CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 076565

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

Sponsor: TEVA Pharmaceuticals USA

Approval Date: June 28, 2010

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APPLICATION NUMBER:

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 076565

TEVA Pharmaceuticals USA
Attention: Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs
1090 Horsham Road
PO Box 1090
North Wales, PA 19454

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 10, 2002, 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 February 13, March 19, March 26, April 1, and April 10, 2003; April 1, and June 29, 2004; March 25, 2005; February 7, April 14, and August 14, 2006; April 27, June 22, September 18, and September 29, 2009; and April 7, April 23, May 17, May 19, June 1, June 7, June 11, June 15, and June 21, 2010.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate 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 Extended-release 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 “interim” dissolution specifications are as follows:

Equipment:	Apparatus 1 (Basket)
Volume:	900 mL
Medium:	Water
Stirring Rate:	100 rpm
Temperature:	37°C ± 0.5°C
Sampling Times:	3, 6, 16, and 24 hours

Specification:

Time (Hours)	% of the Labeled Amount Dissolved
3	[redacted]
6	[redacted]
16	[redacted]
24	NLT [redacted]

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 Extended-release Capsules, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the agency’s publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the “Orange Book”):

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 '120 and '958 patents (treatment of depression), and the ‘171 and ‘708 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 TEVA Pharmaceuticals USA (TEVA) for infringement of one or more of these patents that were the subjects of the paragraph IV certifications. You have notified the agency that TEVA complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation for infringement of the '171, '120, and '958 patents was brought against TEVA within the statutory 45-day period in the United States District Court for the District of New Jersey [Wyeth v. TEVA Pharmaceuticals USA, Inc. and TEVA Pharmaceutical Industries Ltd., Civil Action No. 03-1293]. You have notified the agency that on January 12, 2006, the litigation was dismissed.

With respect to the '120 and '958 patents (treatment of social anxiety disorder and generalized anxiety disorder), and the '923, and '101 patents, 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.

With respect to 180-day generic drug exclusivity, we note that TEVA was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification to the '171, '120, and '958 patents. Therefore, with this approval, TEVA is eligible for 180 days of generic drug exclusivity for Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg (base), 75 mg (base) and 150 mg (base). This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, will begin to run from the earlier of the commercial marketing or court decision dates identified in section 505(j)(5)(B)(iv).[1] Please submit correspondence to this ANDA informing the agency of the date the exclusivity begins to run.

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.

[1] Because your ANDA was filed before the date of enactment of the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) on December 8, 2003, this reference to the 180-day exclusivity provision is to the section of the Act as in effect prior to December 8, 2003. See MMA § 1102(b)(1).

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 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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-76565	ORIG-1	TEVA PHARMACEUTICALS USA INC	VENLAFAXINE HYDROCHLORIDE

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

06/28/2010

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076565

LABELING

R 1 345678 1

VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES

℞ only

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7385
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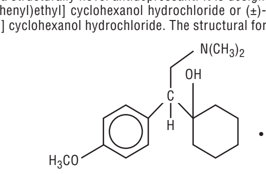
Rev. A 2/2010
322K404940410

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 capsules 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 capsules are 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 (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[α-[(dimethylamino)methyl]-*p*-methoxybenzyl] cyclohexanol hydrochloride. The structural formula is shown below.



venlafaxine hydrochloride

$C_{17}H_{27}NO_2$•HCl M.W. 313.87

Venlafaxine hydrochloride is a white to off-white crystalline solid with 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 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 antifoam DC 1510, black iron oxide, dibutyl sebacate, ethylcellulose, gelatin, polyethylene glycol, povidone, shellac, soya lecithin MC thin, sugar spheres (which contain sucrose and corn starch), sunset yellow FCF FD&C yellow 6, talc, and titanium dioxide. The 37.5 mg and 75 mg capsules also contain D&C yellow 10.

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 capsules (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 venlafaxine hydrochloride tablets (immediate release) [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 capsules, therefore, provide 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 9 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 capsule 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 capsule 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 capsules 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 capsules were 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 (immediate release) 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, 150, or 225 mg, qAM) were randomized to continuation of their same venlafaxine hydrochloride extended-release capsule 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) 2 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 capsule 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 (immediate release) [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 tablet treatment experienced significantly lower relapse rates over the subsequent 52 weeks compared with those receiving placebo.

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 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 two-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 (immediate release) 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 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 (immediate release) 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 Trials**). Nevertheless, the physician who elects to use venlafaxine hydrochloride tablets/venlafaxine hydrochloride extended-release capsules for extended periods should periodically re-evaluate 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 9 antidepressant drugs in over 4400 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 1000 patients treated) are provided in **Table 1**.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 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**, **General**, *Discontinuation of Treatment With Venlafaxine Hydrochloride Extended-Release Capsules* and **DOSAGE AND ADMINISTRATION, Discontinuing Venlafaxine Hydrochloride Extended-Release Capsules,** for a description of the risks of discontinuation of venlafaxine hydrochloride extended-release capsules).

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 capsules 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 capsules are 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 capsule 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 capsules 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 capsules 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 capsules with serotonin precursors (such as tryptophan) is not recommended (see **PRECAUTIONS**, **Drug Interactions**).

Treatment with venlafaxine hydrochloride extended-release capsules 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 capsule 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 3 consecutive on-therapy visits) (see **Table 2**).

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

An insufficient number of patients received mean doses of venlafaxine hydrochloride extended-release capsules 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 Capsules Premarketing Studies by Indication

MDD (75 to 375 mg/day)
19/705 (3)

MDD = major depressive disorder

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

Venlafaxine Hydrochloride Tablets 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 capsule-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).

Sustained increases of SDBP could have adverse consequences. Cases of elevated blood pressure requiring immediate treatment have been reported in postmarketing experience. Preexisting hypertension should be controlled before treatment with venlafaxine. It is recommended that patients receiving venlafaxine hydrochloride extended-release capsules 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 capsule-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 Capsules mg/day				Placebo	
	≤ 75		> 75			
	SSBP[a]	SDBP[b]	SSBP	SDBP	SSBP	SDBP
Major Depressive Disorder						
8 to 12 weeks	-0.28	0.37	2.93	3.56	-1.08	-0.10

[a] Supine Systolic Blood Pressure
[b] Supine Diastolic Blood Pressure

Across all clinical trials in MDD, 1.4% of patients in the venlafaxine hydrochloride extended-release capsule-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 capsule-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 Capsules
Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, to include retrospective surveys of trials in major depressive 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 capsules, 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 capsules. 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, as shown in **Table 5**.

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

	Major Depressive Disorder	
	Venlafaxine Hydrochloride Extended-Release Capsules	Placebo
Symptom	n = 357	n = 285
Insomnia	17%	11%
Nervousness	10%	5%

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

Changes in Weight
Adult patients
A loss of 5% or more of body weight occurred in 7% of venlafaxine hydrochloride extended-release capsule-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 capsules was 0.1% in major depressive disorder studies.

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 capsules and weight loss agents is not recommended. Venlafaxine hydrochloride extended-release capsules are 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 capsules. In a pooled analysis of four eight-week, double-blind, placebo-controlled, flexible dose outpatient trials, venlafaxine hydrochloride extended-release capsule-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 capsules than with placebo experienced a weight loss of at least 3.5% (18% of venlafaxine hydrochloride extended-release capsule-treated patients vs. 3.6% of placebo-treated patients; p < 0.001) (see **PRECAUTIONS**, **General**, *Changes in Appetite*).

The risks associated with longer-term venlafaxine hydrochloride extended-release capsule use were assessed in an open-label MDD study of children and adolescents who received venlafaxine hydrochloride extended-release capsules for up to six 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 eight-week placebo-controlled MDD studies, venlafaxine hydrochloride extended-release capsule-treated patients grew an average of 0.8 cm (n = 146), while placebo-treated patients grew an average of 0.7 cm (n = 147). In the six-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 capsule-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 capsules was 1.0% in major depressive disorder studies.

Pediatric patients
Decreased appetite has been observed in pediatric patients receiving venlafaxine hydrochloride extended-release capsules. In the placebo-controlled trials for MDD, 10% of patients aged 6 to 17 treated with venlafaxine hydrochloride extended-release capsules for up to eight weeks and 3% of patients treated with placebo reported treatment-emergent anorexia (decreased appetite). None of the patients receiving venlafaxine hydrochloride extended-release capsules discontinued for anorexia or weight loss.

Activation of Mania/Hypomania
During premarketing major depressive disorder studies, mania or hypomania occurred in 0.3% of venlafaxine hydrochloride extended-release capsule-treated patients and no placebo patients. In all premarketing major depressive disorder trials with venlafaxine hydrochloride tablets (immediate release), 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 capsules 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 capsules. 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 capsules 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 capsule-treated patients in the major depressive disorder studies. In all premarketing major depressive disorder trials with venlafaxine hydrochloride tablets (immediate release), seizures were reported at various doses in 0.3% (8/3082) of venlafaxine-treated patients. Venlafaxine hydrochloride extended-release capsules, 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 capsules, may increase the risk of bleeding events. Concomitant use of aspirin, non-steroidal 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 capsules 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 0.0% 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 capsules 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 capsules and 220 patients who received placebo in 8 to 12 week double-blind, placebo-controlled trials in major depressive disorder. The mean change from baseline in corrected QT interval (QT_c) for venlafaxine hydrochloride extended-release capsule-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 capsules and decrease of 1.9 msec for placebo).

In these same trials, the mean change from baseline in heart rate for venlafaxine hydrochloride extended-release capsule-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 capsules and 1 beat per minute for placebo).

In a flexible-dose study, with venlafaxine hydrochloride tablet (immediate release) doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, venlafaxine hydrochloride tablet-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 venlafaxine hydrochloride tablets (immediate release) 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 capsules, 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 capsules and should counsel them in its appropriate use. A patient Medication Guide about "**Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions**" is available for venlafaxine hydrochloride extended-release capsules. 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 capsules.

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 capsules and triptans, tramadol, tryptophan supplements or other serotonergic agents (see **WARNINGS**, **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions** and **PRECAUTIONS**, **Drug Interactions**, *CNS-Active Drugs*).

Patients should be cautioned about the concomitant use of venlafaxine hydrochloride extended-release capsules 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**, *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 capsules 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 capsules are 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 (range in PMs - 38% to 105%) subjects, 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 capsules 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 9 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 capsules and the potential for serotonin syndrome, caution is advised when venlafaxine hydrochloride extended-release capsules are 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 or Neuroleptic Malignant Syndrome (NMS)-Like Reactions**). If concomitant treatment of venlafaxine hydrochloride extended-release capsules with these drugs is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS**, **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions**). The concomitant use of venlafaxine hydrochloride extended-release capsules with tryptophan supplements is not recommended (see **WARNINGS**, **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions**).

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 capsules with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS**, **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions**).

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

Postmarketing Spontaneous Drug Interaction Reports
See **ADVERSE REACTIONS**, **Postmarketing 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.

Nonteratogenic Effects
Neonates exposed to venlafaxine hydrochloride extended-release capsules, 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 capsules 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 capsules, 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 capsules, and the data were not sufficient to support a claim for use in pediatric patients.

Anyone considering the use of venlafaxine hydrochloride extended-release capsules 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 capsules' impact on the growth, development, and maturation of children and adolescents, the studies that have been done suggest that venlafaxine hydrochloride extended-release capsules 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 capsules, regular monitoring of weight and height is recommended during treatment, particularly if they are to be continued long term. The safety of venlafaxine hydrochloride extended-release capsule treatment for pediatric patients has not been systematically assessed for chronic treatment longer than six 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) of venlafaxine hydrochloride extended-release capsule-treated patients in placebo-controlled premarketing major depressive disorder were 65 years of age or over. Of 2,897 venlafaxine hydrochloride tablet-treated (immediate release) 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 capsules have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see **PRECAUTIONS**, *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 Capsules** 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). Information on additional adverse events associated with venlafaxine hydrochloride extended-release capsules in the entire development program for the formulation and with venlafaxine hydrochloride tablets (immediate release) is included in the **Other Adverse Events Observed During the Premarketing Evaluation of Venlafaxine Hydrochloride Tablets and Venlafaxine Hydrochloride Extended-Release Capsules** subsection (see also **WARNINGS** and **PRECAUTIONS**).

Adverse Findings Observed in Short-Term, Placebo-Controlled Studies With Venlafaxine Hydrochloride Extended-Release Capsules
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. 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 capsule-treated patients at a rate at least twice that of placebo) are shown in **Table 6**.

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

	Percentage of Patients Discontinuing Due to Adverse Event	
Adverse Event	**Major Depressive Disorder Indication[b]**	
	Venlafaxine Hydrochloride Extended-Release Capsules	**Placebo**
	n = 357	**n = 285**
Digestive System		
Nausea	4%	< 1%
Anorexia	1%	< 1%
Dry Mouth	1%	0%
Nervous System		
Dizziness	2%	1%
Insomnia	1%	< 1%
Somnolence	2%	< 1%

[a] Two of the major depressive disorder studies were flexible dose and one was fixed dose.
[b] 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 capsule-treated patients (% venlafaxine hydrochloride extended-release capsules [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%).

Adverse Events Occurring at an Incidence of 2% or More Among Venlafaxine Hydrochloride Extended-Release Capsule-Treated Patients
Table 7 enumerates 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), in 2% or more of patients treated with venlafaxine hydrochloride extended-release capsules where the incidence in patients treated with venlafaxine hydrochloride extended-release capsules 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 Table 7
Major depressive disorder
Note in particular the following adverse events that occurred in at least 5% of the venlafaxine hydrochloride extended-release capsule 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 capsule-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.

Table 7: Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Venlafaxine Hydrochloride Extended-Release Capsule Clinical Trials in Patients With Major Depressive Disorder[a,b]

	% Reporting Event	
Body System	**Venlafaxine Hydrochloride Extended-Release Capsules**	**Placebo**
Preferred Term	(n = 357)	(n = 285)
Body as a Whole		
Asthenia	8%	7%
Cardiovascular System		
Vasodilatation[c]	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[d]	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[e]	4%	< 1%
Urogenital System		
Abnormal Ejaculation (male)[f,g]	16%	< 1%
Impotence[g]	4%	< 1%
Anorgasmia (female)[h,i]	3%	< 1%

[a] Incidence, rounded to the nearest %, for events reported by at least 2% of patients treated with venlafaxine hydrochloride extended-release capsules, 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.
[b] < 1% indicates an incidence greater than zero but less than 1%.
[c] Mostly "hot flashes."
[d] Mostly "vivid dreams," "nightmares," and "increased dreaming."
[e] Mostly "blurred vision" and "difficulty focusing eyes."
[f] Mostly "delayed ejaculation."
[g] Incidence is based on the number of male patients.
[h] Mostly "delayed orgasm" or "anorgasmia."
[i] Incidence is based on the number of female patients.

Vital Sign Changes
Venlafaxine hydrochloride extended-release capsule 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 (see **WARNINGS**, **Sustained Hypertension** and **Elevations in Systolic and Diastolic Blood Pressure** for effects on blood pressure).

In a flexible-dose study, with venlafaxine hydrochloride tablet (immediate release) 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 capsule 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.

Patients treated with venlafaxine hydrochloride tablets (immediate-release) 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 0.0% of placebo-treated patients (see **PRECAUTIONS**, **General,** *Serum Cholesterol Elevation*).

ECG Changes
In a flexible-dose study, with venlafaxine hydrochloride tablet (immediate release) 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 Ilness.*)

Other Adverse Events Observed During the Premarketing Evaluation of Venlafaxine Hydrochloride Tablets and Venlafaxine Hydrochloride Extended-Release Capsules
During their 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. In addition, in premarketing assessment of venlafaxine hydrochloride tablets, multiple doses were administered to 2897 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 7212 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 **Table 7**, 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:** 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.

Postmarketing 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 torsade 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 capsules, there were 2 reports of acute overdosage with venlafaxine hydrochloride extended-release capsules 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 capsules 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 capsules. This patient reported paresthesia of all four limbs but recovered without sequelae.

Among the patients included in the premarketing evaluation with venlafaxine hydrochloride tablets (immediate release), 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 2 generalized convulsions and a prolongation of QT_c to 500 msec, compared with 405 msec at baseline. Mild sinus tachycardia was reported in 2 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 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 capsules 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 (immediate release), 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 capsule doses higher than 225 mg/day is very limited (see **PRECAUTIONS, General**, *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 (immediate release) may be switched to venlafaxine hydrochloride extended-release capsules at the nearest equivalent dose (mg/day), e.g., 37.5 mg venlafaxine two-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, 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 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.

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 1 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 as follows:

37.5 mg - light-grey opaque cap/buff opaque body with "93" and "7384" on both body and cap. They are available in bottles of 30 and 90.

75 mg - buff opaque cap/buff opaque body with "93" and "7385" on both body and cap. They are available in bottles of 30 and 90.

150 mg - light-orange cap/light-orange body with "93" and "7386" on the body. They are available in bottles of 30 and 90.

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, with a child-resistant closure (as required).

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Rev. A 2/2010

MEDICATION GUIDE
Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

℞ only

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.

This product's label may have been updated. For current package insert and further product information, please call 1-888-838-2872, MEDICAL AFFAIRS.

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Rev. E 5/2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076565

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
APPROVAL SUMMARY Supersedes approval summary dated 10/26/2009
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 076565 Date of Submission: April 7, 2010

Applicant's Name: TEVA Pharmaceuticals USA

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

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REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

BASIS OF APPROVAL:
APPROVAL SUMMARY

CONTAINER LABEL (60's):
Satisfactory in FPL as of September 18, 2009 submission.

PACKAGE INSERT:
Satisfactory in FPL as of April 7, 2010 submission.

MEDICATION GUIDE:
Satisfactory in FPL as of September 18, 2009 submission.

FUTURE REVISIONS:

Delete – "Sealed for your protection" from the principal display panel of container labels.
Indicate that dosages of this product are based on venlafaxine rather than venlafaxine HCl in the DOSAGE AND ADMINSTRATION and HOW SUPPLIED sections.

BASIS OF APPROVAL:
Was this approval based upon a petition?
What is the RLD on the 356(h) form: Effexor XR
NDA Number: 020699/S-090
NDA Drug Name: Effexor XR
NDA Firm: Wyeth Pharmaceuticals, Inc.
Date of Approval of NDA Insert and supplement #: S-090, approved on January 6, 2010
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No

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FOR THE RECORD (Some information taken from the review dated 10/26/2009):

1. Review based on the labeling of Wyeth Pharmaceutical Inc's "Effexor XR", NDA 020699/S-090, approved January 6, 2010. It adds the term "angioedema" to the **ADVERSE REACTIONS, Postmarketing Reports,** *Adverse Events* subsection of the labeling. Also approved since the last approval summary is S-086 on November 9, 2009: for the addition of the term "flu-like symptoms" under **PRECAUTIONS**, **General**, *Discontinuation of Treatment of Effexor* in the Effexor product line labeling. That approved labeling appears in the later (S-090) approved labeling.

Patent

Number	Expiration	Use Code	Description	Filed	Labeling Impact
5916923/*PED	6-28-13 / 12-28-13	U-398	Tx of GAD	MOU	carved out all reference to GAD
6274171/*PED	3-20-17 / 9-20-17		Tx of Depression	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	MOU	Carved out
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	MOU	Carved out
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

Exclusivity	Indication	Expiration Date	Labeling Impact
I-561	Long term treatment of Social Anxiety Disorder	December 14, 2010	Carve out SAD

*The sponsor originally submitted patent certification IV for patents #6403120 (U-451) and #6419958(U-459). Both use codes are defined as Treatment of depression and generalized anxiety disorder (GAD) and since the sponsor challenged both patents, all reference to Treatment of depression and GAD should appear in their labeling. However, the sponsor provided "MOU" statement to patent #5916923, which has the use code U-398, Treatment of general anxiety disorder, and wishes to carve out all references to GAD.

This certification is not consistent and the regulatory support officer contacted the sponsor on January 10, 2003 to either file patent certification IV to all three patents ('120, '958 and '923) or provide both a patent certification IV and a "MOU" statement to the '923 patent.

In response to the regulatory support officer's request, the sponsor submitted a revised patent certification statement on January 17, 2003 with a claim that '120 & '958 were improperly assigned the use codes U-451 & U-459 which are both defined as "Treatment of depression & GAD". However in deference to the Division's request, they filed patent certification III regarding the use in the treatment of GAD and filed patent certification IV regarding the treatment of depression.

However, in their latest patent certification dated February 12, 2003, the sponsor changed the certification regarding the use in the treatment of GAD and filed MOU statements and wishes to carve out all the related wordings. This final certification appears to be acceptable.

*** Please note that since the last review, the RLD has added new use code "U-535" Tx of Social Anxiety Disorder to their two patents #6403120 & #6419958. TEVA certified "MOU" statement to both use codes and all wordings regarding SAD are removed from the labeling as well as GAD.

****The firm has submitted updated patent certification as of 4/27/2009, which is reflected in the chart above.

2. MANUFACTURING FACILITY

TEVA Pharmaceutical Industries, Ltd.
Hashikma Street
Industrial Area
P.O. Box 353
Kfar-Saba 44102 ISRAEL

[Vol. 2.1. page 313]

3. STORAGE CONDITIONS/DISPENSING RECOMMENDATIONS:

RLD: Store at controlled room temperature, 20C to 25 C (68F to 77F)
Bottles: Protect from light. Dispense in light-resistant container
Blisters: Protect from light. Use blister carton to protect contents from light.

ANDA: "Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]
Dispense in a tight , light-resistant container as defined in the USP, with a child-resistant closure as required"

4. INACTIVE INGREDIENTS:

According to the "Components and Composition Statements", the list of inactive ingredients in the DESCRIPTION section appears to be accurate.

