mylan"). Reference is further made to the correspondence dated April 4, 2011 advising OGD that Mylan entered into a licensing agreement with the patent owner(s) and requesting final approval for the above referenced ANDA be granted as of June 1, 2011.

In follow up to our previous correspondence, please find attached a courtesy copy of the May 5, 2011 correspondence from Pfizer to FDA notifying the Agency of the licensing agreement with Mylan.

Accordingly, Mylan seeks approval to market its Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg, 75 mg and 150 mg upon completion of the regulatory review process and upon effective date of the license, June 1, 2011.

Sincerely,

Marcie E. McClintic Coates /by

Marcie E. McClintic Coates
Global Regulatory Counsel

Pfizer Inc
235 East 42nd Street
New York, NY 10017
Tel 212 733 8721
Email: geoffrey.levitt@pfizer.com

Corporate Legal - Regulatory

Geoffrey Levitt
Senior Vice President & Associate General Counsel

May 5, 2011

Robert L. West, Deputy Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration, HFD-601
7500 Standish Place
Rockville, MD 20855

RE: Effexor XR (venlafaxine HCl extended release capsules)
NDA No. 20-699

Dear Mr. West:

We are writing to notify you that Pfizer has granted a license to Mylan Pharmaceuticals Inc. (Mylan) for venlafaxine HCl extended release capsules authorizing Mylan to market and distribute that product in the United States on and after June 1, 2011 and, as such, that the FDA may make approval of Mylan's ANDA No. 78-789 for generic venlafaxine extended release capsules effective on or after June 1, 2011, assuming such ANDA is otherwise approvable.

Sincerely,

Geoffrey M. Levitt

cc: Elizabeth Dickinson
Office of Chief Counsel

Mylan®
Pharmaceuticals

781 Chestnut Ridge Road
Morgantown, WV 26505 USA
Phone 304.599.2595
Web www.mylan.com

April 29, 2011

BIOEQUIVALENCE AMENDMENT
(BIOEQUIVALENCE RESPONSE TO INFORMATION REQUEST)

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: VENLAFAXINE EXTENDED-RELEASE CAPSULES, 37.5 MG, 75 MG AND 150 MG
ANDA 078789
SEQUENCE NUMBER: 0003
(RESPONSE TO AGENCY CORRESPONDENCE DATED APRIL 13, 2011)

Dear Dr. Webber:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the bioequivalence comments pertaining to this application that were provided to Mylan by facsimile in correspondence dated April 13, 2011 (refer to Section 1.4.4, References). In response to the Agency's April 13th comments, Mylan wishes to amend this application as follows:

FDA COMMENT

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional in vitro dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1N HCl, USP apparatus I (basket) at 100 rpm, with and without alcohol;

Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

All strengths of the test and the corresponding reference products must be tested accordingly and data must be provided on individual unit, means, range and %CV including f_2 similarity values and dissolution plots.

Please note: the DBE also requests you to complete all items for vitro study in eCTD format tables for all generated dissolution profiles and submit them electronically, both as an MS Word document and as a *.pdf file. The eCTD format tables are posted on the FDA website (http://www.fda.gov/cder/ogd/DBE_tables.doc).

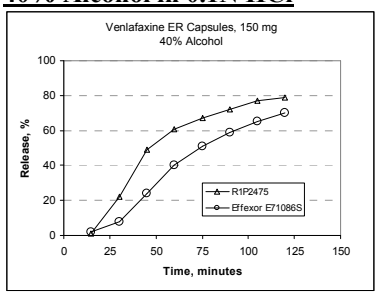
MYLAN RESPONSE

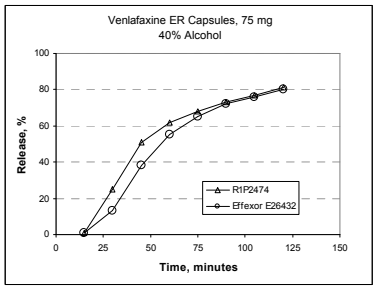
As requested, Mylan has conducted additional in vitro dissolution testing with alcohol. The data suggests that both Mylan's Venlafaxine Hydrochloride Extended-release Capsules and Effexor XR® show increased dissolution as a result of the incorporation of alcohol into the dissolution medium. Dissolution in 40% alcohol results in significant drug release at 120 minutes which is comparable (≤ 25% difference) between Mylan's Venlafaxine HCl Extended-release Capsules and multiple lots of Effexor XR across all strengths as demonstrated in the following table:

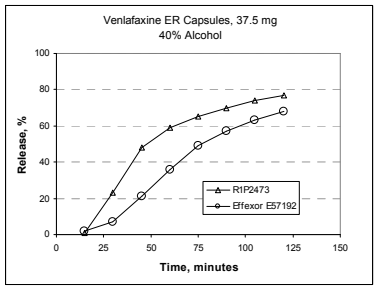
0.1N HCl with 40% Alcohol Dissolution Study			
Lot # (strength)	Mean	Range	RSD
Mylan R1P2473 (37.5mg) n = 12	77%	71%-81%	3.4%
Effexor XR A48018 (37.5 mg) n = 6	77%	72%-82%	4.5%
Effexor XR E57192 (37.5 mg) n = 12	68%	65%-70%	2.3%
Mylan R1P2474 (75 mg) n = 12	81%	77%-83%	2.4%
Effexor XR E57194 (75 mg) n = 6	80%	76%-85%	3.6%
Effexor XR E26432 (75 mg) n = 12	80%	75%-85%	2.9%
Mylan R1P2475 (150 mg) n = 12	79%	75%-81%	2.6%
Effexor XR E4386S (150 mg) n = 12	68%	64%-70%	2.9%
Effexor XR E71086S (150 mg) n = 12	70%	67%-72%	2.4%

Mylan has performed the full dissolution testing, as requested, with 40%, 20%, 5%, and 0% levels of alcohol in 0.1N HCl. The data can be characterized as significant release in 40% alcohol and slight release in 20% alcohol, where 40% alcohol releases more than 50% of label claim and 20 % alcohol releases less than 50% of label claim. Dissolution in 5% alcohol was essentially the same as no alcohol for all of the lots evaluated.

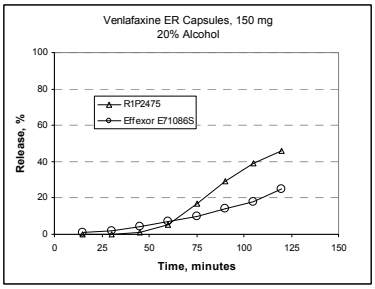
40% Alcohol in 0.1N HCl

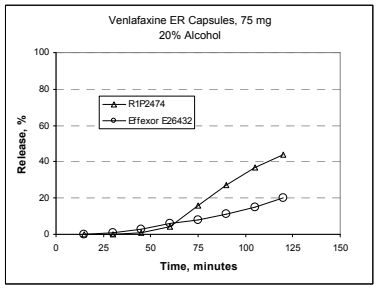


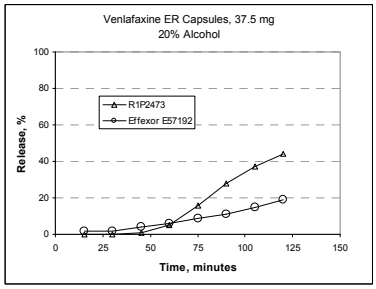




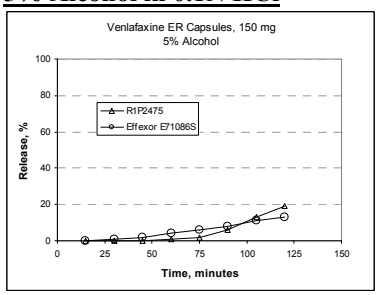
20% Alcohol in 0.1N HCl

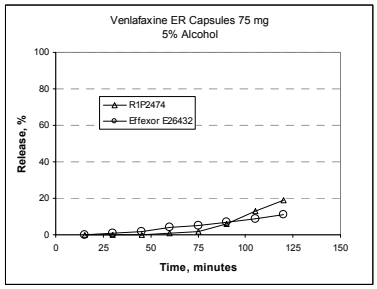


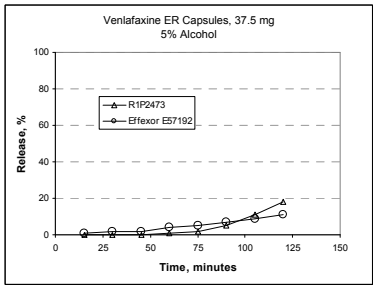




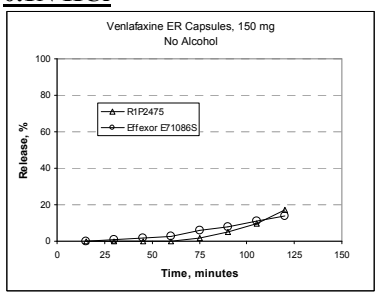
5% Alcohol in 0.1N HCl

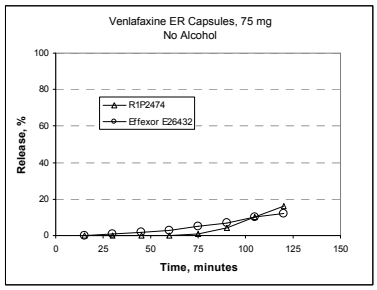


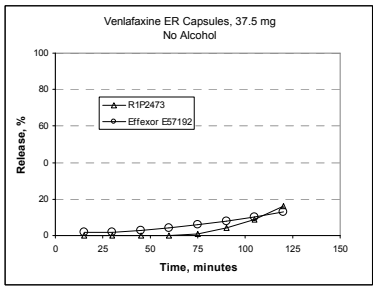




0.1N HCl







Individual unit, mean, range and %CV including similarity and dissolution plots are provided in Module 2.

F_2 similarity calculations were viewed as unsuitable for the data, since extent of dissolution was less than 85% released and early time points exceeded 15% CV. To overcome limitations of variability, Mylan has performed similarity calculations for comparison of these profiles with a "Model Independent Multivariate Confidence Region Procedure." This approach for comparing dissolution profiles is described on pages 9-10 of the FDA Guidance – *Dissolution Testing for Immediate Release Solid Oral Dosage Forms* (August 1997). Similarity of the dissolution profiles in the 40% alcohol media study was confirmed with this approach. Tables of all of the similarity calculations are included in Section 2.7. Also provided in Section 2.7 are a revised Bioequivalence Summary Table 5 and dissolution profiles.

All files in this amendment have been scanned utilizing Norton antivirus software and are free of known viruses. All correspondence regarding this amendment should be directed to the attention of the undersigned at (304) 599-2595, ext. 6551 and/or via facsimile at (304) 285-6407.

Sincerely,

<Please see following page for signature manifestation.>

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/mj

SIGNATURE MANIFESTATION

Document Name : venl-er-cvr-0003-amnd

Document Title : Cover Letter - 0003 - Bioequivalence Amendment - 20110429

Document Version : 0.5; CURRENT; Most-Recent; In Approval

Date	Signed By	Reason for Signing
29-Apr-2011 03:37 PM EDT	Wayne Talton	Approve

Object ID: 0901474e80e07abe

BIOEQUIVALENCE AMENDMENT

ANDA 078789

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Mylan Pharmaceuticals, Inc. TEL: (304) 599-2595

ATTN: S. Wayne Talton FAX: (304) 285-6407

FROM: Chitra Mahadevan FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on January 15, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Venlafaxine Extended Release Capsules, Eq. to 37.5 mg and 75 mg and 150 mg base.