IRON content

The 37.5 mg capsule contains (b) (4) mg of Black Iron Oxide (b) (4). The daily consumption amount based on the dosing schedule is (b) (4) mg which is less than 5 mg/total daily dose, calculated as element iron [refer to 21 CRD 73.1200 (c)].

[Vol. 2.1. page 122-123]

5. PACKAGING CONFIGURATIONS:

RLD – Bottle of 100 capsules & Carton of 10 Redipak blister strips of 10 capsules each.

ANDA – Bottles of 15s, 100s capsules & 500s capsules for 37.5 mg, 75 mg, and 150 mg.

	Component	
37.5 mg capsules	Container	Closure
100's configuration (b) (4)	(b) (4)	
100's configuration (b) (4)		
500's configuration (b) (4)		
75 mg capsules		
100's configuration (b) (4)	(b) (4)	
100's configuration (b) (4)		
500's configuration (b) (4)		
150 mg capsules		
100's configuration (b) (4)	(b) (4)	
100's configuration (b) (4)		
500's configuration		

[Vol. 1.1. page 4562 & Vol 2.3. page 827-828]

6. Imprint/Scoring

Test	Specification
Description	(b) (4)
Capsules Imprinting*	37.5 mg strength: Body: 93 7384 Cap: 93 7384 75 mg strength: Body: 93 7385 Cap: 93 7385 150 mg strength Body: 93 7386 Cap: 93 7386

The sponsor stated in the cover letter that the imprinting for the 150 mg capsules has been revised to "93" and "7386" in the How Supplied section, however, the package insert still states that it has (b) (4) and (b) (4) on the body of 150 mg capsule. I asked the sponsor to clarify and revise accordingly.

**The revision has been made to the labeling submitted on 2/7/2006 and is acceptable.

7. Medication Guide

TEVA has described their distribution of Medication Guides in their June 22, 2009 amendment. TEVA will provide one Medication Guide for every 30 capsules. In addition, they have an existing agreement with the Hibbert Group.

Date of Review: April 13, 2010 Date of Submission: April 7, 2010

Primary Reviewer: Charlie Hoppes Team Leader: John Grace

NDC 0093-**7386**-01

VENLAFAXINE HYDROCHLORIDE

Extended-Release Capsules

150 mg*

SEALED FOR YOUR PROTECTION

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

℞ only

100 CAPSULES

TEVA

*Each capsule contains venlafaxine hydrochloride equivalent to 150 mg venlafaxine.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Iss. 6/2008

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 0093-7386-01
3 8

NDC 0093-7386-85

VENLAFAXINE HYDROCHLORIDE

Extended-Release Capsules

150 mg*

SEALED FOR YOUR PROTECTION

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

℞ only

15 CAPSULES

TEVA

*Each capsule contains venlafaxine hydrochloride equivalent to 150 mg venlafaxine.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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(01)003 0093 7386 85 8

Iss. 6/2008

NDC 0093-**7386**-05

VENLAFAXINE HYDROCHLORIDE
Extended-Release Capsules
150 mg*

SEALED FOR YOUR PROTECTION

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

℞ only

500 CAPSULES

TEVA

*Each capsule contains venlafaxine hydrochloride equivalent to 150 mg venlafaxine.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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Iss. 6/2008

N 0093-7386-05 3 6

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NDC 0093-7384-01

VENLAFAXINE HYDROCHLORIDE
Extended-Release Capsules
37.5 mg*

SEALED FOR YOUR PROTECTION

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

℞ only

100 CAPSULES

TEVA

*Each capsule contains venlafaxine hydrochloride equivalent to 37.5 mg venlafaxine.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. Iss. 6/2008

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N 0093-7384-01
3 4

NDC 0093-7384-85

VENLAFAXINE HYDROCHLORIDE
Extended-Release Capsules
37.5 mg*

SEALED FOR YOUR PROTECTION

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

℞ only

15 CAPSULES

TEVA

*Each capsule contains venlafaxine hydrochloride equivalent to 37.5 mg venlafaxine.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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Iss. 6/2008

(01)003 0093 7384 85 4

NDC 0093-**7384**-05

VENLAFAXINE HYDROCHLORIDE

Extended-Release Capsules

37.5 mg*

SEALED FOR YOUR PROTECTION

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

℞ only

500 CAPSULES

TEVA

*Each capsule contains venlafaxine hydrochloride equivalent to 37.5 mg venlafaxine.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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N 0093-7384-05
3 2

NDC 0093-**7385**-01

VENLAFAXINE HYDROCHLORIDE

Extended-Release Capsules

75 mg*

SEALED FOR YOUR PROTECTION

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

℞ only

100 CAPSULES

TEVA

*Each capsule contains venlafaxine hydrochloride equivalent to 75 mg venlafaxine.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

3 N 0093-7385-01 1

NDC 0093-7385-85

VENLAFAXINE HYDROCHLORIDE

Extended-Release Capsules

75 mg*

SEALED FOR YOUR PROTECTION

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

℞ only

15 CAPSULES

TEVA

*Each capsule contains venlafaxine hydrochloride equivalent to 75 mg venlafaxine.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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Iss. 6/2008

(01)003 0093 7385 85 1

NDC 0093-**7385**-05

VENLAFAXINE HYDROCHLORIDE

Extended-Release Capsules

75 mg*

SEALED FOR YOUR PROTECTION

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

℞ only

500 CAPSULES

TEVA

*Each capsule contains venlafaxine hydrochloride equivalent to 75 mg venlafaxine.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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Sellersville, PA 18960

N 3 0093-7385-05 9

VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES

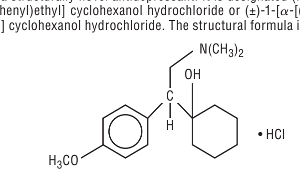
℞ only

7384
7385
7386

Iss. 2/2010

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 capsules 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 capsules are 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 (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[α-[(dimethylamino)methyl]-*p*-methoxybenzyl] cyclohexanol hydrochloride. The structural formula is shown below.



venlafaxine hydrochloride

$C_{17}H_{27}NO_2$•HCl M.W. 313.87

Venlafaxine hydrochloride is a white to off-white crystalline solid with 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 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 antifoam DC 1510, black iron oxide, dibutyl sebacate, ethylcellulose, gelatin, polyethylene glycol, povidone, shellac, soya lecithin MC thin, sugar spheres (which contain sucrose and corn starch), sunset yellow FCF FD&C yellow 6, talc, and titanium dioxide. The 37.5 mg and 75 mg capsules also contain D&C yellow 10.

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 capsules (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 venlafaxine hydrochloride tablets (immediate release) [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 capsules, therefore, provide 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 9 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 capsule 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 capsule 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 capsules 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 capsules were 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 (immediate release) 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, 150, or 225 mg, qAM) were randomized to continuation of their same venlafaxine hydrochloride extended-release capsule 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) 2 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 capsule 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 (immediate release) [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 tablet treatment experienced significantly lower relapse rates over the subsequent 52 weeks compared with those receiving placebo.

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 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 two-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 (immediate release) 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 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 (immediate release) 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 Trials**). Nevertheless, the physician who elects to use venlafaxine hydrochloride tablets/venlafaxine hydrochloride extended-release capsules for extended periods should periodically re-evaluate 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 9 antidepressant drugs in over 4400 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 1000 patients treated) are provided in **Table 1**.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 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**, **General**, *Discontinuation of Treatment With Venlafaxine Hydrochloride Extended-Release Capsules* and **DOSAGE AND ADMINISTRATION, Discontinuing Venlafaxine Hydrochloride Extended-Release Capsules,** for a description of the risks of discontinuation of venlafaxine hydrochloride extended-release capsules).

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 capsules 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 capsules are 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 capsule 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 capsules 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 capsules 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 capsules with serotonin precursors (such as tryptophan) is not recommended (see **PRECAUTIONS**, **Drug Interactions**).

Treatment with venlafaxine hydrochloride extended-release capsules 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 capsule 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 3 consecutive on-therapy visits) (see **Table 2**).

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

An insufficient number of patients received mean doses of venlafaxine hydrochloride extended-release capsules 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 Capsules Premarketing Studies by Indication

MDD (75 to 375 mg/day)
19/705 (3)

MDD = major depressive disorder

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

Venlafaxine Hydrochloride Tablets 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 capsule-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).

Sustained increases of SDBP could have adverse consequences. Cases of elevated blood pressure requiring immediate treatment have been reported in postmarketing experience. Preexisting hypertension should be controlled before treatment with venlafaxine. It is recommended that patients receiving venlafaxine hydrochloride extended-release capsules 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 capsule-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 Capsules mg/day				Placebo	
	≤ 75		> 75			
	SSBP[a]	SDBP[b]	SSBP	SDBP	SSBP	SDBP
Major Depressive Disorder						
8 to 12 weeks	-0.28	0.37	2.93	3.56	-1.08	-0.10

[a] Supine Systolic Blood Pressure
[b] Supine Diastolic Blood Pressure

Across all clinical trials in MDD, 1.4% of patients in the venlafaxine hydrochloride extended-release capsule-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 capsule-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 Capsules
Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, to include retrospective surveys of trials in major depressive 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 capsules, 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 capsules. 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, as shown in **Table 5**.

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

	Major Depressive Disorder	
	Venlafaxine Hydrochloride Extended-Release Capsules	Placebo
Symptom	n = 357	n = 285
Insomnia	17%	11%
Nervousness	10%	5%

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

Changes in Weight
Adult patients
A loss of 5% or more of body weight occurred in 7% of venlafaxine hydrochloride extended-release capsule-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 capsules was 0.1% in major depressive disorder studies.

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 capsules and weight loss agents is not recommended. Venlafaxine hydrochloride extended-release capsules are 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 capsules. In a pooled analysis of four eight-week, double-blind, placebo-controlled, flexible dose outpatient trials, venlafaxine hydrochloride extended-release capsule-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 capsules than with placebo experienced a weight loss of at least 3.5% (18% of venlafaxine hydrochloride extended-release capsule-treated patients vs. 3.6% of placebo-treated patients; p < 0.001) (see **PRECAUTIONS**, **General**, *Changes in Appetite*).

The risks associated with longer-term venlafaxine hydrochloride extended-release capsule use were assessed in an open-label MDD study of children and adolescents who received venlafaxine hydrochloride extended-release capsules for up to six 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 eight-week placebo-controlled MDD studies, venlafaxine hydrochloride extended-release capsule-treated patients grew an average of 0.8 cm (n = 146), while placebo-treated patients grew an average of 0.7 cm (n = 147). In the six-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 capsule-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 capsules was 1.0% in major depressive disorder studies.

Pediatric patients
Decreased appetite has been observed in pediatric patients receiving venlafaxine hydrochloride extended-release capsules. In the placebo-controlled trials for MDD, 10% of patients aged 6 to 17 treated with venlafaxine hydrochloride extended-release capsules for up to eight weeks and 3% of patients treated with placebo reported treatment-emergent anorexia (decreased appetite). None of the patients receiving venlafaxine hydrochloride extended-release capsules discontinued for anorexia or weight loss.

Activation of Mania/Hypomania
During premarketing major depressive disorder studies, mania or hypomania occurred in 0.3% of venlafaxine hydrochloride extended-release capsule-treated patients and no placebo patients. In all premarketing major depressive disorder trials with venlafaxine hydrochloride tablets (immediate release), 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 capsules 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 capsules. 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 capsules 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 capsule-treated patients in the major depressive disorder studies. In all premarketing major depressive disorder trials with venlafaxine hydrochloride tablets (immediate release), seizures were reported at various doses in 0.3% (8/3082) of venlafaxine-treated patients. Venlafaxine hydrochloride extended-release capsules, 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 capsules, may increase the risk of bleeding events. Concomitant use of aspirin, non-steroidal 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 capsules 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 0.0% 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 capsules 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 capsules and 220 patients who received placebo in 8 to 12 week double-blind, placebo-controlled trials in major depressive disorder. The mean change from baseline in corrected QT interval (QT_c) for venlafaxine hydrochloride extended-release capsule-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 capsules and decrease of 1.9 msec for placebo).

In these same trials, the mean change from baseline in heart rate for venlafaxine hydrochloride extended-release capsule-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 capsules and 1 beat per minute for placebo).

In a flexible-dose study, with venlafaxine hydrochloride tablet (immediate release) doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, venlafaxine hydrochloride tablet-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 venlafaxine hydrochloride tablets (immediate release) 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 capsules, 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 capsules and should counsel them in its appropriate use. A patient Medication Guide about "**Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions**" is available for venlafaxine hydrochloride extended-release capsules. 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 capsules.

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 capsules and triptans, tramadol, tryptophan supplements or other serotonergic agents (see **WARNINGS**, **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions** and **PRECAUTIONS**, **Drug Interactions**, *CNS-Active Drugs*).

Patients should be cautioned about the concomitant use of venlafaxine hydrochloride extended-release capsules 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**, *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 capsules 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 capsules are 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 (range in PMs - 38% to 105%) subjects, 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 capsules 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 9 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 capsules and the potential for serotonin syndrome, caution is advised when venlafaxine hydrochloride extended-release capsules are 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 or Neuroleptic Malignant Syndrome (NMS)-Like Reactions**). If concomitant treatment of venlafaxine hydrochloride extended-release capsules with these drugs is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS**, **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions**). The concomitant use of venlafaxine hydrochloride extended-release capsules with tryptophan supplements is not recommended (see **WARNINGS**, **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions**).

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 capsules with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS**, **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions**).

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

Postmarketing Spontaneous Drug Interaction Reports
See **ADVERSE REACTIONS**, **Postmarketing 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.

Nonteratogenic Effects
Neonates exposed to venlafaxine hydrochloride extended-release capsules, 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 capsules 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 capsules, 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 capsules, and the data were not sufficient to support a claim for use in pediatric patients.

Anyone considering the use of venlafaxine hydrochloride extended-release capsules 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 capsules' impact on the growth, development, and maturation of children and adolescents, the studies that have been done suggest that venlafaxine hydrochloride extended-release capsules 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 capsules, regular monitoring of weight and height is recommended during treatment, particularly if they are to be continued long term. The safety of venlafaxine hydrochloride extended-release capsule treatment for pediatric patients has not been systematically assessed for chronic treatment longer than six 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) of venlafaxine hydrochloride extended-release capsule-treated patients in placebo-controlled premarketing major depressive disorder were 65 years of age or over. Of 2,897 venlafaxine hydrochloride tablet-treated (immediate release) 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 capsules have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see **PRECAUTIONS**, *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 Capsules** 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). Information on additional adverse events associated with venlafaxine hydrochloride extended-release capsules in the entire development program for the formulation and with venlafaxine hydrochloride tablets (immediate release) is included in the **Other Adverse Events Observed During the Premarketing Evaluation of Venlafaxine Hydrochloride Tablets and Venlafaxine Hydrochloride Extended-Release Capsules** subsection (see also **WARNINGS** and **PRECAUTIONS**).

Adverse Findings Observed in Short-Term, Placebo-Controlled Studies With Venlafaxine Hydrochloride Extended-Release Capsules
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. 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 capsule-treated patients at a rate at least twice that of placebo) are shown in **Table 6**.

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

	Percentage of Patients Discontinuing Due to Adverse Event	
Adverse Event	**Major Depressive Disorder Indication[b]**	
	Venlafaxine Hydrochloride Extended-Release Capsules	**Placebo**
	n = 357	**n = 285**
Digestive System		
Nausea	4%	< 1%
Anorexia	1%	< 1%
Dry Mouth	1%	0%
Nervous System		
Dizziness	2%	1%
Insomnia	1%	< 1%
Somnolence	2%	< 1%

[a] Two of the major depressive disorder studies were flexible dose and one was fixed dose.
[b] 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 capsule-treated patients (% venlafaxine hydrochloride extended-release capsules [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%).

Adverse Events Occurring at an Incidence of 2% or More Among Venlafaxine Hydrochloride Extended-Release Capsule-Treated Patients
Table 7 enumerates 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), in 2% or more of patients treated with venlafaxine hydrochloride extended-release capsules where the incidence in patients treated with venlafaxine hydrochloride extended-release capsules 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 Table 7
Major depressive disorder
Note in particular the following adverse events that occurred in at least 5% of the venlafaxine hydrochloride extended-release capsule 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 capsule-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.

Table 7: Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Venlafaxine Hydrochloride Extended-Release Capsule Clinical Trials in Patients With Major Depressive Disorder[a,b]

	% Reporting Event	
Body System	**Venlafaxine Hydrochloride Extended-Release Capsules**	**Placebo**
Preferred Term	(n = 357)	(n = 285)
Body as a Whole		
Asthenia	8%	7%
Cardiovascular System		
Vasodilatation[c]	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[d]	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[e]	4%	< 1%
Urogenital System		
Abnormal Ejaculation (male)[f,g]	16%	< 1%
Impotence[g]	4%	< 1%
Anorgasmia (female)[h,i]	3%	< 1%

[a] Incidence, rounded to the nearest %, for events reported by at least 2% of patients treated with venlafaxine hydrochloride extended-release capsules, 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.
[b] < 1% indicates an incidence greater than zero but less than 1%.
[c] Mostly "hot flashes."
[d] Mostly "vivid dreams," "nightmares," and "increased dreaming."
[e] Mostly "blurred vision" and "difficulty focusing eyes."
[f] Mostly "delayed ejaculation."
[g] Incidence is based on the number of male patients.
[h] Mostly "delayed orgasm" or "anorgasmia."
[i] Incidence is based on the number of female patients.

Vital Sign Changes
Venlafaxine hydrochloride extended-release capsule 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 (see **WARNINGS**, **Sustained Hypertension** and **Elevations in Systolic and Diastolic Blood Pressure** for effects on blood pressure).

In a flexible-dose study, with venlafaxine hydrochloride tablet (immediate release) 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 capsule 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.

Patients treated with venlafaxine hydrochloride tablets (immediate-release) 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 0.0% of placebo-treated patients (see **PRECAUTIONS**, **General,** *Serum Cholesterol Elevation*).

ECG Changes
In a flexible-dose study, with venlafaxine hydrochloride tablet (immediate release) 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 their 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. In addition, in premarketing assessment of venlafaxine hydrochloride tablets, multiple doses were administered to 2897 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 7212 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 **Table 7**, 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:** 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.

Postmarketing 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 torsade 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 capsules, there were 2 reports of acute overdosage with venlafaxine hydrochloride extended-release capsules 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 capsules 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 capsules. This patient reported paresthesia of all four limbs but recovered without sequelae.

Among the patients included in the premarketing evaluation with venlafaxine hydrochloride tablets (immediate release), 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 2 generalized convulsions and a prolongation of QT_c to 500 msec, compared with 405 msec at baseline. Mild sinus tachycardia was reported in 2 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 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 capsules 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 (immediate release), 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 capsule doses higher than 225 mg/day is very limited (see **PRECAUTIONS, General**, *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 (immediate release) may be switched to venlafaxine hydrochloride extended-release capsules at the nearest equivalent dose (mg/day), e.g., 37.5 mg venlafaxine two-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, 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 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.

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 1 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 as follows:

37.5 mg - light-grey opaque cap/buff opaque body with "93" and "7384" on both body and cap. They are available in bottles of 15, 100 and 500.

75 mg - buff opaque cap/buff opaque body with "93" and "7385" on both body and cap. They are available in bottles of 15, 100 and 500.

150 mg - light-orange cap/light-orange body with "93" and "7386" on the body. They are available in bottles of 15, 100 and 500.

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, with a child-resistant closure (as required).

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

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MEDICATION GUIDE
Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

℞ only

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.

This product's label may have been updated. For current package insert and further product information, please call 1-888-838-2872, MEDICAL AFFAIRS.

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Rev. E 5/2008

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Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

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- 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.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Rev. E 5/2008

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-76565	ORIG-1	TEVA PHARMACEUTICALS USA INC	VENLAFAXINE HYDROCHLORIDE

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

/s/

CHARLES V HOPPES
04/13/2010

JOHN F GRACE
04/13/2010

APPROVAL SUMMARY

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

ANDA Number:	76-565
Date of Submission:	September 18, 2009
Applicant's Name:	Teva Pharmaceuticals USA
Established Name:	Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg, 75 mg, & 150 mg.
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

1. CONTAINER LABELS – 15s, 100s & 500s bottles for 37.5 mg, 75 mg, and 150 mg.

Satisfactory in FPL as of the September 18, 2009 amendment.

2. PROFESSIONAL PACKAGE INSERT/MEDICATION GUIDE

Satisfactory in FPL as of the September 18, 2009 amendment**.**

3. MEDICATION GUIDE

Satisfactory in FPL as of the September 18, 2009 amendment**.**

Revisions needed post approval: None

Basis of Approval:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Effexor XR®
NDA Number: 20-699
NDA Drug Name: Venlafaxine XR ® (venlafaxine hydrochloride) Extended-Release Capsules
NDA Firm: Wyeth Pharmaceuticals, Inc.
Date of Approval of NDA Insert and supplement #. (S-087), approved 1-30-09
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: side-by-sides
Other Comments

Patent

Number	Expiration	Use Code	Description	Filed	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		Tx of Depression	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	MOU	Carved out
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	MOU	Carved out
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

FOR THE RECORD: (Portions taken from previous reviewer, Melaine Shin)

1. GENERAL

   a. This is the **FIRST GENERIC** for Effexor XR 37.5 mg, 75 mg, and 150 mg capsules.

   b. The original application was filed on December 10, 2002 for 150 mg strength capsules then the sponsor added 37.5 mg and 75 mg strengths on February 13, 2003.