The Division of Bioequivalence has completed its review of the submission referenced above and has identified deficiencies which are presented on the attached **3** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA:	078789
APPLICANT:	Mylan Pharmaceuticals, Inc.
DRUG PRODUCT:	Venlafaxine Hydrochloride Extended-Release Capsules, Eq. to 37.5 mg, 75 mg, and 150 mg base

The Division of Bioequivalence (DBE) has completed its review and the following deficiency has been identified:

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional in vitro dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1N HCl, USP apparatus I (basket) at 100 rpm, with and without alcohol;

Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

All strengths of the test and the corresponding reference products must be tested accordingly and data must be provided on individual unit, means, range and %CV including f_2 similarity values and dissolution plots.

Please note: The DBE also requests you to complete all items for in vitro study in eCTD format tables for all generated dissolution profiles and submit them electronically, both as an MS Word document and as a *. pdf

file. The eCTD format tables are posted on the FDA web site (http://www.fda.gov/cder/ogd/DBE_tables.doc).

Sincerely yours,

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
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/

BARBARA M DAVIT
04/13/2011

Mylan®
Pharmaceuticals

781 Chestnut Ridge Road
Morgantown, WV 26505 USA
Phone 304.599.2595
Web www.mylan.com

April 7, 2011

TELEPHONE AMENDMENT
(CHEMISTRY INFORMATION PROVIDED)

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 078789
SEQUENCE NUMBER: 0002
(RESPONSE TO AGENCY TELEPHONE CALL RECEIVED APRIL 6, 2011)

Dear Dr. Webber:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review and to our Minor Amendment – Request for Final Approval submitted on April 4, 2011 (Sequence No. 0001). Reference is also made to a telephone call received on April 6, 2011 from Zhigang Sun, of your Office, in which he requested that we revise our House Standard specifications to include testing for Optical Rotation, Limit of [redacted] (b) (4) and Limit of Residual Solvents to be consistent with our proposed drug substance specifications. In response to the Agency's April 6th telephone call, Mylan wishes to amend this application as follows:

As requested, the House Reference Standard specifications for Venlafaxine Hydrochloride, USP, provided in Section 3.2.S.5, have been revised to reinstate testing and limits for Optical Rotation, Limit of [redacted] (b) (4) and Limit of Residual Solvents. Consistent with the Venlafaxine Hydrochloride, USP drug substance specifications, Mylan will control for these tests at the following limits and with the following procedures:

Test	Limits	Procedure
Optical Rotation	[redacted] (b) (4)	<781S>
Limit of [redacted] (b) (4)		RA-VENHCL-RS-M
Limit of Residual Solvents		RA-VENHCL-RS-M

All files in this amendment have been scanned utilizing Norton antivirus software and are free of known viruses. All correspondence regarding this amendment should be directed to the attention of the undersigned at (304) 599-2595, ext. 6551 and/or via facsimile at (304) 285-6407.

Sincerely,

<Please see following page for signature manifestation.>

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/mjk

SIGNATURE MANIFESTATION

Document Name : venl-er-cvr-0002-amd

Document Title : Cover Letter - 0002 - Telephone Amendment - 20110407

Document Version : 1.1; Most-Recent; In Approval

Date	Signed By	Reason for Signing
07-Apr-2011 12:47 PM EDT	Wayne Talton	Approve

Object ID: 0901474e80ddb30a

Mylan®
Pharmaceuticals

781 Chestnut Ridge Road
Morgantown, WV 26505 USA
Phone 304.599.2595
Web www.mylan.com

April 4, 2011

MINOR AMENDMENT – FINAL APPROVAL REQUESTED
(CHEMISTRY INFORMATION PROVIDED)

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 078789
SEQUENCE NUMBER: 0001
(Minor Amendment – Request for Final Approval)

Dear Dr. Webber:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above which received Tentative Approval on November 13, 2008. A copy of the Tentative Approval letter is provided in Section 1.4.4 for your reference. Mylan previously filed Paragraph IV certifications with respect to U.S. Patent Nos. 6,274,171; 6,403,120; and 6,419,958. The litigation pending against Mylan on those patents was dismissed on December 21, 2009, pursuant to a Dismissal Order and Judgment in a Civil Action. A copy of the Dismissal Order and Judgment are provided in Section 1.4.4 for your reference.

Pursuant to 21 C.F.R. § 314.94(a)(12)(v), Mylan certifies that it has entered into a licensing agreement with the patent owner(s) of each of these patents, and Mylan has been granted a patent license which permits Mylan to market its Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg, 75 mg and 150 mg prior to the expiration of each of these patents.

In accordance with the patent license, Mylan hereby requests that final approval for Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg, 75 mg and 150 mg be granted as of June 1, 2011.

In association with this request for Final Approval, Mylan wishes to submit the following revisions to the chemistry, manufacturing and controls documentation:

All files in this amendment have been scanned utilizing Norton antivirus software and are free of known viruses. All correspondence regarding this amendment should be directed to the attention of the undersigned at (304) 599-2595, ext. 6551 and/or via facsimile at (304) 285-6407.

Sincerely,

<Please see following page for signature manifestation.>

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/mjk

Cover letter only:

Wyeth Pharmaceuticals
500 Arcola Road
Collegeville, Pennsylvania 19426
Attn: Senior Vice President, Corporate Business Development
Phone: (484) 865-5603
Fax: (484) 865-6476

Wyeth
5 Giralda Farms
Madison, New Jersey 07940
Attn: General Counsel
Phone: (973) 660-5000
Fax: (973) 660-7156

SIGNATURE MANIFESTATION

Document Name : venl-er-cvr-0001-amnd

Document Title : Cover Letter - 0001 - Minor Amendment - 20110404

Document Version : 0.7; CURRENT; Most-Recent; In Approval

Date	Signed By	Reason for Signing
04-Apr-2011 01:34 PM EDT	Wayne Talton	Approve

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-789

11/13/2008 dn
FLT

Mylan Pharmaceuticals Inc.
Attention: S. Wayne Talton
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated January 15, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg (base), 75 mg (base), and 150 mg (base).

Reference is also made to your amendments dated November 6, 2007; and February 15, May 21, June 2, June 23, July 8, August 1, August 19, and October 20, 2008.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the patent issues noted below. Therefore, the ANDA is **tentatively approved.** This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention. This letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The reference listed drug (RLD) upon which you have based your ANDA, Effexor XR Capsules, 37.5 mg, 75 mg, and 150 mg, of Wyeth Pharmaceuticals, Inc., is subject to multiple periods of patent protection and exclusivity. The following unexpired patents (with their expiration dates) are currently listed in the

agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

U.S. Patent Number	Expiration Date
5,916,923 (the '923 patent)	December 28, 2013*
6,274,171 (the '171 patent)	September 20, 2017*
6,310,101 (the '101 patent)	June 28, 2013
6,403,120 (the '120 patent)	September 20, 2017*
6,419,958 (the '958 patent)	September 20, 2017*
6,444,708 (the '708 patent)	December 28, 2013*

*pediatric exclusivity added

With respect to the '101, '923 and '708 patents, as well as the '120 patent insofar as it pertains to U-451 (generalized anxiety disorder), and the '958 patent insofar as it pertains to U-459 (generalized anxiety disorder), your ANDA contains statements under section 505(j)(2)(A)(viii) of the Act that these are method of use patents that do not claim any indication for which you are seeking approval under your ANDA.

With respect to the '171, '120, and '958 patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg (base), 75 mg (base), and 150 mg (base), under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action was brought against Mylan for infringement of one or more of these patents that were the subjects of the paragraph IV certifications. This action must have been brought against Mylan prior to the expiration of 45 days from the date the notice you provided under section 505 (j)(2)(B)(i) was received by the NDA/patent holder(s). You notified the agency that Mylan complied with the requirements of section 505(j)(2)(B) of the Act, and litigation for infringement of the '171, '120, and '958 patents was brought against Mylan in the United States District Court for the Northern District of West Virginia [Wyeth Pharmaceuticals Inc. v. Mylan Pharmaceuticals Inc., Civil Action No. 07-CV-91].

Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii)[1]

   b. the date the court decides[2] that the '171, '120, and '958 patents are invalid or not infringed (see sections 505(j)(5)(B)(iii)(I), (II), and (III) of the Act), or

   c. the '171, '120, and '958 patents have expired, and

2. The agency is assured there is no new information that would affect whether final approval should be granted.

With respect to the exclusivities listed for the RLD, Mylan is not seeking approval, at this time, for the indications covered by the I-538 and I-537 exclusivities (short-term and long-term treatment, respectively, of panic disorder), and is not seeking approval of its ANDA prior to the expiration on December 14, 2010, of the I-561 exclusivity (long-term treatment of social anxiety disorder).

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED.

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[1] Because information on the '171, '120, and '958 patents was submitted to FDA before August 18, 2003, this reference to section 505(j)(5)(B)(iii) is to that section of the Act as in effect prior to December 8, 2003, when the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) was enacted. See MMA § 1101(c)(3).

[2] This decision may be either a decision of the district court or the court of appeals, whichever court is the first to decide that the patent is invalid or not infringed.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book."

For further information on the status of this application, or prior to submitting additional amendments, please contact Thomas Hinchliffe, Project Manager, at 240-276-8536.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
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 L. West
11/13/2008 01:07:20 PM
Deputy Director, for Gary Buehler

AO 450 (Rev. 01/09) Judgment in a Civil Action

UNITED STATES DISTRICT COURT

for the

Northern District of West Virginia

WYETH *Plaintiff* v. MYLAN PHARMACEUTICALS, INC *Defendant*	)))))	Civil Action No. 1:07 CV 91

JUDGMENT IN A CIVIL ACTION

The court has ordered that *(check one)*:

❒ the plaintiff *(name)* _____ recover from the defendant *(name)* _____ the amount of _____ dollars ($ _____), which includes prejudgment interest at the rate of _____ %, plus postjudgment interest at the rate of _____ %, along with costs.

❒ the plaintiff recover nothing, the action be dismissed on the merits, and the defendant *(name)* _____ recover costs from the plaintiff *(name)* _____.

☑ other: pursuant to F.R.C.P. 58, clerk is directed to enter judgment on this matter.

This action was *(check one)*:

❒ tried by a jury with Judge _____ presiding, and the jury has rendered a verdict.

❒ tried by Judge _____ without a jury and the above decision was reached.

☑ decided by Judge Irene M. Keeley

By order of this Court.

Cheryl Dean Riley

Date: 12/21/2009

CLERK OF COURT

Signature of Clerk or Deputy Clerk

Mylan®
Pharmaceuticals

781 Chestnut Ridge Road
Morgantown, WV 26505 USA
Phone 304.599.2595
Web www.mylan.com

March 18, 2011

LABELING AMENDMENT
(LABELING INFORMATION PROVIDED)

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 078789
SEQUENCE NUMBER: 0000
(LABELING REVISIONS PURSUANT TO CDER INTERNET POSTING DATED JANUARY 6, 2010)

Dear Dr. Webber:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which received Tentative Approval on November 13, 2008. Mylan wishes to amend our ANDA with final printed labeling that has been revised pursuant to the CDER Internet Posting dated January 6, 2010 which contained approved labeling revisions for the reference listed drug (RLD), Effexor XR® (venlafaxine hydrochloride) Extended-Release Capsules (NDA 020699/S-090). A copy of the Agency's January 6th approval letter is provided in Section 1.4.4, References. A copy of the RLD's currently approved labeling is provided in Section 1.14.3.2 for your reference. Please note that Mylan's revised labeling also reflects the addition of the USP monograph for the drug substance which will become effective on May 1, 2011. A Minor Amendment to request final approval and to provide chemistry information to support the USP updates will be submitted under separate cover in the near future.

Final printed labeling (outsert code VNLAER:R1mc; March 2011) is provided in Section 1.14.2.2 and corresponding final printed bottle labels are provided in Section 1.14.2.1. A side-by-side comparison of Mylan's proposed final printed outsert/Medication Guide to Mylan's previously submitted draft outsert/Medication Guide is provided in Section 1.14.1.2 (Labeling). A side-by-side comparison of Mylan's proposed final printed bottle labels to Mylan's previously submitted draft bottle labels is provided in Section 1.14.1.2 (Container). Structured Product Labeling (SPL) is provided in Section 1.14.2.3. A copy of Mylan's service agreement with The Hibbert Group for the distribution of Medication Guides is provided in Section 1.4.4, References.

Mylan acknowledges that the Agency may request further changes to the labeling prior to approval. In addition, Mylan may have to revise our labeling pursuant to approved changes for the reference listed drug. Mylan will monitor FDA's website for any approved labeling changes.

For assistance with the electronic components of this application, please contact Jerry Toppins (304) 599-2595, Ext. 6578 or e-mail at jerry.toppins@mylan.com. All other correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6551 and/or facsimile number (304) 285-6407.

Sincerely,

<Please see following page for signature manifestation.>

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/ccc

SIGNATURE MANIFESTATION

Document Name : venl-er-cvr-0000

Document Title : Cover Letter - 0000 - Labeling Amendment - 20110318

Document Version : 0.1; CURRENT; Most-Recent; In Approval

Date	Signed By	Reason for Signing
18-Mar-2011 12:02 PM EDT	Wayne Talton	Approve

Object ID: 0901474e80db5238

OGD APPROVAL ROUTING SUMMARY

ANDA # 78-789 ApplicantMylan Pharmaceuticals Inc.
Drug Venlafaxine Hydrochloride Extended-Release Capsules Strength(s)37.5, 75, 150 mg

APPROVAL ☐ **TENTATIVE APPROVAL** ☒ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date16 Sept 2008 Date 11/13/08
Chief, Reg. Support Branch Initials MHS Initials rlw

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD =Effexor XR NDA#20-699
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked Previously granted
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☒ No ☐ Written request issued ☐
Was applicant sued w/in 45 days:Yes ☒ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☒ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter:T/A
Comments:ANDA submitted on 1/16/2007, BOS=Effexor XR NDA 20-699, PIII to '186, PIV to '171, '120 and '958, MOU to '923 and '708. ANDA ack for filing with PIV on 1/16/2007(LO dated 5/2/2007). On 4/23/2007 the sponsor submitted a revised patent cert which provided for MOU certs to the '120 and '958 so far as these patents and their associated uses apply to GAD. On 5/30/2007-Fed Ex RR from Wyeth(collegeville, PA) signed and dated 5/23/2007, Fed Ex RR from Wyeth(Madison, NJ) signed and dated 5/23/2007. Letter from Finnegan and Henderson received 7/6/2007-CA 07-CV-91 filed in the Northern D of WV(Clarksburg Division on 7/6/2007 for infringement of the '171, '120 and '958 patents. On 7/8/2008 the sponsor submitted a MOU to the '101. Mylan will await the expiration of the I-561 exclusivity before seeking full approval. ANDA is eligible for TA only due to unexpired 30 month stay of approval.

2. Project Manager, Thomas Hinchliffe Team 10 Date_____ Date_____
Review Support Branch Initials_____ Initials_____

Original Rec'd dateJanuary 16, 2007 EER Status Pending ☐ Acceptable ☒ OAI ☐
Date Acceptable for FilingJanuary 16, 2007 Date of EER Status 5/21/2007
Patent Certification (type)4 Date of Office Bio Review 4/16/2008
Date Patent/Exclus.expiresmultiple -c below Date of Labeling Approv. Sum 8/18/2008
Citizens' Petition/Legal Case Yes☐ No ☒ Labeling Acceptable Email Rec'd Yes ☐ No ☐
(If YES, attach email from PM to CP coord) Labeling Acceptable Email filed Yes ☐ No ☐
First Generic Yes ☐ No ☒ Date of Sterility Assur. App. _____
Priority Approval Yes ☐ No ☒ Methods Val. Samples Pending Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise) MV Commitment Rcd. from Firm Yes ☒ No ☐
Acceptable Bio reviews tabbed Yes ☐ No ☒ Modified-release dosage form: Yes ☒ No ☐
Bio Review Filed in DFS: Yes ☒ No ☐ Interim Dissol. Specs in AP Ltr: Yes ☐
Suitability Petition/Pediatric Waiver Yes ☐
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:DATE OF APPLICATION: January 15, 2007

3. Labeling Endorsement
Reviewer: Labeling Team Leader:
Date9/17/08 Date9/17/08
Name/InitialsMD Name/InitialsLDG

Comments:
From: Golson, Lillie D
Sent: Wednesday, September 17, 2008 5:23 PM
To: Hinchliffe, Thomas; Golson, Lillie D

Subject: FW: 78-789 TA Endorsement Needed

Hi Tom,

From a labeling standpoint, this application is acceptable for TA. Please endorse the TA routing form on behalf of Michelle and me.
Thanks
Lillie

From: Dillahunt, Michelle
Sent: Wednesday, September 17, 2008 11:14 AM
To: Golson, Lillie D
Subject: FW: 78-789 TA Endorsement Needed

Labeling is acceptable for TA.

Michelle

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 18Sep08
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials DTR
Comments: Changes to TA ltr saved to V drive.

5. Div. Dir./Deputy Dir. Date 11/12/08
Chemistry Div. II Initials FF

Comments: Addressed in process controls (10/20/08 amendment. CMC ok.

6. Frank Holcombe **First Generics Only** Date 11/13/08
Assoc. Dir. For Chemistry Initials rlw/for
Comments: (First generic drug review)
N/A. IMPAX's ANDA 78-057 for this drug product was granted tentative approval on October 16, 2007.

7. Vacant Date 11/13/08
Deputy Dir., DLPS Initials rlw
RLD = Effexor XR Extended-release Capsules 37.5 mg (base), 75 mg (base) and 150 mg (base)
Wyeth Pharmaceuticals, Inc. NDA 20-699

8. Peter Rickman Date 11/13/08
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments: Bioequivalence studies (fed and fed-sprinkle) on the 150 mg capsule strength found acceptable. In-vitro dissolution testing on all three strengths also found acceptable. Waivers granted to the 37.5 mg and 75 mg capsule strengths under 21 CFr 320.22(d)(2). Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 4/16/08.

Labeling found acceptable for tentative approval 8/18/08.

CMC found acceptable (Chemistry Review #2) 9/9/08.

OR

8. Robert L. West Date 11/13/08
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☒ No☐; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EES dated 5/21/07 (Verified 11/13/08). No "OAI" Alerts noted.

Refer to the patent and exclusivity summary prepared above by M.Shimer.

This ANDa is recommended for tentative approval.

9. Gary Buehler Date 11/13/08
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Thomas Hinchliffe Team 10 Date11/13/08
Review Support Branch Initials tcl
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
2:30 pm Time notified of approval by phone 2:30 pm Time approval letter faxed

FDA Notification:
11/13/08 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
11/13/08 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

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

/s/

Theresa Liu
11/13/2008 01:28:32 PM

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

October 20, 2008

TELEPHONE AMENDMENT
(CHEMISTRY INFORMATION PROVIDED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 78-789
(Response To Agency Telephone Call Received on October 8, 2008)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. Reference is also made to chemistry comments pertaining to this application which were provided to Mylan in a telephone call received on October 8, 2008 from Dr. Zhigang Sun, of your Office. In response to the Agency's comments received on October 8th, Mylan wishes to amend our application as follows:

FDA COMMENT 1

(b) (4)

MYLAN RESPONSE

(b) (4)

Department – Fax Numbers

Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 285-6482	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

Venlafaxine HCl Extended-release Beads
SUPAC Level 1 Factor Calculations

(b) (4)

[redacted]

FDA COMMENT 2

(b) (4)

[redacted]

MYLAN RESPONSE

(b) (4)

[redacted]

FDA COMMENT 3

(b) (4)

[redacted]

MYLAN RESPONSE

(b) (4)

[redacted]

Venlafaxine Extended-release Capsules
In-process and Composite Weight Variation Data

(b) (4)

[redacted]

Should the Agency have any additional questions regarding this response, we would like to request a Telephone Conference to further discuss the issues.

This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on April 17, 2006. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/mj

Desk Copy: Tom Hinchliffe, Project Manager (via facsimile)
Division of Chemistry II, Team 10

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

August 19, 2008

TELEPHONE AMENDMENT
(CHEMISTRY INFORMATION PROVIDED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 78-789
RESPONSE TO AGENCY TELEPHONE CALL RECEIVED AUGUST 15, 2008

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to our Telephone Amendment submitted on August 1, 2008 in which we provided information to demonstrate that Venlafaxine Hydrochloride Extended-release Capsules comply with the requirements of USP General Chapter <467>. Reference is also made to a telephone call received on August 15, 2008 from Dr. Zhigang Sun, of your Office, in which he requested that we provide a representative Certificate of Analysis for the specific grade of Ethylcellulose, NF [redacted] (b) (4)) used in the formulation.

As requested, Mylan has provided a representative Certificate of Analysis in Section 3.2.P.4.1 for Ethylcellulose, NF [redacted] (b) (4)).

This amendment is being submitted electronically in PDF format. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

Desk Copy: Zhigang Sun, Chemistry Reviewer (via facsimile)
Division of Chemistry II, Team 10

Department—Fax Numbers

Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 285-6482	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

August 1, 2008

TELEPHONE AMENDMENT
(CHEMISTRY INFORMATION PROVIDED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 78-789
RESPONSE TO AGENCY TELEPHONE CALL RECEIVED JULY 18, 2008

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to our Telephone Amendment submitted on June 23, 2008, in response to the Agency's correspondence dated June 12, 2008 requesting that the excipients submitted in our ANDA for Venlafaxine Hydrochloride Extended-release Capsules be reviewed for compliance with USP General Chapter <467> for residual solvent testing. Reference is also made to a telephone call received on July 18, 2008 from Mr. Zhigang Sun, of your Office, in which he requested that we establish limits, provide test methods and results for excipients identified as having potential residual solvents.

As requested by the Agency, Mylan is providing the following information for (b) (4)

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 598-5419
Corporate Services (304) 285-6482
Human Resources (304) 598-5406
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Product Development (304) 285-6411
Purchasing (304) 598-5401
Quality Assurance (304) 598-5407
Quality Control (304) 598-5409
Regulatory Affairs (304) 285-6407
Research & Development (304) 285-6419
Sales & Marketing (304) 598-3232

(b) (4)

[redacted]

(b) (4)

[redacted]

As requested by the Agency, a copy of the reference from Pharmacopeial Forum (*Pharmacopeial Forum*. 2007; 33 (1): 19) that indicates that compendial changes can be implemented prior to the effective date is provided in Section 3.3 References.