2. MODEL LABELING

****The model RLD labeling used for this review is NDA 20-699/S-087 approved 1/30/2009.**

3. PATENT/EXCLUSIVITIES

   Patent

Number	Expiration	Use Code	Description	Filed	Labeling Impact
5916923/*PED	6-28-13 / 12-28-13	U-398	Tx of GAD	MOU	carved out all reference to GAD
6274171/*PED	3-20-17 / 9-20-17		Tx of Depression	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	MOU	Carved out
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	MOU	Carved out
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

Exclusivity	Indication	Expiration Date	Labeling Impact
I-561	Long term treatment of Social Anxiety Disorder	December 14, 2010	Carve out SAD

*The sponsor originally submitted patent certification IV for patents #6403120 (U-451) and #6419958(U-459). Both use codes are defined as Treatment of depression and generalized anxiety disorder (GAD) and since the sponsor challenged both patents, all reference to Treatment of depression and GAD should appear in their labeling. However, the sponsor provided "MOU" statement to patent #5916923, which has the use code U-398, Treatment of general anxiety disorder, and wishes to carve out all references to GAD.

This certification is not consistent and the regulatory support officer contacted the sponsor on January 10, 2003 to either file patent certification IV to all three patents ('120, '958 and '923) or provide both a patent certification IV and a "MOU" statement to the '923 patent.

In response to the regulatory support officer's request, the sponsor submitted a revised patent certification statement on January 17, 2003 with a claim that '120 & '958 were improperly assigned the use codes U-451 & U-459 which are both defined as "Treatment of depression & GAD". However in deference to the Division's request, they filed patent certification III regarding the use in the treatment of GAD and filed patent certification IV regarding the treatment of depression.

However, in their latest patent certification dated February 12, 2003, the sponsor changed the certification regarding the use in the treatment of GAD and filed MOU statements and wishes to carve out all the related wordings. This final certification appears to be acceptable.

*** Please note that since the last review, the RLD has added new use code "U-535" Tx of Social Anxiety Disorder to their two patents #6403120 & #6419958. TEVA certified "MOU" statement to both use codes and all wordings regarding SAD are removed from the labeling as well as GAD.

******The firm has submitted updated patent certification as of 4/27/2009, which is reflected in the chart above.**

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

TEVA Pharmaceutical Industries, Ltd.
Hashikma Street
Industrial Area
P.O. Box 353
Kfar-Saba 44102 ISRAEL

[Vol. 2.1. page 313]

5. INACTIVE INGREDIENTS

According to the "Components and Composition Statements", the list of inactive ingredients in the DESCRIPTION section appears to be accurate.

IRON content

The 37.5 mg capsule contains (b) (4) mg of Black Iron Oxide (b) (4). The daily consumption amount based on the dosing schedule is (b) (4) mg which is less than 5 mg/total daily dose, calculated as element iron [refer to 21 CRD 73.1200 (c)].

[Vol. 2.1. page 122-123]

6. PACKAGING CONFIGURATIONS

RLD – Bottle of 100 capsules & Carton of 10 Redipak blister strips of 10 capsules each.

ANDA – Bottles of 15s, 100s capsules & 500s capsules for 37.5 mg, 75 mg, and 150 mg.

7. DISPENSING/STORAGE TEMPERATURE STATEMENT COMPARISION

RLD: Store at controlled room temperature, 20C to 25 C (68F to 77F)
Bottles: Protect from light. Dispense in light-resistant container
Blisters: Protect from light. Use blister carton to protect contents from light.

ANDA: "Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature] Dispense in a tight , light-resistant container as defined in the USP, with a child-resistant closure as required"

8. CONTAINER/CLOSURE

	Component	
37.5 mg capsules	Container	Closure
100's configuration (b) (4)	(b) (4)	
100's configuration (b) (4)		
500's configuration (b) (4)		
75 mg capsules		
100's configuration (b) (4)	(b) (4)	
100's configuration (b) (4)		
500's configuration (b) (4)		
150 mg capsules		
100's configuration (b) (4)	(b) (4)	
100's configuration (b) (4)		
500's configuration		

[Vol. 1.1. page 4562 & Vol 2.3. page 827-828]

9. IMPRINTINGS:

Test	Specification
Description	(b) (4) [redacted]
Capsules Imprinting*	37.5 mg strength: Body: 93 7384 Cap: 93 7384 75 mg strength: Body: 93 7385 Cap: 93 7385 150 mg strength Body: 93 7386 Cap: 93 7386

The sponsor stated in the cover letter that the imprinting for the 150 mg capsules has been revised to "93" and "7386" in the How Supplied section, however, the package insert still states that it has " (b) (4) " and " (b) (4) on the body of 150 mg capsule. I asked the sponsor to clarify and revise accordingly.

****The revision has been made to the labeling submitted on 2/7/2006 and is acceptable.**

10. Medication Guide

TEVA has described their distribution of Medication Guides in their June 22, 2009 amendment. TEVA will provide one Medication Guide for every 30 capsules. In addition, they have an existing agreement with the Hibbert Group.

Date of review: October 15, 2009 Date of submission: September 18, 2009

Primary Reviewer: _____ Date: _____
Michelle Dillahunt

Team Leader: _____ Date:_____
Lillie Golson

Cc:
ANDA 76565:
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)

File Path: **V:\FIRMSNZ\TEVA\LTRS&REV\76565 ap1. labeling.doc**

NDC 0093-**7386**-01

VENLAFAXINE HYDROCHLORIDE

Extended-Release Capsules

150 mg*

SEALED FOR YOUR PROTECTION

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

℞ only

100 CAPSULES

TEVA

*Each capsule contains venlafaxine hydrochloride equivalent to 150 mg venlafaxine.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Iss. 6/2008

Manufactured In Israel By:
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Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 0093-7386-01
3 8

NDC 0093-7386-85

VENLAFAXINE HYDROCHLORIDE

Extended-Release Capsules

150 mg*

SEALED FOR YOUR PROTECTION

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

℞ only

15 CAPSULES

TEVA

*Each capsule contains venlafaxine hydrochloride equivalent to 150 mg venlafaxine.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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(01)003 0093 7386 85 8

Iss. 6/2008

NDC 0093-**7386**-05

VENLAFAXINE HYDROCHLORIDE
Extended-Release Capsules
150 mg*

SEALED FOR YOUR PROTECTION

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

℞ only

500 CAPSULES

TEVA

*Each capsule contains venlafaxine hydrochloride equivalent to 150 mg venlafaxine.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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Sellersville, PA 18960

Iss. 6/2008

N 0093-7386-05 3 6

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NDC 0093-7384-01

VENLAFAXINE HYDROCHLORIDE
Extended-Release Capsules
37.5 mg*

SEALED FOR YOUR PROTECTION

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

℞ only

100 CAPSULES

TEVA

*Each capsule contains venlafaxine hydrochloride equivalent to 37.5 mg venlafaxine.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. Iss. 6/2008

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Sellersville, PA 18960

N 0093-7384-01
3 4

NDC 0093-7384-85

VENLAFAXINE HYDROCHLORIDE
Extended-Release Capsules
37.5 mg*

SEALED FOR YOUR PROTECTION

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

℞ only

15 CAPSULES

TEVA

*Each capsule contains venlafaxine hydrochloride equivalent to 37.5 mg venlafaxine.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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Sellersville, PA 18960

Iss. 6/2008

(01)003 0093 7384 85 4

NDC 0093-**7384**-05

VENLAFAXINE HYDROCHLORIDE

Extended-Release Capsules

37.5 mg*

SEALED FOR YOUR PROTECTION

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

℞ only

500 CAPSULES

TEVA

*Each capsule contains venlafaxine hydrochloride equivalent to 37.5 mg venlafaxine.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Iss. 6/2008

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Sellersville, PA 18960

N 0093-7384-05
3 2

NDC 0093-**7385**-01

VENLAFAXINE HYDROCHLORIDE

Extended-Release Capsules

75 mg*

SEALED FOR YOUR PROTECTION

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

℞ only

100 CAPSULES

TEVA

*Each capsule contains venlafaxine hydrochloride equivalent to 75 mg venlafaxine.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Iss. 6/2008

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Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

3 N 0093-7385-01 1

NDC 0093-7385-85

VENLAFAXINE HYDROCHLORIDE

Extended-Release Capsules

75 mg*

SEALED FOR YOUR PROTECTION

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

℞ only

15 CAPSULES

TEVA

*Each capsule contains venlafaxine hydrochloride equivalent to 75 mg venlafaxine.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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Iss. 6/2008

(01)003 0093 7385 85 1

NDC 0093-**7385**-05

VENLAFAXINE HYDROCHLORIDE

Extended-Release Capsules

75 mg*

SEALED FOR YOUR PROTECTION

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

℞ only

500 CAPSULES

TEVA

*Each capsule contains venlafaxine hydrochloride equivalent to 75 mg venlafaxine.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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Iss. 6/2008

Manufactured For:
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Sellersville, PA 18960

N 3 0093-7385-05 9

VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES

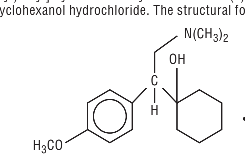
℞ only

7384
7385
7386

Iss. 4/2009

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 capsules 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 capsules are 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 (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[α-[(dimethylamino)methyl]-*p*-methoxybenzyl] cyclohexanol hydrochloride. The structural formula is shown below.



venlafaxine hydrochloride

$C_{17}H_{27}NO_2$•HCl M.W. 313.87

Venlafaxine hydrochloride is a white to off-white crystalline solid with 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 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 antifoam DC 1510, black iron oxide, dibutyl sebacate, ethylcellulose, gelatin, polyethylene glycol, povidone, shellac, soya lecithin MC thin, sugar spheres (which contain sucrose and corn starch), sunset yellow FCF FD&C yellow 6, talc, and titanium dioxide. The 37.5 mg and 75 mg capsules also contain D&C yellow 10.

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, H1-histaminergic, or α1-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 capsules (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 venlafaxine hydrochloride tablets (immediate release) [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 capsules, therefore, provide 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 9 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 capsule 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 capsule 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 capsules 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 capsules were 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 (immediate release) 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, 150, or 225 mg, qAM) were randomized to continuation of their same venlafaxine hydrochloride extended-release capsule 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) 2 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 capsule 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 (immediate release) [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 tablet treatment experienced significantly lower relapse rates over the subsequent 52 weeks compared with those receiving placebo.

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 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 two-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 (immediate release) 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 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 (immediate release) 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 Trials**). Nevertheless, the physician who elects to use venlafaxine hydrochloride tablets/venlafaxine hydrochloride extended-release capsules for extended periods should periodically re-evaluate 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 9 antidepressant drugs in over 4400 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 1000 patients treated) are provided in **Table 1**.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 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**, ***Discontinuation of Treatment With Venlafaxine Hydrochloride Extended-Release Capsules*** and **DOSAGE AND ADMINISTRATION, Discontinuing Venlafaxine Hydrochloride Extended-Release Capsules,** for a description of the risks of discontinuation of venlafaxine hydrochloride extended-release capsules).

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 capsules 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 capsules are 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 capsule 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 capsules 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 capsules 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 capsules with serotonin precursors (such as tryptophan) is not recommended (see **PRECAUTIONS**, **Drug Interactions**). Treatment with venlafaxine hydrochloride extended-release capsules 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 capsule 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 3 consecutive on-therapy visits) (see **Table 2**).

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

An insufficient number of patients received mean doses of venlafaxine hydrochloride extended-release capsules 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 Capsules Premarketing Studies by Indication

MDD (75 to 375 mg/day)
19/705 (3)

MDD = major depressive disorder

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

Venlafaxine Hydrochloride Tablets 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 capsule-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).

Sustained increases of SDBP could have adverse consequences. Cases of elevated blood pressure requiring immediate treatment have been reported in postmarketing experience. Preexisting hypertension should be controlled before treatment with venlafaxine. It is recommended that patients receiving venlafaxine hydrochloride extended-release capsules 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 capsule-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 Capsules 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

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

Across all clinical trials in MDD, 1.4% of patients in the venlafaxine hydrochloride extended-release capsule-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 capsule-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 Capsules
Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, to include retrospective surveys of trials in major depressive 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 capsules, 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 capsules. 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, as shown in **Table 5**.

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

	Major Depressive Disorder	
	Venlafaxine Hydrochloride Extended-Release Capsules	Placebo
Symptom	n = 357	n = 285
Insomnia	17%	11%
Nervousness	10%	5%

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

Changes in Weight
Adult patients
A loss of 5% or more of body weight occurred in 7% of venlafaxine hydrochloride extended-release capsule-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 capsules was 0.1% in major depressive disorder studies.

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 capsules and weight loss agents is not recommended. Venlafaxine hydrochloride extended-release capsules are 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 capsules. In a pooled analysis of four eight-week, double-blind, placebo-controlled, flexible dose outpatient trials, venlafaxine hydrochloride extended-release capsule-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 capsules than with placebo experienced a weight loss of at least 3.5% (18% of venlafaxine hydrochloride extended-release capsule-treated patients vs. 3.6% of placebo-treated patients; p < 0.001) (see **PRECAUTIONS**, **General**, ***Changes in Appetite***).

The risks associated with longer-term venlafaxine hydrochloride extended-release capsule use were assessed in an open-label MDD study of children and adolescents who received venlafaxine hydrochloride extended-release capsules for up to six 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 eight-week placebo-controlled MDD studies, venlafaxine hydrochloride extended-release capsule-treated patients grew an average of 0.8 cm (n = 146), while placebo-treated patients grew an average of 0.7 cm (n = 147). In the six-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 capsule-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 capsules was 1.0% in major depressive disorder studies.

Pediatric patients
Decreased appetite has been observed in pediatric patients receiving venlafaxine hydrochloride extended-release capsules. In the placebo-controlled trials for MDD, 10% of patients aged 6 to 17 treated with venlafaxine hydrochloride extended-release capsules for up to eight weeks and 3% of patients treated with placebo reported treatment-emergent anorexia (decreased appetite). None of the patients receiving venlafaxine hydrochloride extended-release capsules discontinued for anorexia or weight loss.

Activation of Mania/Hypomania
During premarketing major depressive disorder studies, mania or hypomania occurred in 0.3% of venlafaxine hydrochloride extended-release capsule-treated patients and no placebo patients. In all premarketing major depressive disorder trials with venlafaxine hydrochloride tablets (immediate release), 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 capsules 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 capsules. 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 capsules 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 capsule-treated patients in the major depressive disorder studies. In all premarketing major depressive disorder trials with venlafaxine hydrochloride tablets (immediate release), seizures were reported at various doses in 0.3% (8/3082) of venlafaxine-treated patients. Venlafaxine hydrochloride extended-release capsules, 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 capsules, may increase the risk of bleeding events. Concomitant use of aspirin, non-steroidal 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 capsules 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 0.0% 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 capsules 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 capsules and 220 patients who received placebo in 8 to 12 week double-blind, placebo-controlled trials in major depressive disorder. The mean change from baseline in corrected QT interval (QT_c) for venlafaxine hydrochloride extended-release capsule-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 capsules and decrease of 1.9 msec for placebo).

In these same trials, the mean change from baseline in heart rate for venlafaxine hydrochloride extended-release capsule-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 capsules and 1 beat per minute for placebo).

In a flexible-dose study, with venlafaxine hydrochloride tablet (immediate release) doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, venlafaxine hydrochloride tablet-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 venlafaxine hydrochloride tablets (immediate release) 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 capsules, 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 capsules and should counsel them in its appropriate use. A patient Medication Guide about **"Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions"** is available for venlafaxine hydrochloride extended-release capsules. 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 capsules.

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 capsules and triptans, tramadol, tryptophan supplements or other serotonergic agents (see **WARNINGS**, **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions** and **PRECAUTIONS**, **Drug Interactions**, ***CNS-Active Drugs***).

Patients should be cautioned about the concomitant use of venlafaxine hydrochloride extended-release capsules 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**, ***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 capsules 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 capsules are 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 Cmax increased by 26% in EM subjects and 48% in PM subjects. Cmax 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 (range in PMs - 38% to 105%) subjects, 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 capsules 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 9 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 capsules and the potential for serotonin syndrome, caution is advised when venlafaxine hydrochloride extended-release capsules are 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 or Neuroleptic Malignant Syndrome (NMS)-Like Reactions**). If concomitant treatment of venlafaxine hydrochloride extended-release capsules with these drugs is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS**, **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions**). The concomitant use of venlafaxine hydrochloride extended-release capsules with tryptophan supplements is not recommended (see **WARNINGS**, **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions**).

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 capsules with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS**, **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions**).

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

Postmarketing Spontaneous Drug Interaction Reports
See **ADVERSE REACTIONS**, **Postmarketing 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/m² 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/m² 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/m² 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/m²) the maximum human daily dose. The no effect dose for rat pup mortality was 0.25 times the human dose on a mg/m² 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.

Nonteratogenic Effects
Neonates exposed to venlafaxine hydrochloride extended-release capsules, 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 capsules 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 capsules, 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 capsules, and the data were not sufficient to support a claim for use in pediatric patients.

Anyone considering the use of venlafaxine hydrochloride extended-release capsules 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 capsules' impact on the growth, development, and maturation of children and adolescents, the studies that have been done suggest that venlafaxine hydrochloride extended-release capsules 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 capsules, regular monitoring of weight and height is recommended during treatment, particularly if they are to be continued long term. The safety of venlafaxine hydrochloride extended-release capsule treatment for pediatric patients has not been systematically assessed for chronic treatment longer than six 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) of venlafaxine hydrochloride extended-release capsule-treated patients in placebo-controlled premarketing major depressive disorder were 65 years of age or over. Of 2,897 venlafaxine hydrochloride tablet-treated (immediate release) 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 capsules have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see **PRECAUTIONS**, ***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 Capsules** 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). Information on additional adverse events associated with venlafaxine hydrochloride extended-release capsules in the entire development program for the formulation and with venlafaxine hydrochloride tablets (immediate release) is included in the **Other Adverse Events Observed During the Premarketing Evaluation of Venlafaxine Hydrochloride Tablets and Venlafaxine Hydrochloride Extended-Release Capsules** subsection (see also **WARNINGS** and **PRECAUTIONS**).

Adverse Findings Observed in Short-Term, Placebo-Controlled Studies With Venlafaxine Hydrochloride Extended-Release Capsules
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. 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 capsule-treated patients at a rate at least twice that of placebo) 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]**	
	Venlafaxine Hydrochloride Extended-Release Capsules	**Placebo**
	n = 357	**n = 285**
Digestive System		
Nausea	4%	< 1%
Anorexia	1%	< 1%
Dry Mouth	1%	0%
Nervous System		
Dizziness	2%	1%
Insomnia	1%	< 1%
Somnolence	2%	< 1%

[1] Two of the major depressive disorder studies were flexible dose and one was fixed 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 capsule-treated patients (% venlafaxine hydrochloride extended-release capsules [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%).

Adverse Events Occurring at an Incidence of 2% or More Among Venlafaxine Hydrochloride Extended-Release Capsule-Treated Patients
Table 7 enumerates 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), in 2% or more of patients treated with venlafaxine hydrochloride extended-release capsules where the incidence in patients treated with venlafaxine hydrochloride extended-release capsules 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 Table 7
Major depressive disorder
Note in particular the following adverse events that occurred in at least 5% of the venlafaxine hydrochloride extended-release capsule 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 capsule-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.

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

	% Reporting Event	
Body System	**Venlafaxine Hydrochloride Extended-Release Capsules**	**Placebo**
Preferred Term	(n = 357)	(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 capsules, 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.

Vital Sign Changes
Venlafaxine hydrochloride extended-release capsule 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 (see **WARNINGS**, **Sustained Hypertension** and **Elevations in Systolic and Diastolic Blood Pressure** for effects on blood pressure).

In a flexible-dose study, with venlafaxine hydrochloride tablet (immediate release) 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 capsule 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.

Patients treated with venlafaxine hydrochloride tablets (immediate-release) 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 0.0% of placebo-treated patients (see **PRECAUTIONS**, **General,** ***Serum Cholesterol Elevation***).

ECG Changes
In a flexible-dose study, with venlafaxine hydrochloride tablet (immediate release) 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 their 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. In addition, in premarketing assessment of venlafaxine hydrochloride tablets, multiple doses were administered to 2897 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 7212 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 **Table 7**, 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**: 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.

Postmarketing 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, 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 torsade 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 capsules, there were 2 reports of acute overdosage with venlafaxine hydrochloride extended-release capsules 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 capsules 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 capsules. This patient reported paresthesia of all four limbs but recovered without sequelae.

Among the patients included in the premarketing evaluation with venlafaxine hydrochloride tablets (immediate release), 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 2 generalized convulsions and a prolongation of QT_c to 500 msec, compared with 405 msec at baseline. Mild sinus tachycardia was reported in 2 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 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 capsules 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 (immediate release), 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 capsule doses higher than 225 mg/day is very limited (see **PRECAUTIONS, General**, ***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 (immediate release) may be switched to venlafaxine hydrochloride extended-release capsules at the nearest equivalent dose (mg/day), e.g., 37.5 mg venlafaxine two-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, 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 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.

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 1 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 as follows:

37.5 mg - light-grey opaque cap/buff opaque body with "93" and "7384" on both body and cap. They are available in bottles of 15, 100 and 500.

75 mg - buff opaque cap/buff opaque body with "93" and "7385" on both body and cap. They are available in bottles of 15, 100 and 500.

150 mg - light-orange cap/light-orange body with "93" and "7386" on the body. They are available in bottles of 15, 100 and 500.

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, with a child-resistant closure (as required).

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 4/2009

MEDICATION GUIDE
Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

℞ only

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.

This product's label may have been updated. For current package insert and further product information, please call 1-888-838-2872, MEDICAL AFFAIRS.