This amendment is being submitted electronically in PDF format. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/mj

Enclosures

Desk Copy: Zhigang Sun, Chemistry Reviewer (via facsimile)
Division of Chemistry II, Team 10

G:\Project\ANDA\VENLAFAXINE HCl ER CAPSULES\AGENCY-CALL-DATED-071808.doc

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 8, 2008

LABELING AND PATENT AMENDMENT
(ELECTRONIC LABELING AND PATENT INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 78-789
(Labeling Revisions in Accordance with the CDER Internet Posting dated May 23, 2008)

Dear Mr. Buehler:

Mylan wishes to amend the above referenced Abbreviated New Drug Application (ANDA) to provide draft labeling (outsert code VNLAER:RX1mc, Revised June 2008) that has been revised in accordance with the most recently approved labeling for the reference listed drug, Effexor XR® (NDA 20-699/S-081, approved May 23, 2008). Mylan's proposed bottle labels remain the same as those previously submitted in our original ANDA on January 15, 2007. Copies of the letter posted for Effexor XR® on May 23, 2008 and the outsert posted on Wyeth's website are provided herein as Letter.pdf and Innovator OT.pdf, respectively. In addition, Mylan has provided a patent amendment as Attachment A.pdf to address a patent and exclusivities which have been listed in FDA's 'Orange Book' subsequent to our previous submissions. Consistent with our Patent Amendment, Mylan has excluded the treatment of panic disorder from our revised draft labeling.

In addition to including a complete copy of the Medication Guide at the end of the prescribing information, please note that Mylan is participating in an Antidepressants Medication Guide Agreement with other sponsors that uses 'The Hibbert Group' as a vendor to create, manufacture and distribute the standard Medication Guides in tear-off pads to pharmacists and physicians.

In accordance with the Agency's Guidance *Providing Regulatory Submissions in Electronic Format – General Considerations*, we enclose a CD-Rom which contains electronic labeling for Venlafaxine Hydrochloride Extended-release Capsules as described in the electronic Table of Contents. As a review aid, Mylan has also included a Microsoft Word version of our proposed outsert. To access this Word file, a bookmark is provided within the pdf version. Given the amount of time before our ANDA is eligible to receive final approval, the enclosed labeling has been resubmitted in draft in pursuit of a Tentative Approval.

Mylan intends to submit a Structured Product Labeling (SPL) version of our generic product labeling in an amendment to this application at the time we submit Final Printed Labeling.

Mylan acknowledges that the Agency may request further changes to the labeling prior to approval. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's website for any approved labeling changes.

Should you have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407 or email at wayne.talton@mylanlabs.com.

Sincerely,

Rebecca L. Layfer for

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/ccc

Enclosure

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 8, 2008

LABELING AND PATENT AMENDMENT
(ELECTRONIC LABELING AND PATENT INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 78-789
(Labeling Revisions in Accordance with the CDER Internet Posting dated May 23, 2008)

Dear Mr. Buehler:

Mylan wishes to amend the above referenced Abbreviated New Drug Application (ANDA) to provide draft labeling (outsert code VNLAER:RX1mc, Revised June 2008) that has been revised in accordance with the most recently approved labeling for the reference listed drug, Effexor XR® (NDA 20-699/S-081, approved May 23, 2008). Mylan's proposed bottle labels remain the same as those previously submitted in our original ANDA on January 15, 2007. Copies of the letter posted for Effexor XR® on May 23, 2008 and the outsert posted on Wyeth's website are provided herein as Letter.pdf and Innovator OT.pdf, respectively. In addition, Mylan has provided a patent amendment as Attachment A.pdf to address a patent and exclusivities which have been listed in FDA's 'Orange Book' subsequent to our previous submissions. Consistent with our Patent Amendment, Mylan has excluded the treatment of panic disorder from our revised draft labeling.

In addition to including a complete copy of the Medication Guide at the end of the prescribing information, please note that Mylan is participating in an Antidepressants Medication Guide Agreement with other sponsors that uses 'The Hibbert Group' as a vendor to create, manufacture and distribute the standard Medication Guides in tear-off pads to pharmacists and physicians.

In accordance with the Agency's Guidance *Providing Regulatory Submissions in Electronic Format – General Considerations*, we enclose a CD-Rom which contains electronic labeling for Venlafaxine Hydrochloride Extended-release Capsules as described in the electronic Table of Contents. As a review aid, Mylan has also included a Microsoft Word version of our proposed outsert. To access this Word file, a bookmark is provided within the pdf version. Given the amount of time before our ANDA is eligible to receive final approval, the enclosed labeling has been resubmitted in draft in pursuit of a Tentative Approval.

Mylan intends to submit a Structured Product Labeling (SPL) version of our generic product labeling in an amendment to this application at the time we submit Final Printed Labeling.

Mylan acknowledges that the Agency may request further changes to the labeling prior to approval. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's website for any approved labeling changes.

Should you have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407 or email at wayne.talton@mylanlabs.com.

Sincerely,

Rebecca L. Layfer for

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/ccc

Enclosure

MYLAN PHARMACEUTICALS INC.

VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES 37.5 MG, 75 MG AND 150 MG

Attachment A.pdf

PATENT AMENDMENT

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

Office of Generic Drugs, CDER, FDA
Mr. Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

JUL 8 2008

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES, 37.5 MG, 75 MG AND 150 MG

ANDA # 78-789

PATENT AMENDMENT

STATEMENTS PURSUANT TO 21 U.S.C. §355(j)(2)(A)(viii)

U.S. PATENT NO.: 6,310,101

Dear Mr. Buehler:

Mylan Pharmaceuticals Inc. ("Mylan") previously filed its patent certifications and exclusivity information for the above-referenced product. At the time of these filings, Mylan's certifications were correct. This current amendment is submitted to address new patent and exclusivity information which were listed subsequent to Mylan's previous submissions.

With respect to U.S. Patent No. 6,310,101, with an associated Use Code, U-46 ("Treatment of Panic Disorder"), Mylan makes the following statement pursuant to 21 U.S.C. §355(j)(2)(A)(viii):

> With respect to the listed drug referred to in its application for which information was filed under subsection (b) or (c) for this method of use patent, Mylan states that its labeling does not claim such method of use.

Additionally, Mylan certifies that according to the exclusivity information published by FDA in the "Approved Drug Products with Therapeutic Equivalence Evaluations," 28th Edition as set forth in the "Electronic Orange Book" published at FDA's web site, the referenced product is covered by the following exclusivities:

- "Short Term Treatment of Panic Disorder" (I-538), which expires November 18, 2008;
- "Long Term Treatment of Panic Disorder" (I-537), which expires November 18, 2008; and
- "Long Term Treatment of Social Anxiety Disorder" (I-561), which expires on December 14, 2010.

Department—Fax Numbers

Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 285-6482	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

At this time, Mylan is not seeking, in its labeling, approval for the indications covered by the I-538 and I-537 exclusivities identified above. With respect to the I-561 exclusivity, Mylan is not seeking approval of its application until the expiration of such exclusivity (i.e., December 14, 2010).

The patent and exclusivity information identified in the preceding paragraph is in addition to the patent/exclusivity information set forth in Mylan's original submissions. This amendment is merely an update to reflect the newly filed patent and exclusivity information.

Sincerely,

Brian S. Roman

Brian S. Roman
Vice President and General Counsel

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

June 23, 2008

TELEPHONE AMENDMENT
(CHEMISTRY INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 78-789
RESPONSE TO AGENCY CORRESPONDENCE RECEIVED JUNE 12, 2008

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. Reference is also made to the Agency's correspondence received on June 12, 2008 requesting that the excipients submitted in our ANDA for Venlafaxine Hydrochloride Extended-release Capsules be reviewed for compliance with USP General Chapter <467> for residual solvent testing as it will become official on July 1, 2008.

As requested, Mylan has reviewed our excipient specifications for compliance with USP General Chapter <467> and have revised the specifications accordingly. The revised specifications with residual solvents statements from our suppliers are provided in Section 3.2.P.4.1. Any procedures and corresponding method validation reports that were created due to the addition of residual solvents are provided in Sections 3.2.P.4.2 and 3.2.P.4.3, respectively. The following residual solvents have the potential to be present in the formulation of Venlafaxine Hydrochloride Extended-release Capsules, 37.5mg, 75 mg and 150 mg.

Excipients

Component	Solvents	Classification	USP <467> Limits	Proposed Limits
				(b) (4)

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 598-5419
Corporate Services (304) 285-6482
Human Resources (304) 598-5406
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Product Development (304) 285-6411
Purchasing (304) 598-5401
Quality Assurance (304) 598-5407
Quality Control (304) 598-5409
Regulatory Affairs (304) 285-6407
Research & Development (304) 285-6419
Sales & Marketing (304) 598-3232

Component	Solvents	Classification	USP <467> Limits	Proposed Limits
[redacted]				

(b) (4)

* The amount in the excipient contributes to the amount in the finished product and is controlled for in the finished product.

** The amounts of solvents that may be present in the excipient meet Option 1, therefore justification is unnecessary.

The drug substance and excipients in the formulation of Venlafaxine Hydrochloride Extended-release Capsules meet the limits given in *Option 1* of USP General Chapter <467>; therefore, the components of the product may be used in any proportion. For the solvents listed in the excipients above, no further calculation is necessary since the maximum daily dose does not exceed 10 grams per day.

Mylan further controls for [redacted] (b) (4). The following justifies the proposed limits, which are within the limits allowed by USP<467>. The proposed limits with their justification were previously described in our Minor Amendment dated November 6, 2007.

Drug Product

Solvents	Classification	PDE	Maximum Daily Dose	Limit allowed*	Proposed Limits
[redacted]					

(b) (4)

Mylan commits to assess potential changes to the residual solvents that may occur due to a change of source or manufacturing process change for submission in the annual report.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. In addition, a true and accurate electronic copy in PDF format has been provided for your convenience. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Way Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/mj

Enclosures

Desk Copy: Tom Hinchliffe, Project Manager (via facsimile)
Division of Chemistry II, Team 10

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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

June 2, 2008

TELEPHONE AMENDMENT
(CHEMISTRY INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 78-789
RESPONSE TO AGENCY TELEPHONE CALL RECEIVED MAY 23, 2008

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to our Telephone Amendment submitted on May 21, 2008 in response to chemistry comments which were provided to Mylan by facsimile in correspondence dated May 5, 2008. Reference is also made to a telephone conference held on May 23, 2008 with Dr. Zhigang Sun, of your Office, regarding our May 21st Amendment.