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Rev. E 5/2008

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Rev. E 5/2008

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-76565	ORIG-1	TEVA PHARMACEUTICALS USA INC	VENLAFAXINE HYDROCHLORIDE

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
10/22/2009

LILLIE D GOLSON
10/26/2009

TENTATIVE APPROVAL SUMMARY

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

ANDA Number:	76-565
Date of Submission:	June 22, 2009
Applicant's Name:	Teva Pharmaceuticals USA
Established Name:	Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg, 75 mg, & 150 mg.
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

1. CONTAINER LABELS – 15s, 100s & 500s bottles for 37.5 mg, 75 mg, and 150 mg.

Satisfactory in **draft** as of the April 27, 2009 amendment.

2. PROFESSIONAL PACKAGE INSERT/MEDICATION GUIDE

Satisfactory in **draft** as of the April 27, 2009 amendment.

3. MEDICATION GUIDE

Satisfactory in **draft** as of the April 27, 2009 amendment

Revisions needed pre approval:
CONTAINER
Decrease the prominence of the net quantity.
Increase the prominence of the strength.

Final printed container labels and insert labeling are needed before full approval. TEVA stated in their June 22, 2009 amendment that final printed labeling will be provided closer to the anticipated time of approval.

Basis of Approval:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Effexor XR®
NDA Number: 20-699
NDA Drug Name: Venlafaxine XR ® (venlafaxine hydrochloride) Extended-Release Capsules
NDA Firm: Wyeth Pharmaceuticals, Inc.
Date of Approval of NDA Insert and supplement #. (S-087), approved 1-30-09
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: side-by-sides
Other Comments

FOR THE RECORD: (Portions taken from previous reviewer, Melaine Shin)

1. GENERAL

a. This is the **FIRST GENERIC** for Effexor XR 37.5 mg, 75 mg, and 150 mg capsules.

b. The original application was filed on December 10, 2002 for 150 mg strength capsules then the sponsor added 37.5 mg and 75 mg strengths on February 13, 2003.

2. MODEL LABELING

****The model RLD labeling used for this review is NDA 20-699/S-087 approved 1/30/2009.**

3. PATENT/EXCLUSIVITIES

Patent

Number	Expiration	Use Code	Description	Filed	Labeling Impact
5916923/*PED	6-28-13 / 12-28-13	U-398	Tx of GAD	MOU	carved out all reference to GAD
6274171/*PED	3-20-17 / 9-20-17		Tx of Depression	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	MOU	Carved out
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	MOU	Carved out
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

Exclusivity	Indication	Expiration Date	Labeling Impact
I-561	Long term treatment of Social Anxiety Disorder	December 14, 2010	Carve out SAD

*The sponsor originally submitted patent certification IV for patents #6403120 (U-451) and #6419958(U-459). Both use codes are defined as Treatment of depression and generalized anxiety disorder (GAD) and since the sponsor challenged both patents, all reference to Treatment of depression and GAD should appear in their labeling. However, the sponsor provided "MOU" statement to patent #5916923, which has the use code U-398, Treatment of general anxiety disorder, and wishes to carve out all references to GAD.

This certification is not consistent and the regulatory support officer contacted the sponsor on January 10, 2003 to either file patent certification IV to all three patents ('120, '958 and '923) or provide both a patent certification IV and a "MOU" statement to the '923 patent.

In response to the regulatory support officer's request, the sponsor submitted a revised patent certification statement on January 17, 2003 with a claim that '120 & '958 were improperly assigned the use codes U-451 & U-459 which are both defined as "Treatment of depression & GAD". However in deference to the Division's request, they filed patent certification III regarding the use in the treatment of GAD and filed patent certification IV regarding the treatment of depression.

However, in their latest patent certification dated February 12, 2003, the sponsor changed the certification regarding the use in the treatment of GAD and filed MOU statements and wishes to carve out all the related wordings. This final certification appears to be acceptable.

*** Please note that since the last review, the RLD has added new use code "U-535" Tx of Social Anxiety Disorder to their two patents #6403120 & #6419958. TEVA certified "MOU" statement to both use codes and all wordings regarding SAD are removed from the labeling as well as GAD.

******The firm has submitted updated patent certification as of 4/27/2009, which is reflected in the chart above.**

Exclusivity

Exclusivity	Indication	Expiration Date	Labeling Impact
I-561	Long term treatment of Social Anxiety Disorder	December 14, 2010	Carve out SAD

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

TEVA Pharmaceutical Industries, Ltd.
Hashikma Street
Industrial Area
P.O. Box 353
Kfar-Saba 44102 ISRAEL

[Vol. 2.1. page 313]

5. INACTIVE INGREDIENTS

According to the "Components and Composition Statements", the list of inactive ingredients in the DESCRIPTION section appears to be accurate.

IRON content

The 37.5 mg capsule contains (b) (4) mg of Black Iron Oxide (b) (4). The daily consumption amount based on the dosing schedule (b) (4) mg which is less than 5 mg/total daily dose, calculated as element iron [refer to 21 CRD 73.1200 (c)].

[Vol. 2.1. page 122-123]

6. PACKAGING CONFIGURATIONS

RLD – Bottle of 100 capsules & Carton of 10 Redipak blister strips of 10 capsules each.

ANDA – Bottles of 15s, 100s capsules & 500s capsules for 37.5 mg, 75 mg, and 150 mg.

7. DISPENSING/STORAGE TEMPERATURE STATEMENT COMPARISION

RLD: Store at controlled room temperature, 20C to 25 C (68F to 77F)
Bottles: Protect from light. Dispense in light-resistant container
Blisters: Protect from light. Use blister carton to protect contents from light.

ANDA: "Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature] Dispense in a tight , light-resistant container as defined in the USP, with a child-resistant closure as required"

8. CONTAINER/CLOSURE

	Component	
37.5 mg capsules	Container	Closure
100's configuration (b) (4)	(b) (4)	
100's configuration (b) (4)		
500's configuration (b) (4)		
75 mg capsules		
100's configuration (b) (4)	(b) (4)	
100's configuration (b) (4)		
500's configuration (b) (4)		
150 mg capsules		
100's configuration (b) (4)	(b) (4)	
100's configuration (b) (4)		
500's configuration		

[Vol. 1.1. page 4562 & Vol 2.3. page 827-828]

9. IMPRINTINGS:

Test	Specification
Description	(b) (4) [redacted]
Capsules Imprinting*	37.5 mg strength: Body: 93 7384 Cap: 93 7384 75 mg strength: Body: 93 7385 Cap: 93 7385 150 mg strength Body: 93 7386 Cap: 93 7386

The sponsor stated in the cover letter that the imprinting for the 150 mg capsules has been revised to "93" and "7386" in the How Supplied section, however, the package insert still states that it has (b) (4) [redacted]" and (b) (4) [redacted] on the body of 150 mg capsule. I asked the sponsor to clarify and revise accordingly.

****The revision has been made to the labeling submitted on 2/7/2006 and is acceptable.**

10. Medication Guide

TEVA has described their distribution of Medication Guides in their June 22, 2009 amendment. TEVA will provide one Medication Guide for every 30 capsules. In addition, they have an existing agreement with the Hibbert Group.

Date of review: July 6, 2009 Date of submission: June 22, 2009

Primary Reviewer: _____ Date: _____
Michelle Dillahunt

Team Leader: _____ Date:_____
Lillie Golson

Cc:
ANDA 76565:
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)

File Path: **V:\FIRMSNZ\TEVA\LTRS&REV\76565 TA1. labeling.doc**

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
7/8/2009 01:09:51 PM
LABELING REVIEWER

Lillie Golson
7/9/2009 11:39:53 AM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING
(This review supersedes the review of the 4/6/06 submission)
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	76-565
Date of Submission:	April 27, 2009
Applicant's Name:	Teva Pharmaceuticals USA
Established Name:	Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg, 75 mg, & 150 mg.
Proposed Proprietary Name:	None

Labeling Deficiencies

1. CONTAINER LABELS – 15s, 100s & 500s bottles for 37.5 mg, 75 mg, and 150 mg.

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

b. Please submit chemistry supporting data for your 15 count package size if you have not already done so.

2. PROFESSIONAL PACKAGE INSERT/MEDICATION GUIDE

General - You have not addressed the use code (U-398 treatment of GAD) associated with patent 6,444,708. Please clarify.

3. MEDICATION GUIDE

a. Please indicate in your labeling amendment how many patient information inserts will accompany each container size and how they will be presented.

b. Ensure that the medication guide that will be dispensed complies with 21 CFR 208.20.

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://service.govdelivery.com/service/subscribe.html?code=USFDA_17

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

FOR THE RECORD: (Portions taken from previous reviewer, Melaine Shin)

1. GENERAL

a. This is the **FIRST GENERIC** for Effexor XR 37.5 mg, 75 mg, and 150 mg capsules.

b. The original application was filed on December 10, 2002 for 150 mg strength capsules then the sponsor added 37.5 mg and 75 mg strengths on February 13, 2003.

2. MODEL LABELING

****The model RLD labeling used for this review is NDA 20-699/S-087 approved 1/30/2009.**

3. PATENT/EXCLUSIVITIES

Patent

Number	Expiration	Use Code	Description	Filed	Labeling Impact
4535186/*PED	12-13-07 / 6-13-08			III	Expired
5916923/*PED	6-28-13 / 12-28-13	U-398	Tx of GAD	MOU	carved out all reference to GAD
6274171/*PED	3-20-17 / 9-20-17		Tx of Depression	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	MOU	Carved out
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	MOU	Carved out
6444708/*PED	6-28-13 / 12-28-13	U-398		IV	See deficiency
6310101	6-28-13	U-46	Tx of Panic Disorder	MOU	Carved out

*The sponsor originally submitted patent certification IV for patents #6403120 (U-451) and #6419958(U-459). Both use codes are defined as Treatment of depression and generalized anxiety disorder (GAD) and since the sponsor challenged both patents, all reference to Treatment of depression and GAD should appear in their labeling. However, the sponsor provided "MOU" statement to patent #5916923, which has the use code U-398, Treatment of general anxiety disorder, and wishes to carve out all references to GAD.

This certification is not consistent and the regulatory support officer contacted the sponsor on January 10, 2003 to either file patent certification IV to all three patents ('120, '958 and '923) or provide both a patent certification IV and a "MOU" statement to the '923 patent.

In response to the regulatory support officer's request, the sponsor submitted a revised patent certification statement on January 17, 2003 with a claim that '120 & '958 were improperly assigned the use codes U-451 & U-459 which are both defined as "Treatment of depression & GAD". However in deference to the Division's request, they filed patent certification III regarding the use in the treatment of GAD and filed patent certification IV regarding the treatment of depression.

However, in their latest patent certification dated February 12, 2003, the sponsor changed the certification regarding the use in the treatment of GAD and filed MOU statements and wishes to carve out all the related wordings. This final certification appears to be acceptable.

*** Please note that since the last review, the RLD has added new use code "U-535" Tx of Social Anxiety Disorder to their two patents #6403120 & #6419958. TEVA certified "MOU" statement to both use codes and all wordings regarding SAD are removed from the labeling as well as GAD.

******The firm has submitted updated patent certification as of 4/27/2009, which is reflected in the chart above.**

Exclusivity

Exclusivity	Indication	Expiration Date	Labeling Impact
I-561	Long term treatment of Social Anxiety Disorder	December 14, 2010	Carve out SAD

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

TEVA Pharmaceutical Industries, Ltd.
Hashikma Street
Industrial Area
P.O. Box 353
Kfar-Saba 44102 ISRAEL

[Vol. 2.1. page 313]

5. INACTIVE INGREDIENTS

According to the "Components and Composition Statements", the list of inactive ingredients in the DESCRIPTION section appears to be accurate.

IRON content

The 37.5 mg capsule contains (b) (4) mg of Black Iron Oxide (b) (4). The daily consumption amount based on the dosing schedule is (b) (4) mg which is less than 5 mg/total daily dose, calculated as element iron [refer to 21 CRD 73.1200 (c)].

[Vol. 2.1. page 122-123]

6. PACKAGING CONFIGURATIONS

RLD – Bottle of 100 capsules & Carton of 10 Redipak blister strips of 10 capsules each.

ANDA – Bottles of 15s, 100s capsules & 500s capsules for 37.5 mg, 75 mg, and 150 mg.

7. DISPENSING/STORAGE TEMPERATURE STATEMENT COMPARISION

RLD: Store at controlled room temperature, 20C to 25 C (68F to 77F)
Bottles: Protect from light. Dispense in light-resistant container
Blisters: Protect from light. Use blister carton to protect contents from light.

ANDA: "Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]
Dispense in a tight , light-resistant container as defined in the USP, with a child-resistant closure as required"

8. CONTAINER/CLOSURE

	Component	
37.5 mg capsules	Container	Closure
100's configuration (b) (4)	(b) (4)	
100's configuration (b) (4)		
500's configuration (b) (4)		
75 mg capsules		
100's configuration (b) (4)	(b) (4)	
100's configuration (b) (4)		
500's configuration (b) (4)		
150 mg capsules		
100's configuration (b) (4)	(b) (4)	
100's configuration (b) (4)		
500's configuration		

[Vol. 1.1. page 4562 & Vol 2.3. page 827-828]

9. IMPRINTINGS:

Test	Specification
Description	(b) (4) [redacted]
Capsules Imprinting*	37.5 mg strength: Body: 93 7384 Cap: 93 7384 75 mg strength: Body: 93 7385 Cap: 93 7385 150 mg strength Body: 93 7386 Cap: 93 7386

The sponsor stated in the cover letter that the imprinting for the 150 mg capsules has been revised to "93" and "7386" in the How Supplied section, however, the package insert still states that it has "(b) (4)" and "(b) (4)" on the body of 150 mg capsule. I asked the sponsor to clarify and revise accordingly.

****The revision has been made to the labeling submitted on 2/7/2006 and is acceptable.**

10. Medication Guide

The sponsor has been requested to provide information on how the Medication Guides will be distributed.

Date of review: May 13, 2009 Date of submissions: April 27, 2009

Primary Reviewer: _____ Date: _____
Michelle Dillahunt

Team Leader: _____ Date:_____
Lillie Golson

Cc:
ANDA 76565:
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)

V:\FIRMSNZ\TEVA\LTRS&REV\76565na4. labeling.doc

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
5/18/2009 04:18:22 PM
LABELING REVIEWER

Lillie Golson
5/19/2009 11:30:36 AM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING #3
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-565

Date of Submissions: June 1, 2005 & February 7, 2006.

Applicant's Name: Teva Pharmaceutical USA.

Established Name: Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg, 75 mg, & 150 mg.

Proposed Proprietary Name: None

Labeling Deficiencies:

GENERAL

- Please provide us detailed information on how you plan to distribute the medication guides. Tell us how many guides you will provide with your bulk package and how you plan to ensure that they arrive at the pharmacy with your product. If you have submitted your plan already, please indicate which submission contains the information.

CONTAINER – 100s & 500s bottles for 37.5 mg, 75 mg, and 150 mg.

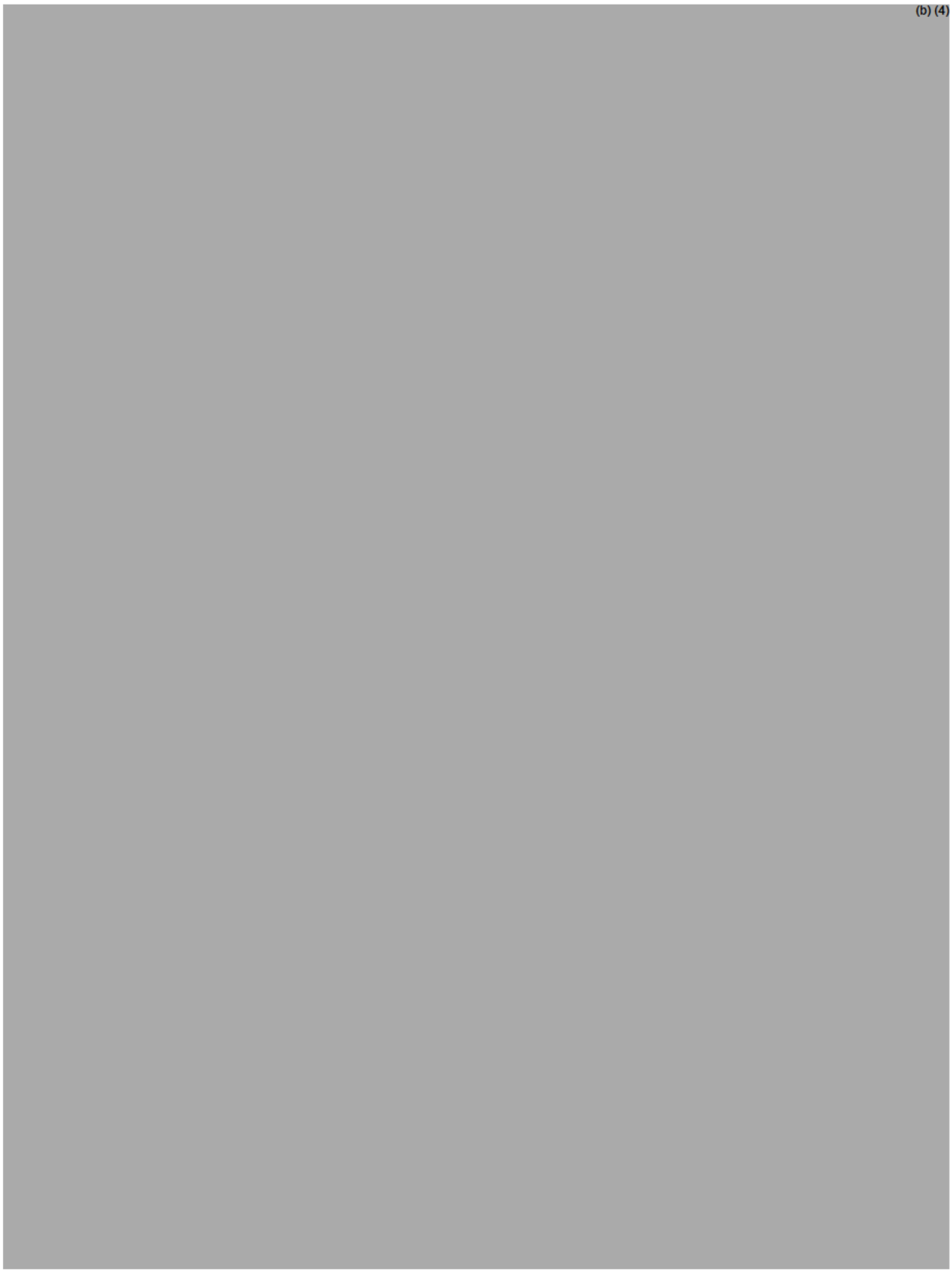
- Please submit your labels in final print in order to determine if the previous revision requests regarding the established name and strength appearing prominently on the labels and differentiating the strengths by using boxing, contrasting colors, and/or some other means have been made accordingly. Also, ensure that the "Attention: Dispense with Medication Guide" statement appears on the principal display panel.

PHYSICIAN INSERT/MEDICATION GUIDE

(b) (4)

[redacted]

(b) (4)



(b) (4)

Please revise your labeling as described above and submit electronically in final print. Although the immediate container labels and carton labeling may be submitted in hard copy, we ask that you submit it electronically for ease of review.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2aIG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32.

Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be submitted in PDF and MS Word until the SPL for the RLD is posted on the DailyMed website at http://dailymed.nlm.nih.gov/dailymed/about.cfm. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Koung Lee at 301-827-7336.

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.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

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 your last submission with all differences annotated and explained.

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

FOR THE RECORD:

1. GENERAL

   a. This is the **FIRST GENERIC** for Effexor XR 37.5 mg, 75 mg, and 150 mg capsules.

   b. The original application was filed on December 10, 2002 for 150 mg strength capsules then the sponsor added 37.5 mg and 75 mg strengths on February 13, 2003.

2. MODEL LABELING

   ****The model RLD labeling used for this review is NDA 20-699/S-056 approved 2/24/2006.**

   The first cycle review was based on the labeling for Effexor® XR, NDA 20-699/S-043 approved on September 2, 2003 for the physician insert and the patient package insert. However, since then the supplement S-052 was approved on May 13, 2004 for the physician insert and subsequent revisions were requested in the second NA review.

   In S-041, the RLD sponsor proposed changes in the patient package insert, however, the reviewing Division didn't agree with it and the sponsor agreed to its decision. Therefore, the approval of S-041 will not affect the current PPI and it is acceptable as submitted by the sponsor in this submission.

3. PATENT/EXCLUSIVITIES

   Patent

Number	Expiration	Use Code	Description	Filed	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 all reference to GAD
6274171/*PED	3-20-17 / 9-20-17		Tx of Depression	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	MOU	Carved out
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	MOU	Carved out
6444708/*PED	6-28-13 / 12-28-13			IV	None

*The sponsor originally submitted patent certification IV for patents #6403120 (U-451) and #6419958(U-459). Both use codes are defined as Treatment of depression and generalized anxiety disorder (GAD) and since the sponsor challenged both patents, all reference to Treatment of depression and GAD should appear in their labeling. However, the sponsor provided "MOU" statement to patent #5916923, which has the use code U-398, Treatment of general anxiety disorder, and wishes to carve out all references to GAD.

This certification is not consistent and the regulatory support officer contacted the sponsor on January 10, 2003 to either file patent certification IV to all three patents ('120, '958 and '923) or provide both a patent certification IV and a "MOU" statement to the '923 patent.

In response to the regulatory support officer's request, the sponsor submitted a revised patent certification statement on January 17, 2003 with a claim that '120 & '958 were improperly assigned the use codes U-451 & U-459 which are both defined as "Treatment of depression & GAD". However in deference to the Division's request, they filed patent certification III regarding the use in the treatment of GAD and filed patent certification IV regarding the treatment of depression.

However, in their latest patent certification dated February 12, 2003, the sponsor changed the certification regarding the use in the treatment of GAD and filed MOU statements and wishes to carve out all the related wordings. This final certification appears to be acceptable.