(b) (4)

[redacted]

Department - Fax Numbers

Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Corporate Services	(304) 285-6482	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232
Information Systems	(304) 285-6404			Purchasing	(304) 598-5401

(b) (4)

(b) (4)

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. In addition, an electronic copy has been provided in PDF format for your convenience. Should you require any additional information, please contact the undersigned at (304) 599-2595, ext. 6551 via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Desk Copy: Tom Hinchliffe, Project Manager (via facsimile)
Division of Chemistry II, Team 10

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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

May 21, 2008

TELEPHONE AMENDMENT
(CHEMISTRY INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 78-789
RESPONSE TO AGENCY CORRESPONDENCE DATED MAY 5, 2008

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the chemistry comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated May 5, 2008 [provided in Section 1.4.4]. In response to the Agency's comments of May 5th, Mylan wishes to amend this application as follows:

FDA COMMENT 1

(b) (4)

[redacted]

MYLAN RESPONSE

(b) (4)

[redacted]

Department - Fax Numbers

Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
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Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

(b) (4)

[redacted]

(b) (4)

[redacted]

(b) (4)

[redacted]

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. In addition, an electronic copy has been provided in PDF format for your convenience. Should you require any additional information, please contact the undersigned at (304) 599-2595, ext. 6551 via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Desk Copy: Tom Hinchliffe, Project Manager (via facsimile)
Division of Chemistry II, Team 10

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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

February 15, 2008

BIOEQUIVALENCE AMENDMENT
(BIOEQUIVALENCE AND CHEMISTRY INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 78-789
RESPONSE TO AGENCY CORRESPONDENCE DATED DECEMBER 11, 2007

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the Bioequivalence comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated December 11, 2007 (refer to Attachment A). In response to the December 11th comments from the Division of Bioequivalence, Mylan wishes to amend this application as follows:

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

FDA COMMENT 1:

(b) (4)

[redacted]

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 285-6482	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

MYLAN RESPONSE:

(b) (4)

FDA COMMENT 2:

MYLAN RESPONSE: (b) (4)

This amendment is submitted in duplicate. In addition, an electronic copy has been provided in PDF format for your convenience. Should you require any additional information, please contact the undersigned at (304) 599-2595, ext. 6551 via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Desk Copy: Aaron Sigler, Project Manager
Division of Bioequivalence

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

February 15, 2008

BIOEQUIVALENCE AMENDMENT
(BIOEQUIVALENCE AND CHEMISTRY INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 78-789
RESPONSE TO AGENCY CORRESPONDENCE DATED DECEMBER 11, 2007

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the Bioequivalence comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated December 11, 2007 (refer to Attachment A). In response to the December 11th comments from the Division of Bioequivalence, Mylan wishes to amend this application as follows:

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

FDA COMMENT 1:

(b) (4)

[redacted]

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 285-6482	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

MYLAN RESPONSE:

(b) (4)

FDA COMMENT 2:

MYLAN RESPONSE:

(b) (4)

[redacted]

This amendment is submitted in duplicate. In addition, an electronic copy has been provided in PDF format for your convenience. Should you require any additional information, please contact the undersigned at (304) 599-2595, ext. 6551 via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Desk Copy: Aaron Sigler, Project Manager
Division of Bioequivalence

BIOEQUIVALENCY AMENDMENT

ANDA 78-789

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Mylan Pharmaceuticals, Inc. TEL: 304-599-2595

ATTN: S. Wayne Talton FAX: 304-285-6407

FROM: Aaron Sigler PROJECT MANAGER: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on January 15, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg, 75 mg, and 150 mg.

Reference is also made to your amendment dated November 06 and 16, 2007.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __2__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

In an effort to improve document flow and availability to review staff, please submit your response in electronic PDF format, with a signed cover letter and 356h form.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-789

APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Venlafaxine Hydrochloride Extended-Release Capsules, 150 mg, 75 mg and 37.5 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your proposed specifications of (b) (4) for the 2, 4, 8, 12, and 24 hour sampling time points,respectively, based on the submitted stability (stored sample) data are not acceptable. As per the Division of Bioequivalence (DBE) practice, the dissolution specifications are established based on the dissolution data on 12 units of the biolot (fresh, not stored lot) that has been used in acceptable bioequivalence studies. The DBE does not revise the dissolution specifications on the basis of the dissolution testing data on the stored lots. In order to justify your proposed specifications, please submit additional dissolution data of three fresh production lots, to determine if a revision of the dissolution specification is warranted. Alternatively, please acknowledge the FDA-recommended dissolution method and specifications given below:

Medium:	Water
Volume:	900 mL
USP Apparatus:	Type 1 (basket)
Rotation (rpm):	100 rpm
Specifications:	(b) (4)

2. There was evidence that an additional bioequivalence study was conducted as Study No. VENL-0548A based on some within-study bioanalytical validation data submitted in the amendment dated November 6, 2007 (Attachment E, pages 67-68) for the Fed Study No. VENL-0548, as well as based on the existence of the SOP Nos. D-400-07 ("Reassay or Reinjection of Clinical Samples", issued October 19, 2006) and D-416-05 ("Reassay of Whole Subjects", issued October 19, 2007). You have submitted a protocol amendment for the Fed Study VENL-0548 to include a *Redose Study* which was to be identified as Study No. VENL-0548A. However, there was no other data or report submitted for Study No. VENL-0548A. You have also indicated in the Fed Study report that Subject 5 was difficult to contact for redosing, and this subject was dropped from your final analysis of the Fed Study results. Please provide explanation for the existence of the bioanalytical validation data for Study No. VENL-0548A as submitted in the amendment dated November 6, 2007, and please confirm if the Redose Study No. VENL-0548A was ever carried out.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
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/

Barbara Davit
12/11/2007 04:53:46 PM
Signing for Dale P Conner

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

November 16, 2007

TELEPHONE AMENDMENT
(BIOEQUIVALENCE INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 78-789
RESPONSE TO AGENCY TELEPHONE CALL OF NOVEMBER 14, 2007

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the Bioequivalence comments pertaining to this application which were provided to Mylan in a telephone call received on November 14, 2007 from Ms. Keri Suh, of your Office. In response to the Agency's comments of November 14th, Mylan wishes to amend this application as follows:

FDA COMMENT 1: Please provide individual dissolution data for all 12 units evaluated in each of the dissolution studies. Also. provide f_2 similarity factor calculations between each strength of the test and reference products in each dissolution medium.

MYLAN RESPONSE: The dissolution data for all 12 units evaluated in each of the dissolution studies were provided in the original ANDA in Section 5.3.1.3 (In vitro-in vivo Correlation, Module 5, Volume 3, pages 5-28) and in Section 1.12.15 (Request for Biowaiver, Module 1, Volume 1, pages 57-84). The individual dissolution data has also been provided in Attachment A for the convenience of the reviewer. The requested f_2 similarity factor calculations are provided in Attachment B.

FDA COMMENT 2: Provide content uniformity data for the biobatch, Lot R1P2475, and for the reference product, Lot B05403, if available. If the information was previously submitted, please provide the location in the ANDA where it can be found.

MYLAN RESPONSE: The content uniformity data for the biobatch Lot R1P2475 and for the reference product Lot B05403 were provided in the original ANDA on the Certificates of Analysis for each lot in Section 3.2.P.5.4 (Batch Analysis, Module 3, Volume 3, pages 165 and 167). Mylan's Certificate of Analysis was revised in response to the Agency's chemistry comments dated July 17, 2007 and bioequivalence comments dated September 6, 2007. Mylan's revised Certificate of Analysis for Lot R1P2475 and the Certificate of Analysis for the reference product (Lot B05403) as originally submitted are provided in Attachment C for the convenience of the reviewer.

Department—Fax Numbers					
Accounting	(304) 285-6483	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411	Quality Control	(304) 598-5409
Corporate Services	(304) 285-6482	Medical Unit	(304) 598-5445	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Research & Development	(304) 285-6419
			(800) 848-0463	Sales & Marketing	(304) 598-3232

FDA COMMENT 3: Provide the production batch size of the biobatch, R1P2475. If the information was previously submitted, please provide the location in the ANDA where it can be found.

MYLAN RESPONSE: The batch size of the biobatch, Lot R1P2475, was [redacted] (b) (4) capsules and the proposed production batch size is [redacted] (b) (4) capsules. This information was provided in various locations of the application such as Section 2.3.R (Quality Overall Summary Regional Information, Module 2, Volume 1, page 52), Section 3.2.P.1 (Description and Composition, Module 3, Volume 2, pages 9-11), and Section 3.2.A.1.1 (Facilities and Equipment, Module 3, Volume 3, pages 300-301). A copy of Section 2.3.R Quality Overall Summary Regional Information (Module 2) from the original ANDA is provided in Attachment D.

This amendment is submitted in duplicate. In addition, an electronic copy has been provided in PDF format for your convenience. Should you require any additional information, please contact the undersigned at (304) 599-2595, ext. 6551 via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/mj

Enclosures

Desk Copy: Keri Suh, Project Manager
Division of Bioequivalence

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

November 6, 2007

BIOEQUIVALENCE AMENDMENT
(BIOEQUIVALENCE INFORMATION AND ELECTRONIC MEDIA ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 78-789
RESPONSE TO AGENCY CORRESPONDENCE DATED SEPTEMBER 6, 2007

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the Bioequivalence comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated September 6, 2007 (refer to Attachment F). In response to the September 6th comments from the Division of Bioequivalence, Mylan wishes to amend this application as follows:

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiencies have been identified:

FDA COMMENT 1: Your proposed dissolution specifications are not acceptable. Based on the data you submitted, please acknowledge your acceptance of the FDA-recommended dissolution method and specifications given below:

USP Apparatus I (basket) at 100 rpm in 900 mL water with the following specifications applicable to all strengths:

(b) (4)

MYLAN RESPONSE: Mylan has evaluated the dissolution specifications recommended by the Division of Bioequivalence in the Agency's correspondence dated September 6, 2007. Retain samples from our 3 month accelerated stability program were tested for all lots of Venlafaxine Hydrochloride Extended-release Capsules included in the

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 598-5419
Corporate Services (304) 285-6482
Human Resources (304) 598-5406
Information Systems (304) 285-6404
Bid Desk (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Product Development (304) 285-6411
Purchasing (304) 598-5401
Quality Assurance (304) 598-5407
Quality Control (304) 598-5409
Regulatory Affairs (304) 285-6407
Research & Development (304) 285-6419
Sales & Marketing (304) 598-3232

original ANDA submission. A summary of the dissolution data for Lots R1P2473 (37.5mg), R1P2474 (75 mg), and R1P2475 (150 mg) encompassing three months of testing at accelerated conditions and twelve months at controlled room temperature are provided in Attachments A and B, respectively. Based upon this body of data, slight adjustments to the tolerances at the 4, 8, and 12 hour sampling times are being proposed as follows:

37.5 mg, 75 mg and 150 mg Capsules

(b) (4)

The dissolution method and specification have been incorporated into Mylan's stability and quality control programs. Revised finished product specifications which apply at release and stability, and the Dissolution procedure (FP-VENCAP-DS2-M) are provided in Attachments C and D, respectively.

Please note that a Minor Chemistry Amendment in response to the Agency's chemistry comment letter dated July 17, 2007 is also being submitted concurrently with this Bioequivalence Amendment under separate cover.

FDA COMMENT 2: The Division of Bioequivalence has developed new data summary tables in a concise format consistent with the Common Technical Document (CTD). Please provide complete tables and send them with the rest of the bioequivalence submission. The tables are available in Word and PDF format under the title "Model Bioequivalence Data Summary Tables" in our website at http://www.fda.gov/cder/ogd/index.htm. To improve the efficiency of the Division, these tables should be provided in all pending and future ANDA submissions.

MYLAN RESPONSE: As requested, Mylan has provided Bioequivalence Summary Tables 1-15 in Attachment E. Electronic copies of these tables in both PDF and Word format are also provided on the enclosed CD-Rom. Please note that Table 16 has not been provided since the "FDA Standard Meal" was used in the bioequivalence studies.

This amendment is submitted in duplicate. In addition, an electronic copy has been provided in PDF format for your convenience. Should you require any additional information, please contact the undersigned at (304) 599-2595, ext. 6551 via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Desk Copy: Aaron Sigler, Project Manager
Division of Bioequivalence

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

November 6, 2007

Brooke Seeman
Acting Pre-Approval Manager
Baltimore District
6000 Metro Drive, Suite 101
Baltimore, MD 21215

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 78-789
RESPONSE TO AGENCY CORRESPONDENCE DATED JULY 17, 2007

Dear Ms. Seeman:

Pursuant to 21 CFR 314.96(b), enclosed is a copy of the technical sections of the amendment to the above referenced application. We certify that this field copy is a true copy of the amendment as submitted to the Office of Generic Drugs.

Sincerely,

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosure

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 285-6482	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

November 6, 2007

MINOR AMENDMENT
(CHEMISTRY INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 78-789
RESPONSE TO AGENCY CORRESPONDENCE DATED JULY 17, 2007

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the chemistry comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated July 17, 2007 (provided in Attachment W). In response to the Agency's comments of July 17th, Mylan wishes to amend this application as follows:

A. Deficiencies:

FDA COMMENT 1: Please provide a debarment statement from the drug substance manufacturer.

MYLAN RESPONSE: A debarment statement from Matrix Laboratories, the drug substance manufacturer, is provided in Attachment A [Section 3.2.S.2].

FDA COMMENT 2: Please consult with the DMF holder to revise acceptance criteria of residual solvents for the drug substance specifications.

MYLAN RESPONSE: In accordance with the amended DMF, Mylan has revised the acceptance criteria for residual solvents in the drug substance as follows:

Residual Solvent	Previous Limit	Revised Limit
[redacted]		

(b) (4)

Department—Fax Numbers					
Accounting	(304) 598-5404	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Legal Services	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 285-6482	Medical Unit	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Product Development	(304) 598-5445	Research & Development	(304) 285-6419
			(304) 285-6411	Sales & Marketing	(304) 598-3232

14 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. In addition, an electronic copy has been provided in PDF format for your convenience. Should you require any additional information, please contact the undersigned at (304) 599-2595, ext. 6551 via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/mj

Enclosures

Desk Copy: Tom Hinchliffe, Project Manager
Division of Chemistry II, Team 10

BIOEQUIVALENCY AMENDMENT

ANDA 78-789

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Mylan Pharmaceuticals, Inc. TEL: 304-599-2595

ATTN: S. Wayne Talton FAX: 304-285-6407

FROM: Aaron Sigler PROJECT MANAGER: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on January 15, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg, 75 mg, and 150 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78789

APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg, 75 mg, and 150 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiencies have been identified:

1. Your proposed dissolution specifications are not acceptable. Based on the data you submitted, please acknowledge your acceptance of the FDA-recommended dissolution method and specifications given below:

USP Apparatus I (basket) at 100 rpm in 900 mL water with the following specifications applicable to all strengths:

(b) (4)

2. The Division of Bioequivalence has developed new data summary tables in a concise format consistent with the Common Technical Document (CTD). Please provide complete tables and send them with the rest of the bioequivalence submission. The tables are available in Word and PDF format under the title "Model Bioequivalence Data Summary Tables" in our website at http://www.fda.gov/cder/ogd/index.htm. To improve the efficiency of the Division, these tables should be provided in all pending and future ANDA submissions.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
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/

Barbara Davit
9/6/2007 05:41:38 PM
Signing for Dale P Conner

Telephone Fax

ANDA 78-789

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240 276 8991

TO: Mylan Pharmaceuticals, Inc

TEL: 304-599-2595

ATTN: S. Wayne Talton

FAX:304-285-6407

FROM: Michelle Dillahunt

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg (base), 75 mg (base) and 150 mg (base).

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	78-789
Date of Submissions:	January 15, 2007
Applicant's Name:	Mylan Pharmaceuticals, Inc.
Established Name:	Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg (base), 75 mg (base) and 150 mg (base)
Proposed Proprietary Name:	None

Labeling Deficiencies:

1. CONTAINER - 100s, and 500s

   Please ensure that you differentiate your product strengths by using boxing, contrasting colors, and/or some other means.

2. PHYSICIAN INSERT

   a. Please revise "Venlafaxine Extended-release" to read "Venlafaxine Hydrochloride Extended-release Capsules" throughout your labeling.

   b. Due to changes in the insert labeling for the reference listed drug, Effexor® Extended-release capsules, (NDA 20-699/S-075), approved August 1, 2007, please revise your labeling to be in accordance with the insert labeling for the reference listed drug. You should address all exclusivities and patents listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") and revise your insert labeling according. The reference listed drug's insert labeling is located on the following website, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

In addition, please make the following changes;

   c. WARNINGS, Clinical Worsening and Suicide Risk, Table 1, change [redacted] (b) (4)" to Increases Compared to Placebo" and change '[redacted] (b) (4)" to "Decreases Compared to Placebo".

3. MEDICATION GUIDE

   a. Please indicate how many medication guides will accompany each container size and how they will be presented.

   b. If you plan to use a tear off pad for your medication guide, please provide a sample sheet electronically in final printed format.

   c. What is the most important information I should know about….

      Revise number 1 to read; "…..young adults within the first few months of treatment."

      Revise number 3 to read; "…an antidepressant medicine is started or when the dose is changed."Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug's labeling with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
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/

Michelle Dillahunt
8/22/2007 11:45:32 AM
LABELING REVIEWER

Lillie Golson
8/23/2007 03:00:35 PM
LABELING REVIEWER
Lillie Golson for Wm. Peter Rickman

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

notice of litigation filed 7/9/07 in District court on '171, '120 and '958 patents.

August 1, 2007

PATENT AMENDMENT

N|XP

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, 37.5MG, 75MG AND 150MG
ANDA 78-789
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. Reference is also made to our patent amendments submitted on May 22, 2007 and May 29, 2007 which provided certification of notice and documentation of receipt of the notice, respectively, as it pertains to the Paragraph IV patent certifications contained in our original application submitted on January 15, 2007 for Venlafaxine Hydrochloride Extended-release Capsules, 37.5mg, 75mg and 150mg.

Wyeth commenced litigation against Mylan on July 9, 2007. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

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AUG 02 2007

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Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 285-6482	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

MINOR AMENDMENT

ANDA 78-789

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Mylan Pharmaceuticals, Inc. TEL: 304-599-2595

ATTN: S. Wayne Talton FAX: 304-285-6407

FROM: Thomas Hinchliffe PROJECT MANAGER: (301) 827-5771

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated January 15, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg, 75 mg, and 150 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__4__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided here.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-789 APPLICANT: Mylan Pharmaceutical Inc.

DRUG PRODUCT: Venlafaxine Hydrochloride Extended Release Capsules, 37.5 mg, 75 mg, and 150 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please provide a debarment statement from the drug substance manufacturer.

2. Please consult with the DMF holder to revise acceptance criteria of residual solvents for the drug substance specification.

(b) (4)

[redacted]

(b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. (b) (4)

2. Please provide all available stability data in your next amendment.

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
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/

Naiqi Ya
7/17/2007 10:28:03 AM

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

901 New York Avenue, NW ▪ Washington, DC 20001-4413 ▪ 202.408.4000 ▪ Fax 202.408.4400
www.finnegan.com

ROBERT D. LITOWITZ
202.408.4048
rob.litowitz@finnegan.com

July 6, 2007

N/XP

Food & Drug Administration
Office of Generic Drugs
(HFD-600)
7500 Standish Place
Rockville, Maryland 20855

HAND DELIVERY

NDA holder filed suit against Mylan in the US Court of W.V. RG/2/20/

Attn: Mr. Gary J. Buehler, Director

Venlafaxine HCl Extended Release Capsules (37.5 mg, 75 mg, and 150 mg)
Abbreviated New Drug Application No. 78-789
Notification of Filing of Legal Action for Patent Infringement

Dear Mr. Buehler:

We represent Wyeth, the owner of United States Patent Nos. 6,274,171 B1, 6,403,120 B1, and 6,419,958 B2. Wyeth-Ayerst Laboratories (now known as Wyeth Pharmaceuticals), a division of Wyeth, also is the holder of approved New Drug Application (NDA) No. 20-699 for EFFEXOR® XR Capsules, an extended release dosage form of venlafaxine. We are sending you this letter on behalf of our client pursuant to 21 C.F.R. § 314.107(f)(2) to notify you of the following:

(1) Brian S. Roman, Vice President and General Counsel, Mylan Pharmaceuticals Inc. ("Mylan"), sent a letter to Wyeth dated May 22, 2007, stating that Mylan was providing notice and information pursuant to "§ 505(j)(2)(B)(i)." Based on that letter, we provide the following information:

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OGD

(i) Mylan submitted to the FDA an abbreviated new drug application (ANDA) which seeks approval to engage in the commercial manufacture, use and sale of venlafaxine HCl extended release capsules (37.5 mg, 75 mg, and 150 mg), before the expiration date of U.S. Patent Nos. 6,274,171 B1; 6,403,120 B1; and 6,419,958 B2.

(ii) Mylan's ANDA number is ANDA 78-789.

(iii) The established name of the proposed drug product is Venlafaxine Hydrochloride Extended Release Capsules (37.5 mg, 75 mg, and 150 mg).

(iv) The active ingredient and strengths and dosage form of the proposed drug product are venlafaxine HCl, 37.5 mg, 75 mg, and 150 mg extended release capsules for oral administration.

(v) The patent numbers and expiration dates of the patents which Mylan alleges are not infringed are United States Patent No. 6,274,171 B1, United States Patent No. 6,403,120 B1, and United States Patent No. 6,419,958 B2, which all expire on March 20, 2017. In addition, the pediatric exclusivity for these three patents expires on September 20, 2017.

(2) Wyeth received Mylan's May 22, 2007 letter on or about May 23, 2007.

CERTIFICATION

We hereby certify that on July 6, 2007, Wyeth filed an action for patent infringement against Mylan Pharmaceuticals Inc. in the United States District Court for the Northern District of West Virginia (Clarksburg Division)(Civil Action No. 1:07-CV-91). Wyeth filed that action within 45 days of receipt of Mylan's notice of the Paragraph IV Certification. In its complaint, Wyeth states, among other things, that Mylan's submission to the FDA of an ANDA to obtain approval for the commercial manufacture, use, or sale of 37.5 mg, 75 mg, or 150 mg venlafaxine HCl extended release capsules before the expiration of United States Patent No. 6,274,171 B1, United States Patent No. 6,403,120 B1, and United States Patent No. 6,419,958 B2 was an infringement of each of those patents under 35 U.S.C. § 271(e)(2)(A).

Accordingly, pursuant to 21 U.S.C. § 355(j)(5)(B)(iii), approval of Mylan's ANDA 78-789 for 37.5 mg, 75 mg, and 150 mg venlafaxine HCl extended release capsules may not be made effective until the expiration of the 30-month period beginning on May 23, 2007, and ending on November 23, 2009, or until such time as ordered by the Court.

Moreover, separate and apart from the expiration of the 30-month period referred to above, Mylan's ANDA cannot be finally approved before June 13, 2008 because Mylan has not notified Wyeth that it has made a Paragraph IV Certification as to U.S. Patent No. 4,535,186, which is also listed in the Orange Book for EFFEXOR® XR. Accordingly, in any event, approval of Mylan's ANDA may not be made effective before the expiration of both that patent and the pediatric exclusivity period on June 13, 2008.

Sincerely,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: _____
Robert D. Litowitz

RDL/hkr

cc: **Via Federal Express:**

Brian S. Roman
Vice President and General Counsel
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, West Virginia 26504-4310

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

June 12, 2007

GENERAL CORRESPONDENCE
(SAMPLES ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Me

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
37.5 MG, 75 MG AND 150 MG
ANDA 78-789
RESPONSE TO AGENCY TELEPHONE CALL RECEIVED JUNE 11, 2007

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above which is currently under review. Reference is also made to a telephone call received on June 11, 2007 from Mr. Zhigang Sun, of your Office, in which he requested that we provide samples of each strength of Venlafaxine Hydrochloride Extended-release Capsules.

As requested by Mr. Sun, bottles containing 100 capsules each for Venlafaxine Hydrochloride Extended-release Capsules, 37.5mg (Lot R1P2473), 75mg (Lot R1P2474) and 150mg (Lot R1P2475) have been provided to his attention.