***** Please note that since the last review, the RLD has added new use code "U-535" Tx of Social Anxiety Disorder to their two patents #6403120 & #6419958. TEVA certified "MOU" statement to both use codes and all wordings regarding SAD will be removed from the labeling as well as GAD.**

Exclusivity

****Currently there are no unexpired exclusivity, however, the below information will be retained in this section for the record.**

Exclusivity	Indication	Expiration Date	Labeling Impact
I-325	Prevention of Relapse and Recurrence of Depression	May 2, 2004	None- will expire prior to patent expiration
I-325 PED		November 2, 2004	None
I-261	Treatment of Social Anxiety Disorder	February 11, 2006	None- will expire prior to patent expiration

The sponsor has been asked to update their exclusivity statement to include I-261, which now appears in the Orange Book, and to include wordings relate to Social Anxiety

Disorder since this exclusivity expires before this product becomes marketable, June 13, 2008.

Please note that this request has been obsolete since the introduction of use codes for SAD for two existing patents which both expire in year 2017 and the sponsor will carve out all wordings relate to SAD indication.

[Vol.5.1. page 391-393]

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

TEVA Pharmaceutical Industries, Ltd.
Hashikma Street
Industrial Area
P.O. Box 353
Kfar-Saba 44102 ISRAEL

[Vol. 2.1. page 313]

5. INACTIVE INGREDIENTS

According to the "Components and Composition Statements", the list of inactive ingredients in the DESCRIPTION section appears to be accurate.

IRON content

The 37.5 mg capsule contains (b) (4) mg of Black Iron Oxide in (b) (4) The daily consumption amount based on the dosing schedule is (b) (4) mg which is less than 5 mg/total daily dose, calculated as element iron [refer to 21 CRD 73.1200 (c)].

[Vol. 2.1. page 122-123]

6. PACKAGING CONFIGURATIONS

RLD – Bottle of 100 capsules & Carton of 10 Redipak blister strips of 10 capsules each.

ANDA – Bottles of 100 capsules & 500 capsules for 37.5 mg, 75 mg, and 150 mg.

7. DISPENSING/STORAGE TEMPERATURE STATEMENT COMPARISION

RLD: Store at controlled room temperature, 20C to 25 C (68F to 77F)
Bottles: Protect from light. Dispense in light-resistant container
Blisters: Protect from light. Use blister carton to protect contents from light.

ANDA: "Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]
Dispense in a tight , light-resistant container as defined in the USP, with a child-resistant closure as required"

8. CONTAINER/CLOSURE

	Component	
37.5 mg capsules	Container	Closure
100's configuration (b) (4)	(b) (4)	
100's configuration (b) (4)		
500's configuration (b) (4)		
75 mg capsules		
100's configuration (b) (4)	(b) (4)	
100's configuration (b) (4)		
500's configuration (b) (4) (b) (4)		
150 mg capsules		
100's configuration (b) (4)	(b) (4)	
100's configuration (b) (4)		
500's configuration		

[Vol. 1.1. page 4562 & Vol 2.3. page 827-828]

9. IMPRINTINGS:

The sponsor stated in the cover letter that the imprinting for the 150 mg capsules has been revised to "93" and "7386" in the How Supplied section, however, the package insert still states that it has "(b) (4)" and "(b) (4)" on the body of 150 mg capsule. I asked the sponsor to clarify and revise accordingly.

****The revision has been made to the labeling submitted on 2/7/2006 and is acceptable.**

Date of review: March 17, 2006 Date of submissions: February 7, 2006

Primary Reviewer: Melaine Shin Date: 3/27/06

Team Leader: Lillie Golson Date: 3/27/06

Cc:
ANDA 76565:
DUP/DIVISION FILE
HFD-613/Mshin/LGolson (no cc)
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Review

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

ANDA Number: 76-565

Date of Submissions: April 1, 2004.

Applicant's Name: Teva Pharmaceutical USA.

Established Name: Venlafaxine Hydrochloride Extended-Release Capsules,
37.5 mg, 75 mg, & 150 mg.

Proposed Proprietary Name: None

Labeling Deficiencies:

CONTAINER – 100 & 500 bottles for 37.5 mg, 75 mg, and 150 mg.

- Please submit your labels in final print so that I can determine if the previous revisions regarding the established name and strength appearing prominently on the labels and differentiating the strengths by using boxing, contrasting colors, and/or some other means have been made accordingly.

PHYSICIAN INSERT:

(b) (4)

(b) (4)

5. PATIENT PACKAGE INSERT

- Satisfactory in draft.

Please revise your labels and labeling, as instructed above and submit in final. Please note that the electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the guidance for industry regarding electronic submissions (Providing Regulatory Submissions in Electronic Format - ANDAs, issued 6/2002) available at the following website:

http://www.fda.gov/cder/guidance/5004fnl.htm.

Although the guidance specifies labeling to be submitted in PDF format, we request that labeling also be submitted in MS Word format to assist our review."

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labels with your last submission with all differences annotated and explained.

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

FOR THE RECORD:

1. GENERAL

a. This is the **FIRST GENERIC** for Effexor XR 37.5 mg, 75 mg, and 150 mg capsules.

b. The original application was filed on December 10, 2002 for 150 mg strength capsules then the sponsor added 37.5 mg and 75 mg strengths on February 13, 2003.

2. MODEL LABELING

The first cycle review was based on the labeling for Effexor® XR, NDA 20-699/S-043 approved on September 2, 2003 for the physician insert and the patient package insert. However, since then the supplement S-052 was approved on May 13, 2004 for the physician insert and subsequent revisions were requested in the second NA review.

In S-041, the RLD sponsor proposed changes in the patient package insert, however, the reviewing Division didn't agree with it and the sponsor agreed to its decision. Therefore, the approval of S-041 will not affect the current PPI and it is acceptable as submitted by the sponsor in this submission.

3. PATENT/EXCLUSIVITIES

Patent

Number	Expiration	Use Code	Description	Filed	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 all wording reference to GAD
6274171/*PED	3-20-17 / 9-20-17		Tx of Depression	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	MOU ✓	Carved out
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	MOU ✓	Carved out
6444708/*PED	6-28-13 / 12-28-13			IV ✓	None

*The sponsor originally submitted patent certification IV for patents #6403120 (U-451) and #6419958(U-459). Both use codes are defined as Treatment of depression and

generalized anxiety disorder (GAD) and since the sponsor challenged both patents, all reference to Treatment of depression and GAD should appear in their labeling. However, the sponsor provided "MOU" statement to patent #5916923, which has the use code U-398, Treatment of general anxiety disorder, and wishes to carve out all references to GAD.

This certification is not consistent and the regulatory support officer contacted the sponsor on January 10, 2003 to either file patent certification IV to all three patents ('120, '958 and '923) or provide both a patent certification IV and a "MOU" statement to the '923 patent.

In response to the regulatory support officer's request, the sponsor submitted a revised patent certification statement on January 17, 2003 with a claim that '120 & '958 were improperly assigned the use codes U-451 & U-459 which are both defined as "Treatment of depression & GAD". However in deference to the Division's request, they filed patent certification III regarding the use in the treatment of GAD and filed patent certification IV regarding the treatment of depression.

However, in their latest patent certification dated February 12, 2003, the sponsor changed the certification regarding the use in the treatment of GAD and filed MOU statements and wishes to carve out all the related wordings. This final certification appears to be acceptable.

***** Please note that since the last review, the RLD has added new use code "U-535" Tx of Social Anxiety Disorder to their two patents #6403120 & #6419958. TEVA certified "MOU" statement to both use codes and all wordings regarding SAD will be removed from the labeling as well as GAD.**

Exclusivity

Exclusivity	Indication	Expiration Date	Labeling Impact
I-325	Prevention of Relapse and Recurrence of Depression	May 2, 2004	None- will expire prior to patent expiration
I-325 PED		November 2, 2004	None
I-261	Treatment of Social Anxiety Disorder	February 11, 2006	None- will expire prior to patent expiration

The sponsor has been asked to update their exclusivity statement to include I-261, which now appears in the Orange Book, and to include wordings relate to Social Anxiety Disorder since this exclusivity expires before this product becomes marketable, June 13, 2008.

Please note that this request has been obsolete since the introduction of use codes for SAD for two existing patents which both expire in year 2017 and the sponsor will carve out all wordings relate to SAD indication.

[Vol.5.1. page 391-393]

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

TEVA Pharmaceutical Industries, Ltd.
Hashikma Street
Industrial Area
P.O. Box 353
Kfar-Saba 44102 ISRAEL

[Vol. 2.1. page 313]

5. INACTIVE INGREDIENTS

According to the "Components and Composition Statements", the list of inactive ingredients in the DESCRIPTION section appears to be accurate.

IRON content

The 37.5 mg capsule contains (b) (4) mg of Black Iron Oxide (b) (4) The daily consumption amount based on the dosing schedule is (b) (4) mg which is less than 5 mg/total daily dose, calculated as element iron [refer to 21 CRD 73.1200 (c)].

[Vol. 2.1. page 122-123]

6. PACKAGING CONFIGURATIONS

RLD – Bottle of 100 capsules & Carton of 10 Redipak blister strips of 10 capsules each.

ANDA – Bottles of 100 capsules & 500 capsules for 37.5 mg, 75 mg, and 150 mg.

500 capsule bottle size has never been approved, but it seems acceptable.

7. DISPENSING/STORAGE TEMPERATURE STATEMENT COMPARISION

RLD: Store at controlled room temperature, 20C to 25 C (68F to 77F)
Bottles: Protect from light. Dispense in light-resistant container
Blisters: Protect from light. Use blister carton to protect contents from light.

ANDA: "Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]
Dispense in a tight , light-resistant container as defined in the USP, with a child-resistant closure as required"

8. CONTAINER/CLOSURE

37.5 mg capsules	Component	
	Container	Closure
100's configuration (b) (4)	(b) (4)	

100's configuration (b) (4)	(b) (4)
500's configuration (b) (4)	
75 mg capsules	
100's configuration (b) (4)	(b) (4)
100's configuration (b) (4)	
500's configuration (b) (4)	
150 mg capsules	
100's configuration (b) (4)	(b) (4)
100's configuration (b) (4)	
500's configuration	

[Vol. 1.1. page 4562 & Vol 2.3. page 827-828]

9. IMPRINTINGS:

The sponsor stated in the cover letter that the imprinting for the 150 mg capsules has been revised to "93" and "7386" in the How Supplied section, however, the package insert still states that it has " (b) (4) and " (b) (4) on the body of 150 mg capsule. I asked the sponsor to clarify and revise accordingly.

Date of review: Septebmer 8, 2004 Date of submissions: April 1, 2004

Primary Reviewer: Melaine Shin Date: 9-8-04

Team Leader: Lillie Golson Date: 9/8/04

Cc:

ANDA:
DUP/DIVISION FILE
HFD-613/Mshin/LGolson (no cc)
V:\FRIMSNZ\TEVA\ltrs&rev\76565 NA2.Labeling.doc
Review

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

ANDA Number: 76-565

Date of Submissions: December 10, 2002, February 13, 2003, and, & April 1, 2003.

Applicant's Name: Teva Pharmaceutical Ind. Ltd.

Established Name: Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg, 75 mg, & 150 mg.

Proposed Proprietary Name: None

Labeling Deficiencies:

1. GENERAL

   a. Please note that there is a "Patient Information Sheet" available for the reference listed drug, Effexor XR, and it should be a part of the generic labeling as well. You may use the attached text as a model. Please include a statement "Pharmacist: Patient Information Sheet enclosed" or something similar on the container label.

   b. We note that you filed "Change of company name" on December 31, 2002. Please update your labeling accordingly.

   c. Effexor XR now has a new exclusivity for the treatment of social anxiety disorder (I-261) which expires on February 11, 2006. Please submit an updated exclusivity statement to reflect the change and revise your labeling to include wording regarding social anxiety disorder as provided below.

   d. Revise the storage temperature recommendation as follows:

      "Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature] Dispense in a tight , light-resistant container as defined in the USP, with a child-resistant closure as required"

   e. Please note that this product would not be eligible for marketing with the Major Depressive Disorder indication until June 13, 2008 when the patent #4535186 expires and the General Anxiety Disorder indication until September 20, 2017 when the patent #6419958 expires.

2. CONTAINER – 100 & 500 bottles for 37.5 mg, 75 mg, and 150 mg.

a. See comments (a) and (d) under GENERAL.

b. Please ensure that the established name and strength appear prominently on the labels.

c. Since your drug product is available in multiple strength, we strongly encourage you to differentiate the strengths by using boxing, contrasting colors, and/or some other means.

3. PHYSICIAN INSERT:

*Deletions are marked with cross outs and additions with underlines.

(b) (4)

[redacted]

9 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (DRAFT LABELING) IMMEDIATELY FOLLOWING THIS PAGE

4. PATIENT PACKAGE INSERT

Please follow the attached Patient Information sheet for Effexor XR as a model.

Please revise your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labels with your last submission with all differences annotated and explained.

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Patient Information sheet for Effexor XR

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	

Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label). (See comment under CONTAINER)		x	
Has applicant failed to clearly differentiate multiple product strengths? (See comment under CONTAINER)	x		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x

Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			x
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	x		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) [redacted] (b) (4) **requested a waiver of the in-vivo bioavailability requirement and is under review)**			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	x		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

FOR THE RECORD:

1. GENERAL

   a. This is the **FIRST GENERIC** for Effexor XR 37.5 mg, 75 mg, and 150 mg capsules.

   b. The original application was filed on December 10, 2002 for 150 mg strength capsules then the sponsor added 37.5 mg and 75 mg strengths on February 13, 2003.

   c. The sponsor filed "Change of company name" on December 31, 2002. The new company name is to be "Assia Chemical Industries Ltd". I asked the sponsor to update the labeling accordingly. [Vol. 2.1]

d. The following storage temperature recommendation was made:

"Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature] Dispense in a tight , light-resistant container as defined in the USP, with a child-resistant closure as required"

2. MODEL LABELING

This review was based on the labeling for Effexor® XR, NDA 20-699/S-043 approved on September 2, 2003 for the physician insert and the patient package insert. I've attached the patient package insert to be used as a model since the firm didn't include it in their submission.

3. PATENT/EXCLUSIVITIES

Patent

Number	Expiration	Use Code	Description	Filed	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 all wording reference to GAD
6274171/*PED	3-20-17 / 9-20-17		Tx of Depression	IV	None
6403120/*PED	3-20-17 / 9-20-17	U-451	Tx of Depression	IV	None
			Tx of GAD	MOU	Carved out
6419958/*PED	3-20-17 / 9-20-17	U-459	Tx of Depression	IV	None
			Tx of GAD	MOU	Carved out
6444708/*PED	6-28-13 / 12-28-13			IV	None

*The sponsor originally submitted patent certification IV for patents #6403120 (U-451) and #6419958(U-459). Both use codes are defined as Treatment of depression and generalized anxiety disorder (GAD) and since the sponsor challenged both patents, all reference to Treatment of depression and GAD should appear in their labeling. However, the sponsor provided "MOU" statement to patent #5916923, which has the use code U-398, Treatment of general anxiety disorder, and wishes to carve out all references to GAD.

This certification is not consistent and the regulatory support officer contacted the sponsor on January 10, 2003 to either file patent certification IV to all three patents ('120, '958 and '923) or provide both a patent certification IV and a "MOU" statement to the '923 patent.

In response to the regulatory support officer's request, the sponsor submitted a revised patent certification statement on January 17, 2003 with a claim that '120 & '958 were improperly assigned the use codes U-451 & U-459 which are both defined as "Treatment of depression & GAD". However in deference to the Division's request, they filed patent

certification III regarding the use in the treatment of GAD and filed patent certification IV regarding the treatment of depression.

However, in their latest patent certification dated February 12, 2003, the sponsor changed the certification regarding the use in the treatment of GAD and filed MOU statements and wishes to carve out all the related wordings. This final certification appears to be acceptable.

Exclusivity

Exclusivity	Indication	Expiration Date	Labeling Impact
I-251	Treatment of Generalized Anxiety Disorder	March 11, 2002	None- expired
I-325	Prevention of Relapse and Recurrence of Depression	May 2, 2004	None- will expire prior to patent expiration
I-325 PED		November 2, 2004	None
I-261	Treatment of Social Anxiety Disorder	February 11, 2006	None- will expire prior to patent expiration

The sponsor has been asked to update their exclusivity statement to include I-261, which now appears in the Orange Book, and to include wordings relate to Social Anxiety Disorder since this exclusivity expires before this product becomes marketable, June 13, 2008.
[Vol.2.1. page 10]

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

TEVA Pharmaceutical Industries, Ltd.
Hashikma Street
Industrial Area
P.O. Box 353
Kfar-Saba 44102 ISRAEL

[Vol. 2.1. page 313]

5. INACTIVE INGREDIENTS

According to the "Components and Composition Statements", the list of inactive ingredients in the DESCRIPTION section appears to be accurate.

IRON content

The 37.5 mg capsule contains (b) (4) mg of Black Iron Oxide (b) (4) The daily consumption amount based on the dosing schedule is (b) (4) mg which is less than 5 mg/total daily dose, calculated as element iron [refer to 21 CRD 73.1200 (c)].

[Vol. 2.1. page 122-123]

6. PACKAGING CONFIGURATIONS

RLD – Bottle of 100 capsules & Carton of 10 Redipak blister strips of 10 capsules each.

ANDA – Bottles of 100 capsules & 500 capsules

500 capsule bottle size has never been approved, but it seems acceptable.

7. DISPENSING/STORAGE TEMPERATURE STATEMENT COMPARISION

RLD: Store at controlled room temperature, 20C to 25 C (68F to 77F)
Bottles: Protect from light. Dispense in light-resistant container
Blisters: Protect from light. Use blister carton to protect contents from light.

ANDA: (b) (4)

The following was recommended:

"Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature] Dispense in a tight , light-resistant container as defined in the USP, with a child-resistant closure as required"

8. CONTAINER/CLOSURE

	Component	
37.5 mg capsules	Container	Closure
100's configuration (b) (4)	(b) (4)	
100's configuration (b) (4)		
500's configuration (b) (4)		
75 mg capsules		
100's configuration (b) (4)	(b) (4)	
100's configuration (b) (4)		
500's configuration (b) (4) (b) (4)		

150 mg capsules		
100's configuration (b) (4)		(b) (4)
100's configuration (b) (4)		
500's configuration		

[Vol. 1.1. page 4562 & Vol 2.3. page 827-828]

Date of review: October 20, 2003 Date of submissions:

Primary Reviewer: Melaine Shin Date: 11-14-03

Team Leader: Lillie Golson Date: 11/14/03

Cc:

ANDA:
DUP/DIVISION FILE
HFD-613/Mshin/LGolson (no cc)
V:\FRIMSNZ\TEVA\ltrs&rev\76565 NA1.Labeling.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076565

CHEMISTRY REVIEWS

ANDA 76-565

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

Teva Pharmaceuticals, USA

Naiqi Ya, Ph.D. (Review #1 and 2)
and H. Ashley Jung, Pharm.D., Ph.D. (Review #3, #4, #5, #6)
Office of Generic Drugs/Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-565

2. REVIEW #: 6

3. REVIEW DATE: May 28, 2010; 6/10/10; 6/14/10; 6/17/10

4. REVIEWER: Naiqi Ya, Ph.D. (Review #1 and #2)
H. Ashley Jung, Pharm.D., Ph.D. (Review #3, #4, #5, #6)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	December 10, 2002
New Correspondence	January 17, 2003
Unsolicited Amendment	February 13, 2003
Telephone Amendment	March 19, 2003
Minor Amendment	April 1, 2004
Minor Amendment	June 1, 2005
Telephone Amendment	July 6, 2006
Telephone Amendment	December 22, 2005
Telephone Amendment	August 14, 2006
Major Amendment	August 19, 2008
Unsolicited Amendment	January 28, 2009
Major Amendment	September 24, 2009
Samples submitted	September 28, 2009

FDA Correspondences	Document Date
Review #1 (NA Minor)	May 22, 2003
Review #2 (NA Minor)	August 23, 2004
T-con: DS and DP Specifications	December 22, 2005
T-con: DMF Deficiency	May 25, 2006
T-con: In-process & requested samples	June 26, 2006
Fax: In-process Controls	July 24, 2006
Review #3 (NA Major)	September 25, 2006
Review #4 (NA Major)	June 11, 2009
Review #5 (NA Major)	May 11, 2010
Telephone deficiency	**6/10/10**
Telephone deficiency	**6/14/10**

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Major Amendment converted to Telephone Amendment for expedited review	May 17, 2010
Samples submitted	May 19, 2010
Telephone Amendment	June 7, 2010
Telephone Amendment	June 11, 2010
Telephone Amendment	June 15, 2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Pharmaceuticals USA
Address:	1090 Horsham Road PO Box 1090 North Wales, PA 19454
Representative:	Philips Erickson
Telephone:	215-591-3141
Fax:	215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Venlafaxine Hydrochloride Extended Release Capsules

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Effexor® XR Capsules 150mg, held by Wyeth Ayerst, NDA 20-699.
There are six listed patents which claim the reference listed drug Effexor® XR Capsules.

Patent No.	Expiration Dates	Pediatric Exclusivity	Use Code
4,535,186	12/13/07	6/13/08	
6,444,708	6/28/13	12/28/13	
5,916,923	6/28/13	12/28/13	U-398
6,274,171	3/20/17	9/20/17	
6,403,120	3/20/17	9/20/17	U-451
6,419,958	3/20/17	9/20/17	U-459

Teva filed Paragraph IV certification for U.S. Patents 6,444,708, 6,274,171, 6,403,120, and 6,419,958. Teva also filed Paragraph III Certification for U.S. Patents 4,535,186 and its associated pediatric exclusivity.

The wording related to the MOU patents 5,916,923, 6,403,120 and 6,419,958 will not be included in the product labeling until the expiration of the respective patent and its associated exclusivity or the patens are invalidated or the use code is changed.

Updated Patent Certification is provided in the Unsolicited Amendment submitted on 2/13/03.

Exclusivity Statement (pp. 11, 2/13/03 Amendment):

Exclusivity	Indication	Expiration Date
I-251	Treatment of Generalized Anxiety Disorder	3/11/02
I-325	Prevention of Relapse and Recurrence of Depression	5/2/04
I-325 (PED)		11/2/04

The I-251 has expired. Teva does not intend to commercially market this product prior to the expiration of I-325 and its associated pediatric exclusivity on 11/2/04.

10. PHARMACOL. CATEGORY:
Anti-depressant

11. DOSAGE FORM:
Extended Release Capsules

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

13. ROUTE OF ADMINISTRATION:
Oral Administration

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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

_____SPOTS product – Form Completed

__X___Not a SPOTS product

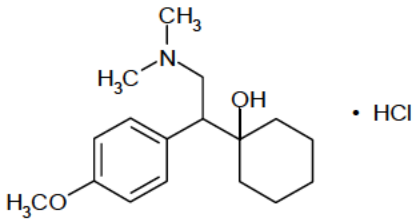
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name:

1. (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride
2. (±)-1-[α- [(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride
3. N,N-Dimethyl-2-(1-hydroxycyclohexyl)-2-(4-ethoxyphenyl) ethylamine hydrochloride

CAS 99300-78-4

Venlafaxine Hydrochloride has the empirical formula of $C_{17}H_{27}NO_2$•HCl. Its molecular weight is 313.87. The structural formula is shown below.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
16281	II	Teva-Tech Ltd.	Venlafaxine Hydrochloride	3	Adequate	2/12/09	**IR'sent on 4/23/10 & 6/14/10- NAI'ed**
				(b) (4)			
							Added in 1/28/09 amend
							Added in 1/28/09 amend
							Added in 1/28/09 amend
							Added in 1/28/09 amend

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]				(b) (4)			Added in 8/19/08 amend

[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
N/A		

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending	4/28/10	Per OC
Methods Validation	Not required		
Labeling	Approval	4/13/10	Charles Hoppes
Bioequivalence	Acceptable	1/22/10	Svetlana Cherstniakova
EA	N/A		
Radiopharmaceutical	N/A		

Labeling: See Section 32. On 3/30/09, Michelle Dillahunt, the labeling reviewer, asked the firm to submit an updated labeling since the last labeling was submitted in 2006. Since 2006 there has been many labeling revisions to the RLD.
EES: See Section 33.
DBE: See Section 34.
Samples: Firm sent samples per faxed amendment dated 7/6/06. The firm noted that the samples (Batch No. K-30703 manufactured 11/5/02, K-30702 manufactured 11/5/02, and K-30455 manufactured 8/27/02) have expired. Firm will be asked to send additional samples in the next amendment.

Comment per Review #4: Please provide us samples for your batches submitted in your amendments dated 8/19/08 and 1/28/09.

Response (9/24/09): Please note that samples of the Kfar Saba batches as submitted in Teva's August 19, 2008 amendment have been forwarded under separate cover to Tom Hinchliffe of the Office of Generic Drugs.

Evaluation: The firm sent the following requested samples on 9/28/09:

Site of Manufacture	Batch No. (strength)	Date of Manufacture	Date Submitted
Kfar Saba	K-37681 (37.5 mg) K-37682 (75 mg) K-37683 (150 mg)	February 21, 2007	8/19/08 Major Amendment

Teva has requested (b) (4) **facility that were submitted in the** (b) (4) **amendment are not included in this correspondence.**

The conditions of the capsules is satisfactory with clear, legible imprints. The capsule appearance (outside of the capsules) is pharmaceutically elegant. The capsules contain small, generally-spherical beads varying somewhat in sizes. However, such variability in size is typical of beads made of sugar spheres. There are not many fines but a few beads in each capsule appear broken.

In their amendment dated 5/19/10, the firm provided additional samples of new batches:

Site of Manufacture	Batch No. (strength)	Date of Manufacture	Date Submitted
Kfar Saba	W17003 (37.5 mg) W24010 (75 mg) W26004 (150 mg)	2/8/10 1/24/10 1/3/10	5/19/10

The sample condition is similar to the original. The capsule sizes are updated for the 37.5 mg strength and the 150 mg strength (see review for details). Some capsules contain a small number of fines or broken beads. See under "Stability" for more discussion on the samples.

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 76-565

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval is recommended per CMC.

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

Per telephone amendment dated 6/15/10, due to concern regarding the firm's ability to consistently meet L1 dissolution testing, the firm committed to submit a CBE-0 containing a summary of all dissolution data accrued for the validations batches when 12 month CRT stability testing is complete.

II. Summary of Chemistry Assessments

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

Venlafaxine Hydrochloride, a structurally novel antidepressant, is chemically unrelated to tricyclic, tetracyclic, and other available antidepressants. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[(alpha)- [(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride. Venlafaxine Hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/mL (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 will be manufactured by Teva API Division in Netanya and Be'er Sheva, Israel. For future commercial production, each lot of Venlafaxine Hydrochloride received at Teva Kfar Saba will be tested for identification only and will be released as per Teva-Tech's CoA. Teva Kfar Saba will perform full monograph testing on a (b) (4) basis.

Venlafaxine Hydrochloride Extended Release Capsules is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion of Venlafaxine Hydrochloride through the coating membrane on the spheroids and is not pH dependent. Capsules contain Venlafaxine Hydrochloride equivalent to 37.5 mg, 75 mg, and 150 mg Venlafaxine. Inactive ingredients consist of antifoam DC1510, Black Iron Oxide, Dibutyl Sebacate, Ethylcellulose, Gelatin, Polyethylene Glycol, Povidone, Shellac, Soya Lecithin MC thin, Sugar Spheres, Sunset Yellow FCF FD&C Yellow 6, Talc, and Titanium Dioxide. The 37.5 mg and 75 mg capsules also contain D&C Yellow 10.

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

Venlafaxine Extended Release capsules are indicated for the treatment of depression.

Venlafaxine Hydrochloride extended-release capsules should be administered in a single dose with food. Each capsule should be swallowed whole with fluid and not divided, crushed, chewed, or placed in water. For most patients, the recommended starting dose is 75 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. The maximum recommended dose for moderately depressed outpatients is 225 mg/day.

C. Basis for Approvability or Not-Approval Recommendation

Approval is recommended per CMC. At the time of submission, there was a lack of clear understanding of in-process controls. One example of that was the use of capsule size that was too small. Some of the demonstration batches did not pass dissolution at L1 stage during stability testing. The firm also proposed to add an alternate manufacturing site. However, the batches did not pass the bioequivalence study, and the firm withdrew the site. Through subsequent studies the firm was able to demonstrate that they are able to manufacture their product consistently at the commercial scale. Pending EES.

cc: ANDA 76-565
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/HAJung/6/17/10
HFD-640/NYa/6/18/10
HFD-617/THinchliffe/6/18/10

F/T by: TOH/

File: 76565rev06.doc

TYPE OF LETTER: Approvable; Pending OC

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-76565	ORIG-1	TEVA PHARMACEUTICALS USA INC	VENLAFAXINE HYDROCHLORIDE

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

/s/

HUIJEONG A JUNG
06/18/2010

NAIQI YA
06/18/2010

DAT T DOAN on behalf of THOMAS O HINCHLIFFE
06/22/2010

ANDA 76-565

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

Teva Pharmaceuticals, USA

Naiqi Ya, Ph.D. (Review #1 and 2)
and H. Ashley Jung, Pharm.D., Ph.D. (Review #3, #4, #5)
Office of Generic Drugs/Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-565

2. REVIEW #: 5

3. REVIEW DATE: April 23, 2010

4. REVIEWER: Naiqi Ya, Ph.D. (Review #1 and #2)
H. Ashley Jung (Review #3, #4, and #5)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	December 10, 2002
New Correspondence	January 17, 2003
Unsolicited Amendment	February 13, 2003
Telephone Amendment	March 19, 2003
Minor Amendment	April 1, 2004
Minor Amendment	June 1, 2005
Telephone Amendment	July 6, 2006
Telephone Amendment	December 22, 2005
Telephone Amendment	August 14, 2006
Major Amendment	August 19, 2008
Unsolicited Amendment	January 28, 2009

FDA Correspondences	Document Date
Review #1 (NA Minor)	May 22, 2003
Review #2 (NA Minor)	August 23, 2004
T-con: DS and DP Specifications	December 22, 2005
T-con: DMF Deficiency	May 25, 2006
T-con: In-process & requested samples	June 26, 2006
Fax: In-process Controls	July 24, 2006
Review #3 (NA Major)	September 25, 2006
Review #4 (NA Major)	June 11, 2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Major Amendment	**September 24, 2009**

Samples submitted **September 28, 2009**

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Pharmaceuticals USA
Address:	1090 Horsham Road
	PO Box 1090
	North Wales, PA 19454
Representative:	Philips Erickson
Telephone:	215-591-3141
Fax:	215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Venlafaxine Hydrochloride Extended Release Capsules

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Effexor® XR Capsules 150mg, held by Wyeth Ayerst, NDA 20-699.
There are six listed patents which claim the reference listed drug Effexor® XR Capsules.

Patent No.	Expiration Dates	Pediatric Exclusivity	Use Code
4,535,186	12/13/07	6/13/08	
6,444,708	6/28/13	12/28/13	
5,916,923	6/28/13	12/28/13	U-398
6,274,171	3/20/17	9/20/17	
6,403,120	3/20/17	9/20/17	U-451
6,419,958	3/20/17	9/20/17	U-459

Teva filed Paragraph IV certification for U.S. Patents 6,444,708, 6,274,171, 6,403,120, and 6,419,958. Teva also filed Paragraph III Certification for U.S. Patents 4,535,186 and its associated pediatric exclusivity.

The wording related to the MOU patents 5,916,923, 6,403,120 and 6,419,958 will not be included in the product labeling until the expiration of the respective patent and its associated exclusivity or the patens are invalidated or the use code is changed.

Updated Patent Certification is provided in the Unsolicited Amendment submitted on 2/13/03.

Exclusivity Statement (pp. 11, 2/13/03 Amendment):

Exclusivity	Indication	Expiration Date
I-251	Treatment of Generalized Anxiety Disorder	3/11/02

I-325	Prevention of Relapse and Recurrence of Depression	5/2/04
I-325 (PED)		11/2/04

The I-251 has expired. Teva does not intend to commercially market this product prior to the expiration of I-325 and its associated pediatric exclusivity on 11/2/04.

10. PHARMACOL. CATEGORY:
Anti-depressant

11. DOSAGE FORM:
Extended Release Capsules

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

13. ROUTE OF ADMINISTRATION:
Oral Administration

14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

_____SPOTS product – Form Completed

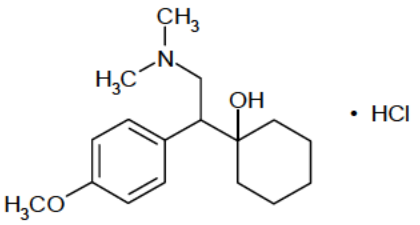
__X___Not a SPOTS product

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

Chemical Name:
1. (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride
2. (±)-1-[α- [(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride
3. N,N-Dimethyl-2-(1-hydroxycyclohexyl)-2-(4-ethoxyphenyl) ethylamine hydrochloride

CAS 99300-78-4

Venlafaxine Hydrochloride has the empirical formula of $C_{17}H_{27}NO_2$•HCl. Its molecular weight is 313.87. The structural formula is shown below.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
16281	II	Teva-Tech Ltd.	Venlafaxine Hydrochloride	3	Adequate	2/12/09	Reviewed by Julia Pinto; **IR sent on 4/23/10**
[redacted]				(b) (4)			
							Added in 1/28/09 amend
							Added in 1/28/09 amend
							Added in 1/28/09 amend
							Added in 1/28/09 amend
							Added in 8/19/08 amend

[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
N/A		

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending	2/26/09	Per OC
Methods Validation	Not required		
Labeling	Approval	4/13/10	Charles Hoppes
Bioequivalence	Acceptable	1/22/10	Svetlana Cherstniakova
EA	N/A		
Radiopharmaceutical	N/A		

Labeling: See Section 32. On 3/30/09, Michelle Dillahunt, the labeling reviewer, asked the firm to submit an updated labeling since the last labeling was submitted in 2006. Since 2006 there has been many labeling revisions to the RLD.
EES: See Section 33.
DBE: See Section 34.
Samples: Firm sent samples per faxed amendment dated 7/6/06. The firm noted that the samples (Batch No. K-30703 manufactured 11/5/02, K-30702 manufactured 11/5/02, and K-30455 manufactured 8/27/02) have expired. Firm will be asked to send additional samples in the next amendment.

Comment per Review #4: Please provide us samples for your batches submitted in your amendments dated 8/19/08 and 1/28/09.

Response (9/24/09): Please note that samples of the Kfar Saba batches as submitted in Teva's August 19, 2008 amendment have been forwarded under separate cover to Tom Hinchliffe of the Office of Generic Drugs.

Evaluation: The firm sent the following requested samples on 9/28/09:

Site of Manufacture	Batch No. (strength)	Date of Manufacture	Date Submitted
Kfar Saba	K-37681 (37.5 mg) K-37682 (75 mg)	February 21, 2007	8/19/08 Major Amendment

	K-37683 (150 mg)		

Teva has requested [redacted] **that were submitted in the** [redacted] **amendment are not included in this correspondence.**

The conditions of the capsules is satisfactory with clear, legible imprints. The capsule appearance (outside of the capsules) is pharmaceutically elegant. The capsules contain small, generally-spherical beads varying somewhat in sizes. However, such variability in size is typical of beads made of sugar spheres. There are no fines but a few beads in each capsule appear broken. See under "Stability for more discussion on the samples."

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 76-565

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Unapprovable (Major) is recommended because of issues relating to process controls and drug product controls. The firm is asked to manufacture a commercial batch to demonstrate consistent manufacturability even at scale up. Product did not meet dissolution at L1 for some of the stability testing and there are changes in capsule sizes for the 37.5 mg and 150 mg strengths which need to be adequately addressed.

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

N/A

II. Summary of Chemistry Assessments

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

Venlafaxine Hydrochloride, a structurally novel antidepressant, is chemically unrelated to tricyclic, tetracyclic, and other available antidepressants. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[(alpha)- [(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride. Venlafaxine Hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/mL (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 will be manufactured by Teva API Division in Netanya and Be'er Sheva, Israel. For future commercial production, each lot of Venlafaxine Hydrochloride received at Teva Kfar Saba will be tested for identification only and will be released as per Teva-Tech's CoA. Teva Kfar Saba will perform full monograph testing on a (b) (4) basis.

Venlafaxine Hydrochloride Extended Release Capsules is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion of Venlafaxine Hydrochloride through the coating membrane on the spheroids and is not pH dependent. Capsules contain Venlafaxine Hydrochloride equivalent to 37.5 mg, 75 mg, and 150 mg Venlafaxine. Inactive ingredients consist of antifoam DC1510, Black Iron Oxide, Dibutyl Sebacate, Ethylcellulose, Gelatin, Polyethylene Glycol, Povidone, Shellac, Soya Lecithin MC thin, Sugar Spheres, Sunset Yellow FCF FD&C Yellow 6, Talc, and Titanium Dioxide. The 37.5 mg and 75 mg capsules also contain D&C Yellow 10.

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

Venlafaxine Extended Release capsules are indicated for the treatment of depression. Venlafaxine Hydrochloride extended-release capsules should be administered in a single dose with food. Each capsule should be swallowed whole with fluid and not divided, crushed, chewed, or placed in water. For most patients, the recommended starting dose is 75 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. The maximum recommended dose for moderately depressed outpatients is 225 mg/day.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not recommended for approval because the firm's in-process controls are inadequate.

cc: ANDA 76-565
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/HAJung/4/23/10
HFD-640/NYa/5/10/10
HFD-617/THinchliffe/5/11/10

F/T by: TOH/

File: 76565rev05.doc

TYPE OF LETTER: Not Approvable; MAJOR

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-76565	ORIG-1	TEVA PHARMACEUTICALS USA INC	VENLAFAXINE HYDROCHLORIDE

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

/s/

HUIJEONG A JUNG
05/11/2010

THOMAS O HINCHLIFFE
05/11/2010

NAIQI YA
05/11/2010

ANDA 76-565

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

Teva Pharmaceuticals, USA

Naiqi Ya, Ph.D. (Review #1 and 2)
and Huijeong Ashley Hahm, Ph.D. (Review #3 and #4)
Office of Generic Drugs/Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-565

2. REVIEW #: 4

3. REVIEW DATE: March 31, 2009

4. REVIEWER: Naiqi Ya, Ph.D. (Review #1 and 2)
Huijeong Ashley Hahm (Review #3 and Review #4)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	December 10, 2002
New Correspondence	January 17, 2003
Unsolicited Amendment	February 13, 2003
Telephone Amendment	March 19, 2003
Minor Amendment	April 1, 2004
Minor Amendment	June 1, 2005
Telephone Amendment	July 6, 2006
Telephone Amendment	December 22, 2005
Telephone Amendment	August 14, 2006

FDA Correspondences	Document Date
Review #1 (NA Minor)	May 22, 2003
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T-con: DMF Deficiency	May 25, 2006
T-con: In-process & requested samples	June 26, 2006
Fax: In-process Controls	July 24, 2006
Review #3 (NA Major)	September 25, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	**Document Date**
Major Amendment	**August 19, 2008**
Unsolicited Amendment	**January 28, 2009**

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Pharmaceuticals USA
Address:	1090 Horsham Road
	PO Box 1090
	North Wales, PA 19454
Representative:	Philips Erickson
Telephone:	215-591-3141
Fax:	215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Venlafaxine Hydrochloride Extended Release Capsules

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Effexor® XR Capsules 150mg, held by Wyeth Ayerst, NDA 20-699.
There are six listed patents which claim the reference listed drug Effexor® XR Capsules.

Patent No.	Expiration Dates	Pediatric Exclusivity	Use Code
4,535,186	12/13/07	6/13/08	
6,444,708	6/28/13	12/28/13	
5,916,923	6/28/13	12/28/13	U-398
6,274,171	3/20/17	9/20/17	
6,403,120	3/20/17	9/20/17	U-451
6,419,958	3/20/17	9/20/17	U-459

Teva filed Paragraph IV certification for U.S. Patents 6,444,708, 6,274,171, 6,403,120, and 6,419,958. Teva also filed Paragraph III Certification for U.S. Patents 4,535,186 and its associated pediatric exclusivity.

The wording related to the MOU patents 5,916,923, 6,403,120 and 6,419,958 will not be included in the product labeling until the expiration of the respective patent and its associated exclusivity or the patens are invalidated or the use code is changed.

Updated Patent Certification is provided in the Unsolicited Amendment submitted on 2/13/03.

Exclusivity Statement (pp. 11, 2/13/03 Amendment):

Exclusivity	Indication	Expiration Date
I-251	Treatment of Generalized Anxiety Disorder	3/11/02
I-325	Prevention of Relapse and Recurrence of Depression	5/2/04
I-325 (PED)		11/2/04

The I-251 has expired. Teva does not intend to commercially market this product prior to the expiration of I-325 and its associated pediatric exclusivity on 11/2/04.

10. PHARMACOL. CATEGORY:
Anti-depressant

11. DOSAGE FORM:
Extended Release Capsules

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

13. ROUTE OF ADMINISTRATION:
Oral Administration

14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

_____SPOTS product – Form Completed

__X___Not a SPOTS product

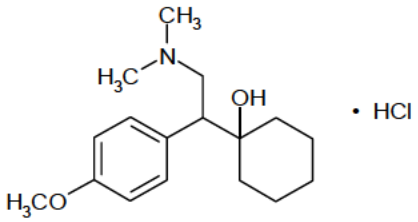
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name:

1. (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride
2. (±)-1-[α- [(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride
3. N,N-Dimethyl-2-(1-hydroxycyclohexyl)-2-(4-ethoxyphenyl) ethylamine hydrochloride

CAS 99300-78-4

Venlafaxine Hydrochloride has the empirical formula of $C_{17}H_{27}NO_2$•HCl. Its molecular weight is 313.87. The structural formula is shown below.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
16281	II	Teva-Tech Ltd.	Venlafaxine Hydrochloride	3	Adequate	2/12/09	Reviewed by Julia Pinto
[redacted] (b) (4)							
							Added in 1/28/09 amend
							Added in 1/28/09 amend
							Added in 1/28/09 amend
							Added in 1/28/09 amend
							Added in 8/19/08 amend

[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
N/A		

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending	2/26/09	Per OC
Methods Validation	Not required		
Labeling	Acceptable on 5/4/06 by M. Shin, but needs updated review		
Bioequivalence	Acceptable on 4/6/05 by Nhan Tran but needs update by firm		
EA	N/A		
Radiopharmaceutical	N/A		

Labeling: See Section 32. On 3/30/09, Michelle Dillahunt, the labeling reviewer, asked the firm to submit an updated labeling since the last labeling was submitted in 2006. Since 2006 there has been many labeling revisions to the RLD.
EES: See Section 33.
DBE: See Section 34.
Samples: Firm sent samples per faxed amendment dated 7/6/06. The firm noted that the samples (Batch No. K-30703 manufactured 11/5/02, K-30702 manufactured 11/5/02, and K-30455 manufactured 8/27/02) have expired. Firm will be asked to send additional samples in the next amendment.