This correspondence is submitted in duplicate. Should you require any additional information, please contact the undersigned at (304) 599-2595, ext. 6551 via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

cc: Thomas Hinchliffe, Project Manager
Division of Chemistry II, Team 10

RECEIVED
JUN 12 2007
OGD

Department – Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 598-5419
Corporate Services (304) 285-6482
Human Resources (304) 598-5406
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Product Development (304) 285-6411
Purchasing (304) 598-5401
Quality Assurance (304) 598-5407
Quality Control (304) 598-5409
Regulatory Affairs (304) 285-6407
Research & Development (304) 285-6419
Sales & Marketing (304) 598-3232

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

May 29, 2007

PATENT AMENDMENT

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, 37.5MG, 75MG AND 150MG
ANDA 78-789
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. In accordance with 21 CFR 314.95(e), this amendment provides documentation of receipt of the notice required by 21 CFR 314.95(a) and (b), as it pertains to the Paragraph IV patent certification contained in our original application submitted on January 15, 2007 for Venlafaxine Hydrochloride Extended-release Capsules, 37.5mg, 75mg and 150mg. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

The owner of the patents and the holder of the application for the listed drug were served with the required notice. Proof of delivery by Federal Express evidences receipt by Wyeth and Wyeth Pharmaceuticals, Inc. on May 23, 2007. A copy of the documentation evidencing Mylan's service and receipt is enclosed.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

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MAY 30 2007
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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

MAY 29 2007

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES 37.5 MG, 75 MG AND 150 MG

ANDA # 78-789

PATENT AMENDMENT

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above. This amendment provides documentation of receipt of notice required by 21 C.F.R. § 314.95(e), as it pertains to the Paragraph IV patent certification contained in our original application submitted on January 15, 2007 for Venlafaxine Hydrochloride Extended-release Capsules, 37.5mg, 75mg and 150mg. On May 18, 2007 Mylan requested FDA's permission to serve the required notice by Federal Express. FDA approved this request and on May 22, 2007 the notice was sent *via* Federal Express. I have enclosed documentation of both receipts by the owner(s) of the patent and the holder of the application for the listed drug claimed by said patent.

Proof of delivery by Federal Express (see attached) evidences receipt by Wyeth on May 23, 2007. Proof of delivery by Federal Express (see attached) evidences receipt by Wyeth Pharmaceuticals Inc. on May 23, 2007.

Sincerely,

Brian S. Roman DLG

Brian S. Roman
Vice President and General Counsel

Department—Fax Numbers

Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
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Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

From: Shimer, Martin
Sent: Friday, May 18, 2007 2:13 PM
To: 'Wayne.Talton@mylanlabs.com'
Cc: Shimer, Martin
Subject: RE: Request to use FedEx in Lieu of U.S. Postal Service

Wayne,

It is acceptable to use FedEx in lieu of the US Postal Service for the purpose of providing notice to the NDA holder and any patent assignees associated with PIV certifications contained within ANDA 78-789.

Regards,

Marty

From: Wayne.Talton@mylanlabs.com [mailto:Wayne.Talton@mylanlabs.com]
Sent: Friday, May 18, 2007 1:52 PM
To: Shimer, Martin
Subject: Request to use FedEx in Lieu of U.S. Postal Service

Good afternoon Marty

We received our acceptance for filing letter on 5/2/07 for our ANDA for Venlafaxine HCl Extended-release Capsules (ANDA 78-789) submitted on January 15, 2007. This application contained a PIV certification statement. We would to request permission to use Federal Express in lieu of the U.S. Postal service for the purposes of sending and documenting the receipt of notice by the patent holder. Thanks.

Wayne
Mylan

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

/s/

Martin Shimer
5/23/2007 01:46:49 PM
CSO

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

May 22, 2007

PATENT AMENDMENT ORIG AMENDMENT

N | XP

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, 37.5MG, 75MG AND 150MG
ANDA 78-789
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above and to the Agency's letter dated May 2, 2007 notifying us that the ANDA has been found acceptable for filing (refer to Attachment A).

In accordance with 21 CFR 314.95(b) and as detailed in the Agency's May 2nd letter, this amendment provides a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c). A Patent Amendment is provided in Attachment B.

In accordance with the Agency's May 2, 2007 letter, Mylan will submit further documentation of receipt of the notice required by 21 CFR 314.95(e), as it pertains to the Paragraph IV patent certification contained in our original application submitted on January 15, 2007 for Venlafaxine Hydrochloride Extended-release Capsules, 37.5mg, 75mg and 150mg.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

RECEIVED
MAY 23 2007
OGD

G:\Project\ANDA\VENLAFAXINE HCl ER CAPSULES\PATENT-AMENDMENT-052207.doc

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
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Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-789

Mylan Pharmaceuticals Inc.
Attention: S. Wayne Talton
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated April 18, 2007 and your correspondence dated April 23, 2007.

NAME OF DRUG: Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg, 75 mg and 150 mg

DATE OF APPLICATION: January 15, 2007

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 16, 2007

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet “PATENT AMENDMENT” with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or

judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Thomas Hinchliffe
Project Manager
301-827-5771

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
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/

Martin Shimer
5/2/2007 07:52:06 AM
Signing for Wm Peter Rickman

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to: http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf**
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
*** **A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ ***

ANDA #: 78-789 **FIRM NAME**: MYLAN PHARMACEUTICALS INC.

PIV: YES **Electronic or Paper Submission:** PAPER (CTD FORMAT)

RELATED APPLICATION(S): SEE 77-166 FOR VENLAFAXINE HYDROCHLORIDE TABLETS, 25 MG, 37.5 MG, 50 MG, 75 MG AND 100 MG FROM MYLAN PHARMACEUTICALS INC. TA 8/14/06 (RLD EFFEXOR XR)

Bio Assignments:		☐ **Micro Review (No)**
☒ **BPH**	☐ **BCE**	
☐ **BST**	☒ **BDI**	

First Generic Product Received? NO

DRUG NAME: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE
DOSAGE FORM: TABLETS, 37.5 MG, 75 MG AND 150 MG

Random Queue: 10
Chem Team Leader: Naiqi Ya PM: Tom Hinchliffe Labeling Reviewer: Michelle Dillahunt

Letter Date: JANUARY 15, 2007 **Received Date**: JANUARY 16, 2007

Comments: EC - 3 YES **On Cards:** YES
Therapeutic Code: 2020100 ANTIDEPRESSANTS

Archival copy: PAPER (CTD FORMAT) **Sections** I
Review copy: I E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Rebekah Granger **Date 04/18/2007**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: _____	**Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:
Firm needs to address Patent #6403120 and 6419958 on its labeling concerning the MOU on the treatment of Generalized Anxiety Disorder.

Per correspondence submitted by sponsor dated 4/23/2007 the above is adequate for filing.

Sugar Sphere is equivalent to Non-Pareil Seed according to the Handbook of Pharmaceutical Excipient. Hypromellose is equivalent to Hydroxypropyl Methylcellulose according to the Handbook of Pharmaceutical Excipients. The DOW product name for Hypromellose is METHOCEL Cellulose ether (K, F or E type) Premium G Hydroxypropyl Methylcellulose.

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2** **Signed and Completed Application Form (356h) (original signature)** YES (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: JANUARY 15, 2007 YES	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature)	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455) YES	☒
1.3.5	**1.3.5.1** **Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2** **Patent Certification** 1. Patent number(s) 6,274,171; 6,403,120; 6,419,958 2. Paragraph: (Check all certifications that apply) MOU ☒ PI ☐ PII ☐ PIII ☐ PIV ☒ No Relevant Patents ☐ 3. Expiration of Patent(s): 9/20/2017 a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES	☒

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES – DMF #17525 b. Type III DMF authorization letter(s) for container closure YES 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h])	☒
1.12.11	**Basis for Submission** NDA# : 20-699 Ref Listed Drug: EFFEXOR XR Firm: WYETH PHARMS INC. ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use SAME 2. Active ingredients SAME 3. Inactive ingredients JUSTIFIED 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): Paper, YES ON 37.5 MG AND 75 MG	☒

1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) YES **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES **1.14.1.3** 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.) **<u>HOW SUPPLIED:</u>** 37.5 mg: Bottles of 100 Capsules Bottles of 500 Capsules 75 mg: Bottles of 100 Capsules Bottles of 500 Capsules 150 mg: Bottles of 100 Capsules Bottles of 500 Capsules	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES **1.14.3.3** 1 RLD label and 1 RLD container label YES	☒

ACCEPTABLE

2.3	**Quality Overall Summary** **E-Submission: __X_PDF (archive) _X_ Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **Question based Review (QbR) __X__ YES _____ NO** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** YES **2.3.S.1** **General Information** **2.3.S.2** **Manufacture** **2.3.S.3** **Characterization** **2.3.S.4** **Control of Drug Substance** **2.3.S.5** **Reference Standards or Materials** **2.3.S.6** **Container Closure System** **2.3.S.7** **Stability** **2.3.P** **Drug Product YES** **2.3.P.1** **Description and Composition of the Drug Product** **2.3.P.2** **Pharmaceutical Development** **2.3.P.2.1** **Components of the Drug Product** **2.3.P.2.1.1** **Drug Substance** **2.3.P.2.1.2** **Excipients** **2.3.P.2.2** **Drug Product** **2.3.P.2.3** **Manufacturing Process Development** **2.3.P.2.4** **Container Closure System** **2.3.P.3** **Manufacture** **2.3.P.4** **Control of Excipients** **2.3.P.5** **Control of Drug Product** **2.3.P.6** **Reference Standards or Materials** **2.3.P.7** **Container Closure System** **2.3.P.8** **Stability**	☒

2.7	**Clinical Summary (Bioequivalence)** **E-Submission: _____PDF (archive) ____ Word Processed e.g., MS Word** **2.7.1** **Summary of Biopharmaceutic Studies and Associated Analytical Methods** YES **2.7.1.1** **Background and Overview** YES **2.7.1.2** **Summary of Results of Individual Studies** YES **2.7.1.3** **Comparison and Analyses of Results Across Studies** 1. Summary Bioequivalence tables: Table 1. Summary of Comparative Bioavailability (BA) Studies YES Table 2. Statistical Summary of the Comparative BA Data YES Table 4. Summary of In Vitro Dissolution Studies YES **2.7.1.4** **Appendix**	☒

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1** **Nomenclature** YES **3.2.S.1.2** **Structure** YES **3.2.S.1.3** **General Properties** YES	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers YES 2. Manufacturing Responsibilities YES 3. Type II DMF number for API YES – DMF #17525 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization** YES - Refer to DMF #17525	☒

3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1** **Specification** Testing specifications and data from drug substance manufacturer(s) YES **3.2.S.4.2** **Analytical Procedures** YES **3.2.S.4.3** **Validation of Analytical Procedures** **1.** Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES b. Same lot number(s) YES **3.2.S.4.4** **Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) YES 2. Applicant certificate of analysis YES **3.2.S.4.5** **Justification of Specification** YES	☒
3.2.S.5	**Reference Standards or Materials** YES	☒
3.2.S.6	**Container Closure Systems** YES - Refer to DMF #17525	☒
3.2.S.7	**Stability** YES - Refer to DMF #17525	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition YES 2) Inactive ingredients are appropriate per IIG YES	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report YES	☒
3.2.P.3	**Manufacture** **3.2.P.3.1** **Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers **3.2.P.3.2** **Batch Formula** Batch Formulation YES **3.2.P.3.3** **Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES 3. If sterile product: Aseptic fill / Terminal sterilization 4. Reprocessing Statement YES **3.2.P.3.4** **Controls of Critical Steps and Intermediates** YES **3.2.P.3.5** **Process Validation and/or Evaluation** YES 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill) **PROPOSED COMMERCIAL BATCH SIZE:** 37.5 mg (b) (4) Capsules 75 mg: (b) (4) Capsules 150 mg: (b) (4) Capsules	☒

3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified YES **3.2.P.4.1** **Specifications** 1. Testing specifications (including identification and characterization) YES 2. Suppliers' COA (specifications and test results) YES **3.2.P.4.2** **Analytical Procedures** NONE **3.2.P.4.3** **Validation of Analytical Procedures** NOT APPLICABLE **3.2.P.4.4** **Justification of Specifications** Applicant COA YES	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1** **Specification(s)** YES **3.2.P.5.2** **Analytical Procedures** YES **3.2.P.5.3** **Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form YES 2. Same lot numbers YES **3.2.P.5.4** **Batch Analysis** Certificate of Analysis for Finished Dosage Form YES **3.2.P.5.5** **Characterization of Impurities** YES **3.2.P.5.6** **Justification of Specifications** YES	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes YES 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
3.2.P.8	**3.2.P.8.1** **Stability (Finished Dosage Form)** 1. Stability Protocol submitted YES 2. Expiration Dating Period YES – 24 MONTHS **3.2.P.8.2** **Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments YES **3.2.P.8.3** **Stability Data** 1. 3 month accelerated stability data YES 2. Batch numbers on stability records the same as the test batch YES	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R **(Drug Substance)**	**3.2.R.1.S** **Executed Batch Records for drug substance (if available)** NOT AVAILABLE **3.2.R.2.S** **Comparability Protocols** NO **3.2.R.3.S** **Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 3
3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation YES 37.5 mg Theoretical Yield: (b) (4) Capsules Actual Yield: (b) (4) Capsules Packaged Yield: (b) (4) Capsules Bottles of 100 – (b) (4) Bottles of 500 – 75 mg Theoretical Yield: (b) (4) Capsules Actual Yield: (b) (4) Capsules Packaged Yield: (b) (4) Capsules Bottles of 100 – (b) (4) Bottles of 500 – 37.5 mg Theoretical Yield (b) (4) Capsules Actual Yield: (b) (4) Capsules Packaged Yield (b) (4) Capsules Bottles of 100 – (b) (4) Bottles of 500 – **3.2.R.1.P.2** **Information on Components** YES – See Module 2, Sec2.3.P.2.1 **3.2.R.2.P** **Comparability Protocols** No **3.2.R.3.P** **Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5
CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies** YES	☒

5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) YES b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** LOT #R1P2475 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
	5.3.1.2 **Comparative BA/BE Study Reports** 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) YES 2. Summary Bioequivalence tables: Table 6. Demographic Profile of Subjects Completing the Comparative BA Study YES Table 7. Incidence of Adverse Events in Individual Studies YES Table 8. Reanalysis of Study Samples YES **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 4. Summary of In Vitro Dissolution Studies YES Table 5. Formulation Data YES **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 3. Bioanalytical Method Validation YES **5.3.7** **Case Report Forms and Individual Patient Listing** YES	☒
5.4	**Literature References** YES	
	Possible Study Types:	
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FED ONLY ON 150 MG 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) YES 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: YES	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% or 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 10/10/2006 C. Bina

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

APR 2 3 2007

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, 37.5MG, 75MG AND 150MG

ANDA #78-789

PATENT AMENDMENT

U.S.PATENT NOS.: 6,403,120 AND 6,419,958
STATEMENTS MADE PURSUANT TO 21 U.S.C. §355(j)(2)(A)(viii)

Dear Mr. Buehler:

Reference is made to Abbreviated New Drug Application (ANDA) identified above. Mylan Pharmaceuticals Inc. ("Mylan") previously filed its patent certifications for the above-referenced product. In addition to the patent certifications previously made by Mylan, we make the following amendment:

To the extent Use Code 451 and Use Code 459 relate to Generalized Anxiety Disorder, Mylan states pursuant to 21 U.S.C. §355(j)(2)(A)(viii) that its labeling does not include the methods of use indicated by the use code information published by FDA in the document entitled "Approved Drug Products with Therapeutic Equivalence Evaluations", 27th Edition as updated in the "Electronic Orange Book" published at FDA's web site in connection with U.S. Patent Nos. 6,403,120 (Use Code 451)and 6,419,958 (Use Code 459).

Sincerely,

Brian S. Roman

Brian S. Roman
Vice President and General Counsel

Department—Fax Numbers

Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7264	Label Control	(800) 848-0463	Quality Assurance	(304) 598-6407
Business Development	(304) 598-5419	Legal Services	(304) 598-6408	Quality Control	(304) 598-5409
Corporate Services	(304) 284-6482	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 599-5445	Research & Development	(304) 285-6019
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

2.7.1.3 STATISTICAL SUMMARY OF THE COMPARATIVE BA DATA (BIOEQUIVALENCE SUMMARY TABLE 2)

VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES 37.5MG, 75MG AND 150MG

(VENL-0548 and VENL-0549)

Venlafaxine Hydrochloride Extended-Release 150 mg Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Food Bioequivalence Study VENL-0548 - venlafaxine				
Parameter	Test	Reference	Ratio*	90% C.I.**
AUCL	1643	1555	1.06	98% - 114%
AUCI	1725	1668	1.03	96% - 112%
C_{max}	106.7	97.0	1.10	101% - 119%

Venlafaxine Hydrochloride Extended-Release 150 mg Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Food Bioequivalence Study VENL-0548 – o-desmethylvenlafaxine				
Parameter	Test	Reference	Ratio*	90% C.I.**
AUCL	5252	4879	1.08	105% - 110%
AUCI	5429	5102	1.06	104% - 109%
C_{max}	176.2	159.2	1.11	106% - 115%

Venlafaxine Hydrochloride Extended-Release 150 mg Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Applesauce Bioequivalence Study VENL-0549 - venlafaxine				
Parameter	Test	Reference	Ratio*	90% C.I.**
AUCL	1259	1219	1.03	95% - 110%
AUCI	1350	1297	1.03	96% - 111%
C_{max}	83.7	81.9	1.01	94% - 109%

Venlafaxine Hydrochloride Extended-Release 150 mg Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Applesauce Bioequivalence Study VENL-0549 – o-desmethylvenlafaxine				
Parameter	Test	Reference	Ratio*	90% C.I.**
AUCL	5079	4929	1.03	99% - 106%
AUCI	5262	5159	1.02	99% - 105%
C_{max}	168.6	165.8	1.02	97% - 107%

*Ratio (A/B) = $e^{[\text{LSMEAN of LNA} - \text{LSMEAN of LNB}]}$

**Used Natural Log Transformed Parameter

Do any excipients exceed the IIG limit for this route of administration?

All of the excipients used in Mylan's Venlafaxine Hydrochloride Extended-release Capsules, 37.5mg, 75mg and 150mg are within the limits for an oral route of administration as listed in the Inactive Ingredient Database. A comparison is summarized in the table below. The proposed inactive ingredients do not affect the safety of the proposed drug product and the requirements outlined in 21CFR314.95 (a) (ii) have been satisfied.

Ingredient	Amount per unit of Venlafaxine HCl ER Capsules, 37.5mg (mg)	Amount per unit of Venlafaxine HCl ER Capsules, 75mg (mg)	Amount per unit of Venlafaxine HCl ER Capsules, 150mg (mg)	Maximum Level[1] listed in the FDA *Inactive Ingredient Database for Approved Drug Products*
				(b) (4)

[1] FDA's electronic *Inactive Ingredient Database for Approved Drug Products* (Database Last Updated October 5, 2006).

(b) (4)

1 page has been withheld as b4 (CCI/TS) immediately following this page

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

/s/

Martin Shimer
5/1/2007 07:49:51 AM

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

April 23, 2007

TELEPHONE AMENDMENT
(PATENT INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

XP

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, 37.5 MG, 75 MG AND 150 MG
ANDA 78-789
RESPONSE TO AGENCY TELEPHONE CALL RECEIVED APRIL 18, 2007

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above which is currently under review. Reference is also made to a telephone call received on April 18, 2007 from Mr. Martin Shimer, of your Office, in which he requested that we provide an amendment to our patent certification statement with respect to U.S. Patent Nos. 6,403,120 and 6,419,958 based on the information that appears in the current version of FDA's "Orange Book."

As requested by Mr. Shimer, Attachment A contains a Patent Amendment from our legal department which amends our certification statement with respect to the '120 and '958 patents.

This amendment is submitted in duplicate. Should you require any additional information, please contact the undersigned at (304) 599-2595, ext. 6551 via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

cc: Mr. Martin Shimer, Branch Chief
Regulatory Support, Office of Generic Drugs

RECEIVED
APR 24 2007
OGD / CDER

G:\Project\ANDA\VENLAFAXINE HCl ER CAPSULES\AGENCY-CALL-DATED-041807.doc

Department - Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

January 15, 2007

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
(ELECTRONIC DATA AND BIOEQUIVALENCE DATA ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, 37.5MG, 75MG AND 150MG

Dear Mr. Buehler:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.92 and §314.94, we submit the enclosed Abbreviated New Drug Application in the ICH Common Technical Document (CTD) format in paper for:

Proprietary Name: None
Established Name: Venlafaxine Hydrochloride Extended-release Capsules
Reference Listed Drug: Effexor XR® Capsules, NDA 20-699
This application consists of a total of 30 volumes

Archival Copy - 13 volumes
- Module 1, Administrative Information - 1 volume
- Module 2, Summaries - 1 volume
- Module 3, Quality - 3 volumes
- Module 5, Clinical Study Reports - 7 volumes

Review Copy - 14 volumes
- Technical Section for Chemistry - 6 volumes
  - Module 1, Administrative Information - 1 volume
  - Module 2, Summaries - 1 volume
  - Module 3, Quality - 4 volumes
- Technical Section for Pharmacokinetics - 9 volumes
  - Module 1, Administrative Information - 1 volume
  - Module 2, Summaries - 1 volume
  - Module 5, Clinical Study Reports - 7 volumes

Analytical Methods Validation Package, Section 3.2.R.2 - 2 extra copies; 1 volume each

Department—Fax Numbers					
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		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

CD-Rom - Electronic File Contents

Document Name	**File Format**
Cover Letter	Adobe Acrobat .PDF
FDA Form 356h and Attachments	Adobe Acrobat .PDF
Quality Overall Summary	MS Word and Adobe Acrobat .PDF
Bioequivalence Summary Tables (1-8)	MS Word and Adobe Acrobat .PDF
Data Listings for Bioequivalence Studies Conducted in Support of this Application	SAS .XPT
Labeling Components	MS Word and Adobe Acrobat .PDF

Please note that the electronic components of this submission are not submitted in the CTD backbone; rather, they are included in electronic format for your convenience. Each Module contains a Module Table of Contents. In addition, Module 1 contains a complete Table of Contents for the reviewer's reference.

This application provides for the manufacture of Venlafaxine Hydrochloride Extended-release Capsules, 37.5mg, 75mg and 150mg. Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730 performs all operations in the manufacture, packaging, and labeling of the drug product.

This Abbreviated New Drug Application has been formatted as described in the ICH Guidance 'M4: Organization of the CTD (January 2004)' and associated guidances.

Mylan commits to resolve any issues identified in the methods validation during review or after approval. Samples of the drug product, drug substance, reference standard and related materials will be made available to the Agency upon request and/or at time of the pre-approval inspection at the Morgantown, West Virginia facility.

As required by 21 CFR 314.94(d)(5), we certify that a true copy of Module 3 (Quality) of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6551 and/or facsimile number (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/np