Comment: Please provide us samples for your batches submitted in your amendments dated 8/19/08 and 1/28/09.

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 76-565

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Unapprovable because of inadequate in-process controls. New bio data needed.

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

N/A

II. Summary of Chemistry Assessments

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

Venlafaxine Hydrochloride, a structurally novel antidepressant, is chemically unrelated to tricyclic, tetracyclic, and other available antidepressants. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[(alpha)- [(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride. Venlafaxine Hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/mL (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 will be manufactured by Teva API Division in Netanya and Be'er Sheva, Israel. For future commercial production, each lot of Venlafaxine Hydrochloride received at Teva Kfar Saba will be tested for identification only and will be released as per Teva-Tech's CoA. Teva Kfar Saba will perform full monograph testing on a (b) (4) basis.

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

Venlafaxine Extended Release capsules are indicated for the treatment of depression. Venlafaxine Hydrochloride extended-release capsules should be administered in a single dose with food. Each capsule should be swallowed whole with fluid and not divided, crushed, chewed, or placed in water. For most patients, the recommended starting dose is

75 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. The maximum recommended dose for moderately depressed outpatients is 225 mg/day.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not recommended for approval because the firm's in-process controls are inadequate. New biostudy is needed to approve the additional manufacturing site. Full length stability study is needed because several samples pass dissolution at L2 and L3 stages.

cc: ANDA 76-565
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/HAHahm/3/31/09
HFD-640/NYa/6/5/09
HFD-617/THinchliffe/6/9/09

F/T by: TOH/

V:\FIRMSNZ\TEVA\LTRS&REV\76565rev04.doc

TYPE OF LETTER: Not Approvable; MAJOR

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

/s/

Huijeong Ashley Hahm
6/9/2009 06:21:08 PM
CHEMIST

Thomas Hinchliffe
6/9/2009 08:39:39 PM
CSO

Naiqi Ya
6/11/2009 03:57:05 PM
CHEMIST

ANDA 76-565

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

Teva Pharmaceuticals, USA

Naiqi Ya, Ph.D. (Review #1 and 2)
and Huijeong Ashley Hahm, Ph.D. (Review #3)
Office of Generic Drugs/Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-565

2. REVIEW #: 3

3. REVIEW DATE: November 14, 2005; December 27, 2005; May 24, 2006; July 24, 2006; September 25, 2006

4. REVIEWER: Naiqi Ya, Ph.D. (Review #1 and 2)
Huijeong Ashley Hahm (Review #3)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	December 10, 2002
New Correspondence	January 17, 2003
Unsolicited Amendment	February 13, 2003
Telephone Amendment	March 19, 2003
Minor Amendment	April 1, 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	June 1, 2005
Telephone Amendment	December 22, 2005
Telephone Amendment	July 6, 2006
Telephone Amendment	August 14, 2006

FDA Correspondences	Document Date
T-con: DS and DP Specifications	December 22, 2005
T-con: DMF Deficiency	May 25, 2006
T-con: In-process & requested samples	June 26, 2006
Fax: In-process Controls	July 24, 2006

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Pharmaceuticals USA

Chemistry Review Data Sheet

Address: 1090 Horsham Road
PO Box 1090
North Wales, PA 19454
Representative: Philips Erickson
Telephone: 215-591-3000
Fax: 215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Venlafaxine Hydrochloride Extended Release Capsules

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Effexor® XR Capsules 150mg, held by Wyeth Ayerst, NDA 20-699.
There are six listed patents which claim the reference listed drug Effexor® XR Capsules.

Patent No.	Expiration Dates	Pediatric Exclusivity	Use Code
4,535,186	12/13/07	6/13/08	
6,444,708	6/28/13	12/28/13	
5,916,923	6/28/13	12/28/13	U-398
6,274,171	3/20/17	9/20/17	
6,403,120	3/20/17	9/20/17	U-451
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Teva filed Paragraph IV certification for U.S. Patents 6,444,708, 6,274,171, 6,403,120, and 6,419,958. Teva also filed Paragraph III Certification for U.S. Patents 4,535,186 and its associated pediatric exclusivity.

The wording related to the MOU patents 5,916,923, 6,403,120 and 6,419,958 will not be included in the product labeling until the expiration of the respective patent and its associated exclusivity or the patens are invalidated or the use code is changed.

Updated Patent Certification is provided in the Unsolicited Amendment submitted on 2/13/03.

Exclusivity Statement (pp. 11, 2/13/03 Amendment):

Exclusivity	Indication	Expiration Date
I-251	Treatment of Generalized Anxiety Disorder	3/11/02
I-325	Prevention of Relapse and Recurrence of Depression	5/2/04
I-325 (PED)		11/2/04

The I-251 has expired. Teva does not intend to commercially market this product prior to the expiration of I-325 and its associated pediatric exclusivity on 11/2/04.

10. PHARMACOL. CATEGORY:
Anti-depressant

11. DOSAGE FORM:
Extended Release Capsules

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

13. ROUTE OF ADMINISTRATION:
Oral Administration

14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

_____SPOTS product – Form Completed

__X___Not a SPOTS product

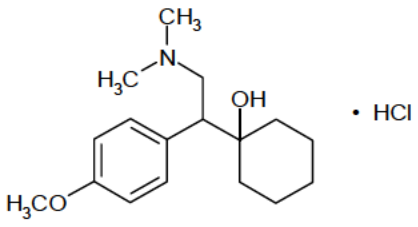
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name:

1. (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride
2. (±)-1-[α- [(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride
3. N,N-Dimethyl-2-(1-hydroxycyclohexyl)-2-(4-ethoxyphenyl) ethylamine hydrochloride

CAS 99300-78-4

Venlafaxine Hydrochloride has the empirical formula of $C_{17}H_{27}NO_2$•HCl. Its molecular weight is 313.87. The structural formula is shown below.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
16281	II	Teva-Tech Ltd.	Venlafaxine Hydrochloride	3	Adequate	6/14/06	Reviewed by D. Skanchy
				(b) (4)			

[redacted]

[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
N/A		

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending	5/24/06	Per OC

Methods Validation	Not required		
Labeling	Acceptable	5/4/2006	Melaine Shin
Bioequivalence	Acceptable	4/6/2005	Nhan L. Tran
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 76-565

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Unapprovable because of inadequate in-process controls.

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

N/A

II. Summary of Chemistry Assessments

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

Venlafaxine Hydrochloride, a structurally novel antidepressant, is chemically unrelated to tricyclic, tetracyclic, and other available antidepressants. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[(alpha)- [(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride. Venlafaxine Hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/mL (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 will be manufactured by Teva API Division in Netanya and Be'er Sheva, Israel. For future commercial production, each lot of Venlafaxine Hydrochloride received at Teva Kfar Saba will be tested for identification only and will be released as per Teva-Tech's CoA. Teva Kfar Saba will perform full monograph testing on a (b) (4) basis.

Venlafaxine Hydrochloride Extended Release Capsules is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion of Venlafaxine Hydrochloride through the coating membrane on the spheroids and is not pH dependent. Capsules contain Venlafaxine Hydrochloride equivalent to 37.5 mg, 75 mg, and 150 mg Venlafaxine. Inactive ingredients consist of antifoam DC1510, Black Iron Oxide, Dibutyl Sebacate, Ethylcellulose, Gelatin, Polyethylene Glycol, Povidone, Shellac, Soya Lecithin MC thin, Sugar Spheres, Sunset Yellow FCF FD&C Yellow 6, Talc, and Titanium Dioxide. The 37.5 mg and 75 mg capsules also contain D&C Yellow 10.

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

Venlafaxine Extended Release capsules are indicated for the treatment of depression. Venlafaxine Hydrochloride extended-release capsules should be administered in a single dose with food. Each capsule should be swallowed whole with fluid and not divided, crushed, chewed, or placed in water. For most patients, the recommended starting dose is

75 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. The maximum recommended dose for moderately depressed outpatients is 225 mg/day.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not recommended for approval because the firm's in-process controls are inadequate.

cc: ANDA 76-565
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/HAHahm/12/27/05; 5/24/06; 7/24/06; 9/25/06
HFD-640/NYa/1/5/06;10/5/06
HFD-617/THinchliffe/5/8/06;10/6/06

F/T by: TOH/

V:\FIRMSNZ\TEVA\LTRS&REV\76565rev03.doc

TYPE OF LETTER: Not Approvable; MAJOR

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

/s/

Huijeong Ashley Hahm
10/10/2006 04:06:34 PM
CHEMIST

Thomas Hinchliffe
10/12/2006 08:01:48 AM
PHARMACIST

Naiqi Ya
10/12/2006 09:49:49 AM
CHEMIST

ANDA 76-565

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

Teva Pharmaceuticals, USA

Naiqi Ya, Ph.D.
Office of Generic Drugs/Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-565

2. REVIEW #: 2

3. REVIEW DATE: August 3, 2004

4. REVIEWER: Naiqi Ya, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	December 10, 2002
New Correspondence	January 17, 2003
Unsolicited Amendment	February 13, 2003
Telephone Amendment	March 19, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	April 1, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Pharmaceuticals USA
Address:	1090 Horsham Road PO Box 1090 North Wales, PA 19454
Representative:	Philips Erickson
Telephone:	215-591-3000
Fax:	215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN):
Venlafaxine Hydrochloride Extended Release Capsules

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Effexor® XR Capsules 150mg, held by Wyeth Ayerst, NDA 20-699.
There are six listed patents which claim the reference listed drug Effexor® XR Capsules.

Patent No.	Expiration Dates	Pediatric Exclusivity	Use Code
4,535,186	12/13/07	6/13/08	
6,444,708	6/28/13	12/28/13	
5,916,923	6/28/13	12/28/13	U-398
6,274,171	3/20/17	9/20/17	
6,403,120	3/20/17	9/20/17	U-451
6,419,958	3/20/17	9/20/17	U-459

Teva filed Paragraph IV certification for U.S. Patents 6,444,708, 6,274,171, 6,403,120, and 6,419,958. Teva also filed Paragraph III Certification for U.S. Patents 4,535,186 and its associated pediatric exclusivity.

The wording related to the MOU patents 5,916,923, 6,403,120 and 6,419,958 will not be included in the product labeling until the expiration of the respective patent and its associated exclusivity or the patens are invalidated or the use code is changed.

Updated Patent Certification is provided in the Unsolicited Amendment submitted on 2/13/03.

Exclusivity Statement (pp. 11, 2/13/03 Amendment):

Exclusivity	Indication	Expiration Date
I-251	Treatment of Generalized Anxiety Disorder	3/11/02
I-325	Prevention of Relapse and Recurrence of Depression	5/2/04
I-325 (PED)		11/2/04

The I-251 has expired. Teva does not intend to commercially market this product prior to the expiration of I-325 and its associated pediatric exclusivity on 11/2/04.

10. PHARMACOL. CATEGORY:

Anti-depressant

11. DOSAGE FORM:

Extended Release Capsules

12. STRENGTH/POTENCY:

37.5 mg, 75 mg, and 150 mg

13. ROUTE OF ADMINISTRATION:

Oral Administration

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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

_____SPOTS product – Form Completed

__X___Not a SPOTS product

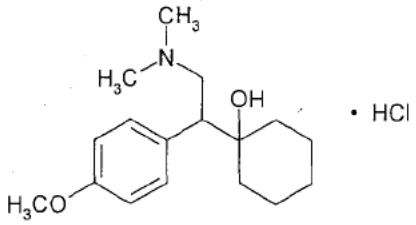
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name:

1. (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride
2. (±)-1-[α- [(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride
3. N,N-Dimethyl-2-(1-hydroxycyclohexyl)-2-(4-ethoxyphenyl) ethylamine hydrochloride

CAS 99300-78-4

Venlafaxine Hydrochloride has the empirical formula of $C_{17}H_{27}NO_2 \cdot HCl$. Its molecular weight is 313.87. The structural formula is shown below.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
16281	II	Teva-Tech Ltd.	Venlafaxine Hydrochloride	1	Inadequate (b) (4)	7/30/04	Reviewed by D. Skanchy

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
N/A		

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	5/6/03	
Methods Validation	Not required		
Labeling	Pending		
Bioequivalence	Deficient		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 76-565

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable – The firm will be requested to address the minor deficiencies identified in the review.

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

N/A

II. Summary of Chemistry Assessments

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

Venlafaxine Hydrochloride, a structurally novel antidepressant, is chemically unrelated to tricyclic, tetracyclic, and other available antidepressants. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[(alpha)- [(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride. Venlafaxine Hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/mL (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 will be manufactured by Teva API Division in Netanya and Be'er Sheva, Israel. For future commercial production, each lot of Venlafaxine Hydrochloride received at Teva Kfar Saba will be tested for identification only and will be released as per Teva-Tech's CoA. Teva Kfar Saba will perform full monograph testing on a (b) (4) basis.

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crushed, chewed, or placed in water. For most patients, the recommended starting dose is 75 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. The maximum recommended dose for moderately depressed outpatients is 225 mg/day.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not recommended for approval due to minor deficiencies. The DMF for Venlafaxine Hydrochloride is deficient. The firm will also be provided with comments regarding the raw material controls, manufacturing and processing, container, laboratory controls, analytical methods, and labeling.

III. Administrative

A. Reviewer's Signature 8/24/04

B. Endorsement Block

Endorsements (Draft and Final with Dates)

HFD-640/NYa/8/12/04; 8/19/04; 8/24/04
HFD-643/SRosencrance/8/13/04; 8/19/04; 8/24/04
HFD-617/THinchliffe/8/23/04; 8/23/04

C. CC Block

ANDA 76-565
DIV FILE
Field Copy

cc: ANDA 76-565
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/NYa/8/12/04; 8/19/04
HFD-640/SRosecrance/8/13/04; 8/19/04
HFD-617/THinchliffe/8/23/04

F/T by: toh/8/23/04

V:\FIRMSNZ\TEVA\LTRS&REV\76565rev02.doc

TYPE OF LETTER: NOT APPROVABLE – MINOR AMENDMENT

ANDA 76-565

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

Teva Pharmaceuticals, USA

Tao-Chin L. Wang, Ph.D.
Office of Generic Drugs/Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-565

2. REVIEW #: 1

3. REVIEW DATE: 5/5/03

4. REVIEWER: Tao-Chin L. Wang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	December 10, 2002
New Correspondence	January 17, 2003
Unsolicited Amendment	February 13, 2003
Telephone Amendment	March 19, 2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Pharmaceuticals USA
Address:	1090 Horsham Road PO Box 1090 North Wales, PA 19454
Representative:	Philips Erickson
Telephone:	215-591-3000
Fax:	215-591-8812

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a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN):

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Exclusivity	Indication	Expiration Date
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11. DOSAGE FORM:

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12. STRENGTH/POTENCY:

37.5 mg, 75 mg, and 150 mg

13. ROUTE OF ADMINISTRATION:

Oral Administration

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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

_____SPOTS product – Form Completed

__X___Not a SPOTS product

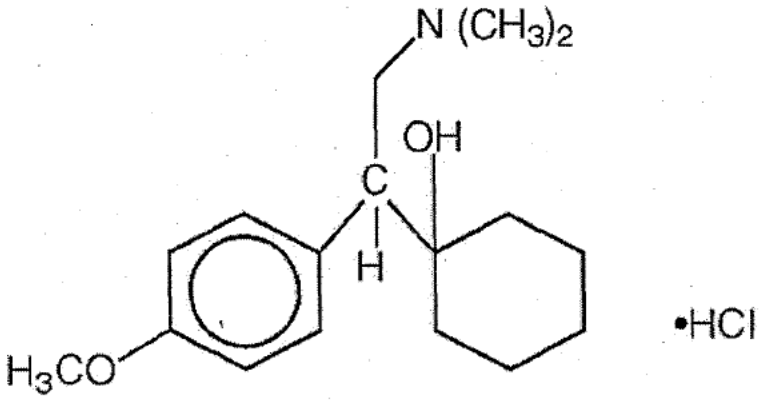
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Venlafaxine Hydrochloride
Chemical Name:

1. (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride
2. (±)-1-[α- [(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride
3. N,N-Dimethyl-2-(1-hydroxycyclohexyl)-2-(4-ethoxyphenyl) ethylamine hydrochloride

CAS 99300-78-4

Venlafaxine Hydrochloride has the empirical formula of $C_{17}H_{27}NO_2$•HCl. Its molecular weight is 313.87. The structural formula is shown below.



venlafaxine hydrochloride

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
16281	II	Teva-Tech Ltd.	Venlafaxine Hydrochloride	1	Inadequate	4/25/03	Reviewed by T.-C. L. Wang
[redacted]				(b) (4)			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
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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
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER

Microbiology	N/A		
EES	Acceptable	5/6/03	
Methods Validation	Will be requested		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

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 76-565

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable -- The firm will be requested to address the minor deficiencies identified in the review.

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

N/A

II. Summary of Chemistry Assessments

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

Venlafaxine Hydrochloride, a structurally novel antidepressant, is chemically unrelated to tricyclic, tetracyclic, and other available antidepressants. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[(alpha)- [(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride. Venlafaxine Hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/mL (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 will be manufactured by Teva API Division in Netanya and Be'er Sheva, Israel. For future commercial production, each lot of Venlafaxine Hydrochloride received at Teva Kfar Saba will be tested for identification only and will be released as per Teva-Tech's CoA. Teva Kfar Saba will perform full monograph testing on a (b) (4) basis.

Venlafaxine Hydrochloride Extended Release Capsules is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion of Venlafaxine Hydrochloride through the coating membrane on the spheroids and is not pH dependent. Capsules contain Venlafaxine Hydrochloride equivalent to 37.5 mg, 75 mg, and 150 mg Venlafaxine. Inactive ingredients consist of antifoam DC1510, Black Iron Oxide, Dibutyl Sebacate, Ethylcellulose, Gelatin, Polyethylene Glycol, Povidone, Shellac, Soya Lecithin MC thin, Sugar Spheres, Sunset Yellow FCF FD&C Yellow 6, Talc, and Titanium Dioxide. The 37.5 mg and 75 mg capsules also contain D&C Yellow 10.

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

Venlafaxine Extended Release capsules are indicated for the treatment of depression. Venlafaxine Hydrochloride extended-release capsules should be administered in a single dose with food. Each capsule should be swallowed whole with fluid and not divided, crushed, chewed, or placed in water. For most patients, the recommended starting dose is 75 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. The maximum recommended dose for moderately depressed outpatients is 225 mg/day.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not recommended for approval due to minor deficiencies. The DMF for Venlafaxine Hydrochloride is deficient. The firm will also be provided with comments regarding the raw material controls, manufacturing and processing, container, laboratory controls, analytical methods, and labeling.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Endorsements (Draft and Final with Dates)

HFD-640/TCLWang/5/5/03 TCLWang 5/22/03
HFD-643/SRosencrance/5/19/03 SRosencrance 5/22/03
HFD-617/THinchliffe/5/21/03

C. CC Block

ANDA 76-565
DIV FILE
Field Copy

cc: ANDA 76-565
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/TCLWang/5/5/03 TCLWang 5/22/03

HFD-640/SRosecrance/5/19/03 5/22/03

HFD-617/THinchliffe/5/21/03 5/23/03

F/T by: EW 5/22/03

V:\Firmsnz\Teva\Ltrs&Rev\76565R01.RTW

TYPE OF LETTER: NOT APPROVABLE – MINOR AMENDMENT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076565

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	076565
Drug Product Name	Venlafaxine Hydrochloride Extended Release Capsules
Strength(s)	37.5 mg, 75 mg and 150 mg
Applicant Name	Teva Pharmaceuticals USA
Address	1090 Horsham Road North Wales, PA 19454
Applicant's Point of Contact	Philip Erickson, R.Ph.
Contact's Telephone Number	(215) 591-3141
Contact's Fax Number	(215) 591-8812
Original Submission Date(s)	January 28, 2009
Submission Date(s) of Amendment(s) Under Review	April 23, 2010
Reviewer	Svetlana Cherstniakova, Ph.D.
Study Number (s)	(b) (4)
Study Type (s)	
Strength (s)	
Clinical Site	Pharma Medica Research Inc.
Clinical Site Address	4770 Sheppard Avenue East, Toronto, Ontario, Canada, M1S 3V6
Analytical Site	(b) (4)
Analytical Site Address	(b) (4)

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**

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 providing in vitro dissolution studies conducted using various concentrations of ethanol in the dissolution medium, in accord with the Agency's bioequivalence recommendations for this drug product. Originally the firm conducted three bioequivalence (BE) studies, i.e. fasting, fed and fasting sprinkle (submission date December 10, 2002), comparing a test product Venlafaxine Hydrochloride Extended Release Capsules, 150 mg to the corresponding reference product Effexor XR® (venlafaxine hydrochloride), eq. 150 mg base (v:/firmsnz/Teva/ltrs&rev/76565N1202.doc). The firm's application was found acceptable (DARRTS N 076565 REV-BIOEQ-01(General Review); 01/22/2010). Currently, the Division of Bioequivalence requests that generic applicants submit the alcohol dose dumping studies for Venlafaxine HCl ER Capsules.

In the current amendment, the firm submitted the in vitro alcohol dose-dumping dissolution testing conducted on recently manufactured batches of 37.5 mg, 75 mg and 150 mg strengths of its product versus the respective strengths of the RLD. The results of the comparative dissolution testing on all strengths of the test and the RLD products using various concentrations of ethanol in the dissolution medium show similar drug release (% dissolved data) at 2 hours in 40% ethanol. Therefore, the firm's in vitro alcohol dose dumping testing is acceptable.

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

The application is acceptable.

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3 SUBMISSION SUMMARY

3.1 Review of Submission

The firm submitted the in vitro alcohol dose-dumping dissolution testing conducted on recently manufactured batches of 37.5 mg, 75 mg and 150 mg strengths of Teva's product versus the respective strengths of the RLD using various concentrations of ethanol in the dissolution medium, as follows:

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

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.

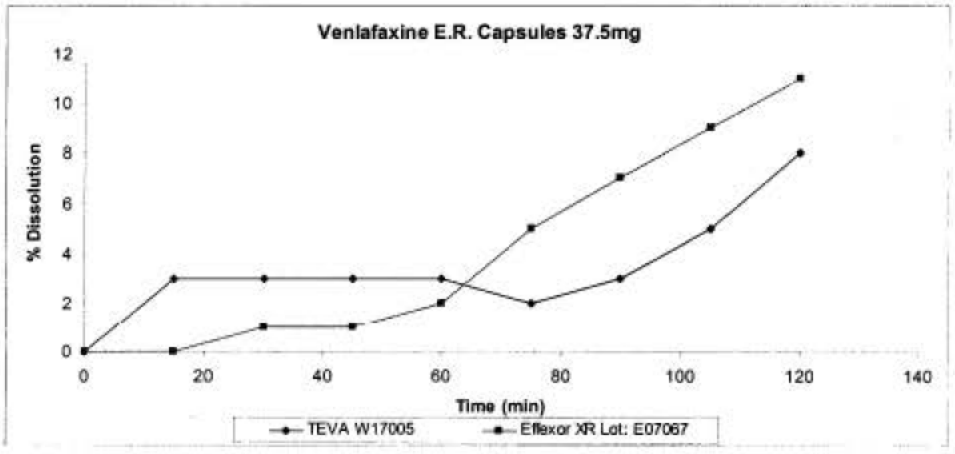
Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

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.

The in vitro alcohol dose-dumping testing for the Venlafaxine Hydrochloride Extended Release Capsules and the RLD are summarized in the tables below:

37.5 mg strength
0.1 N HCl

		% OF LABELED AMOUNT DISSOLVED							
Batch No.	Parameters	15 Minutes	30 Minutes	45 Minutes	60 Minutes	75 Minutes	90 Minutes	105 Minutes	120 Minutes
TEVA W17005	Mean of 12 tablets	3	3	3	3	2	3	5	8
	RSD%	5.2	32.7	21.3	12.4	54.4	61.0	27.3	16.8
Effexor XR Lot: E07067	Mean of 12 tablets	0	1	1	2	5	7	9	11
	RSD%	0	0	73.9	67.9	21.0	18.4	18.8	17.0



TAB#	% OF LABELED AMOUNT DISSOLVED							
	15 Minutes		30 Minutes		45 Minutes		60 Minutes	
	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067
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Mean	3	0	3	1	3	1	3	2
RSD%	5.2	0	32.7	0	21.3	73.9	12.4	67.9

TAB#	% OF LABELED AMOUNT DISSOLVED							
	75 Minutes		90 Minutes		105 Minutes		120 Minutes	
	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067
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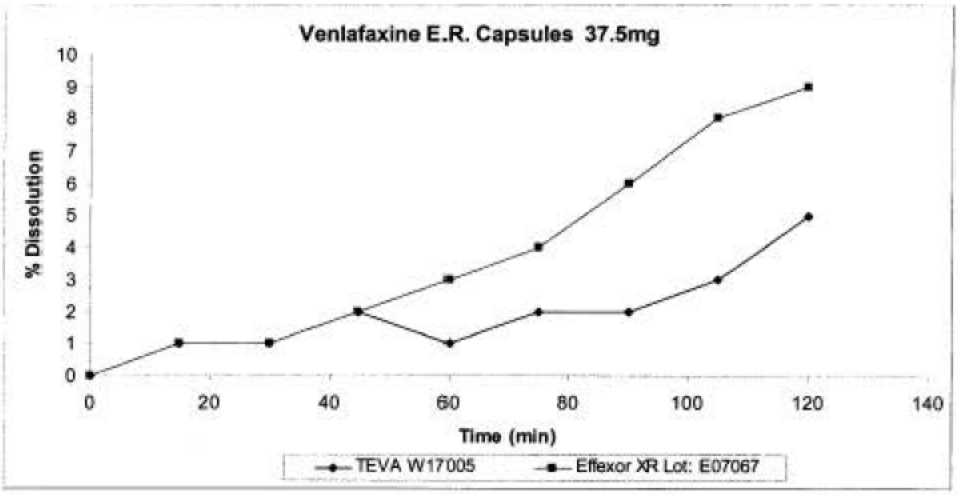
Mean	2	5	3	7	5	9	8	11
RSD%	54.4	21.0	61.0	18.4	27.3	18.8	16.8	17.0

0.1 N HCl with 5% alcohol

Batch No.	Parameters	% OF LABELED AMOUNT DISSOLVED							
		15 Minutes	30 Minutes	45 Minutes	60 Minutes	75 Minutes	90 Minutes	105 Minutes	120 Minutes
TEVA W17005	Mean of 12 tablets	1	1	2	1	2	2	3	5
	RSD%	69.5	58.3	53.4	60.8	61.0	52.7	26.5	19.3
Effexor XR Lot: E07067	Mean of 12 tablets	1	1	2	3	4	6	8	9
	RSD%	26.3	30.0	21.8	16.3	14.8	15.0	15.4	13.6



TAB#	% OF LABELED AMOUNT DISSOLVED							
	15 Minutes		30 Minutes		45 Minutes		60 Minutes	
	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067
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Mean	1	1	1	1	2	2	1	3
RSD%	69.5	26.3	58.3	30.0	53.4	21.8	60.8	16.3

TAB#	% OF LABELED AMOUNT DISSOLVED							
	75 Minutes		90 Minutes		105 Minutes		120 Minutes	
	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067
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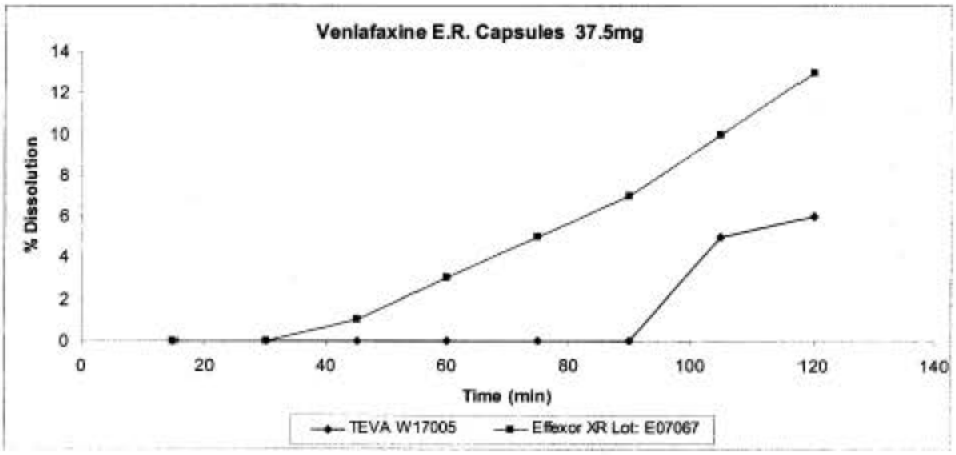
Mean	2	4	2	6	3	8	5	9
RSD%	61.0	14.8	52.7	15.0	26.5	15.4	19.3	13.6

0.1 N HCl with 20% alcohol

Batch No.	Parameters	% OF LABELED AMOUNT DISSOLVED							
		15 Minutes	30 Minutes	45 Minutes	60 Minutes	75 Minutes	90 Minutes	105 Minutes	120 Minutes
TEVA W17005	Mean of 12 tablets	0	0	0	0	0	0	5	6
	RSD%	0	0	0	0	0	0	0	23.9
Effexor XR Lot: E07067	Mean of 12 tablets	0	0	1	3	5	7	10	13
	RSD%	0	0	31.9	51.2	38.7	36.1	28.9	30.4



TAB#	% OF LABELED AMOUNT DISSOLVED							
	15 Minutes		30 Minutes		45 Minutes		60 Minutes	
	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067
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Mean	0	0	0	0	0	1	0	3
RSD%	0	0	0	0	0	31.9	0	51.2

TAB#	% OF LABELED AMOUNT DISSOLVED							
	75 Minutes		90 Minutes		105 Minutes		120 Minutes	
	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067
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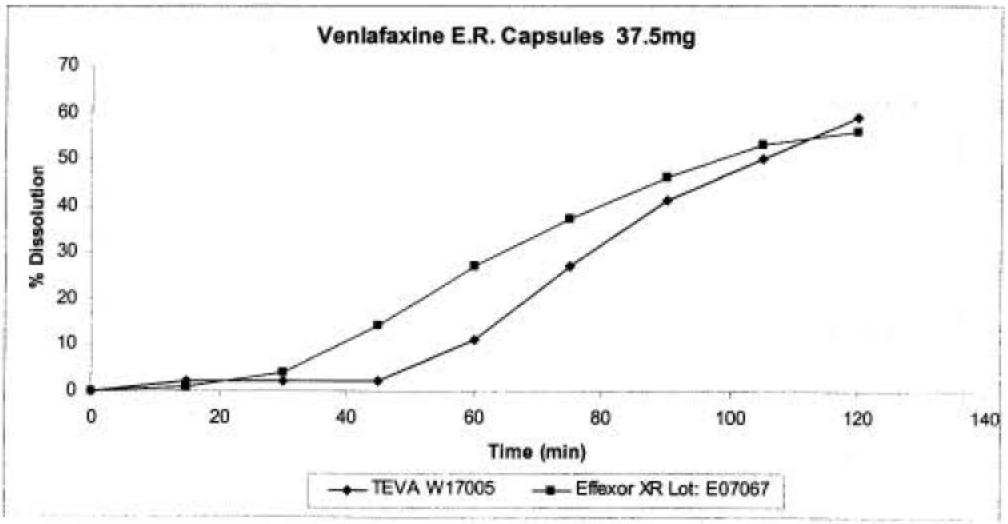
Mean	0	5	0	7	5	10	6	13
RSD%	0	38.7	0	36.1	0	28.9	23.9	30.4

0.1 N HCl with 40% alcohol

Batch No.	Parameters	% OF LABELED AMOUNT DISSOLVED							
		15 Minutes	30 Minutes	45 Minutes	60 Minutes	75 Minutes	90 Minutes	105 Minutes	120 Minutes
TEVA W17005	Mean of 12 tablets	2	2	2	11	27	41	50	59
	RSD%	47.5	52.8	64.5	68.3	36.7	23.8	15.0	11.9
Effexor XR Lot: E07067	Mean of 12 tablets	1	4	14	27	37	46	53	56
	RSD%	35.6	47.0	41.6	40.6	38.8	37.3	36.9	34.8



TAB#	% OF LABELED AMOUNT DISSOLVED							
	15 Minutes		30 Minutes		45 Minutes		60 Minutes	
	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067
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Mean	2	1	2	4	2	14	11	27
RSD%	47.5	35.6	52.8	47.0	64.5	41.6	68.3	40.6

TAB#	% OF LABELED AMOUNT DISSOLVED							
	75 Minutes		90 Minutes		105 Minutes		120 Minutes	
	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot: E07067	TEVA W17005	Effexor XR Lot:
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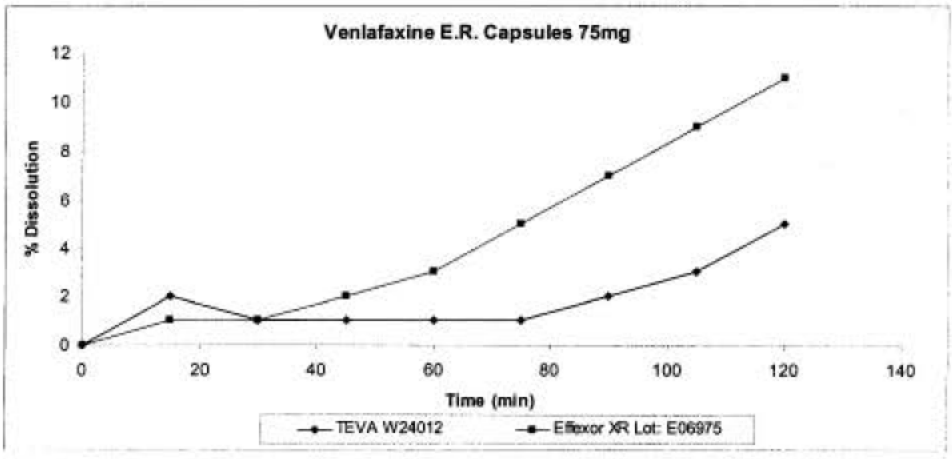
Mean	27	37	41	46	50	53	59	56
RSD%	36.7	38.8	23.8	37.3	15.0	36.9	11.9	34.8

75 mg strength
0.1 N HCl

		% OF LABELED AMOUNT DISSOLVED							
Batch No.	Parameters	15 Minutes	30 Minutes	45 Minutes	60 Minutes	75 Minutes	90 Minutes	105 Minutes	120 Minutes
TEVA W24012	Mean of 12 tablets	2	1	1	1	1	2	3	5
	RSD%	101.8	81.4	72.6	74.2	68.1	63.0	41.6	25.0
Effexor XR Lot: E06978	Mean of 12 tablets	1	1	2	3	5	7	9	11
	RSD%	16.5	17.3	14.3	10.4	10.3	10.3	9.4	9.0



TAB#	% OF LABELED AMOUNT DISSOLVED							
	15 Minutes		30 Minutes		45 Minutes		60 Minutes	
	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978
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Mean	2	1	1	1	1	2	1	3
RSD%	101.8	16.5	81.4	17.3	72.6	14.3	74.2	10.4

TAB#	% OF LABELED AMOUNT DISSOLVED							
	75 Minutes		90 Minutes		105 Minutes		120 Minutes	
	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978
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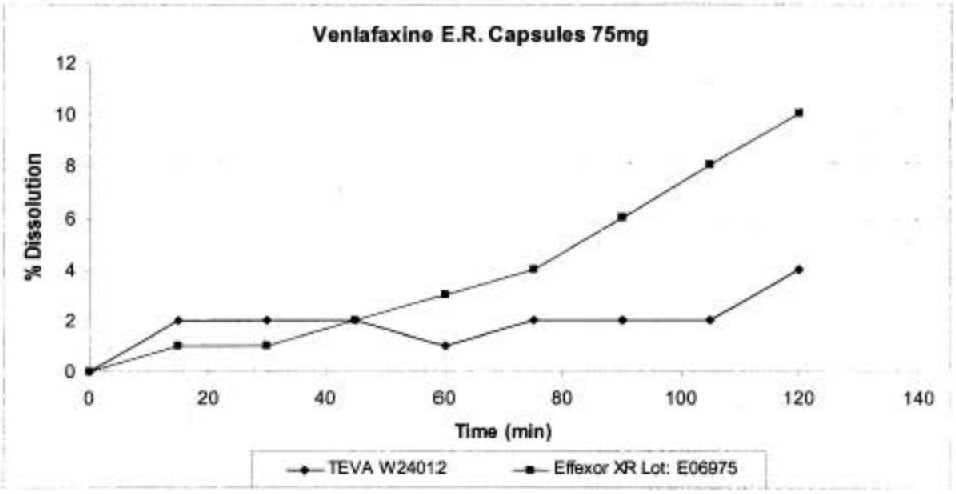
Mean	1	5	2	7	3	9	5	11
RSD%	68.1	10.3	63.0	10.3	41.6	9.4	25.0	9.0

0.1 N HCl with 5% alcohol

Batch No.	Parameters	% OF LABELED AMOUNT DISSOLVED							
		15 Minutes	30 Minutes	45 Minutes	60 Minutes	75 Minutes	90 Minutes	105 Minutes	120 Minutes
TEVA W24012	Mean of 12 tablets	2	2	2	1	2	2	2	4
	RSD%	79.1	71.3	81.1	90.0	80.2	70.6	56.3	42.7
Effexor XR Lot: E06978	Mean of 12 tablets	1	1	2	3	4	6	8	10
	RSD%	24.3	30.5	26.9	22.1	19.6	17.1	18.0	15.2



TAB#	% OF LABELED AMOUNT DISSOLVED							
	15 Minutes		30 Minutes		45 Minutes		60 Minutes	
	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978
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12								
Mean	2	1	2	1	2	2	1	3
RSD%	79.1	24.3	71.3	30.5	81.1	26.9	90.0	22.1

TAB#	% OF LABELED AMOUNT DISSOLVED							
	75 Minutes		90 Minutes		105 Minutes		120 Minutes	
	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978
1	(b) (4)							
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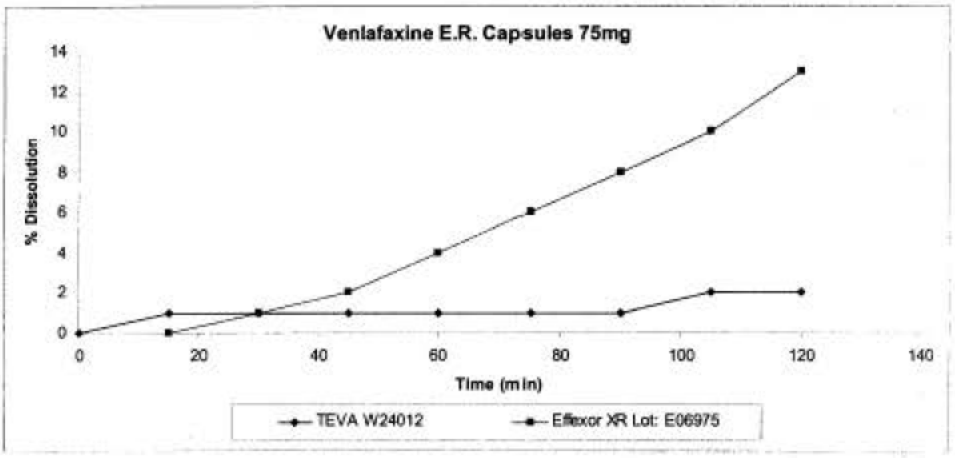
12								
Mean	2	4	2	6	2	8	4	10
RSD%	80.2	19.6	70.6	17.1	56.3	18.0	42.7	15.2

0.1 N HCl with 20% alcohol

Batch No.	Parameters	% OF LABELED AMOUNT DISSOLVED							
		15 Minutes	30 Minutes	45 Minutes	60 Minutes	75 Minutes	90 Minutes	105 Minutes	120 Minutes
TEVA W24012	Mean of 12 tablets	1	1	1	1	1	1	2	2
	RSD%	78.9	71.2	66.6	67.3	65.6	66.1	69.2	66.0
Effexor XR Lot: E06978	Mean of 12 tablets	0	1	2	4	6	8	10	13
	RSD%	36.1	24.6	17.2	15.4	15.0	13.6	13.1	11.6



TAB#	% OF LABELED AMOUNT DISSOLVED							
	15 Minutes		30 Minutes		45 Minutes		60 Minutes	
	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978
1	[redacted] (b) (4)							
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12								
Mean	1	0	1	1	1	2	1	4
RSD%	78.9	36.1	71.2	24.6	66.6	17.2	67.3	15.4

TAB#	% OF LABELED AMOUNT DISSOLVED							
	75 Minutes		90 Minutes		105 Minutes		120 Minutes	
	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978
1	[redacted] (b) (4)							
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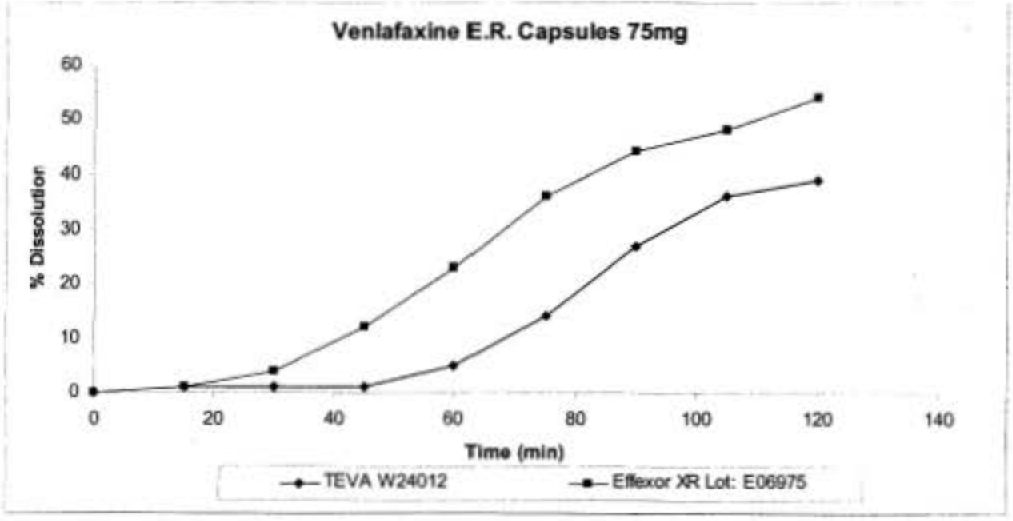
12								
Mean	1	6	1	8	2	10	2	13
RSD%	65.6	15.0	66.1	13.6	69.2	13.1	66.0	11.6

0.1 N HCl with 40% alcohol

Batch No.	Parameters	% OF LABELED AMOUNT DISSOLVED							
		15 Minutes	30 Minutes	45 Minutes	60 Minutes	75 Minutes	90 Minutes	105 Minutes	120 Minutes
TEVA W24012	Mean of 12 tablets	1	1	1	5	14	27	36	39
	RSD%	69.8	61.7	71.8	64.8	59.6	47.6	43.4	41.4
Effexor XR Lot: E06978	Mean of 12 tablets	1	4	12	23	36	44	48	54
	RSD%	61.8	53.9	49.7	45.0	43.6	38.9	36.5	33.5



TAB#	% OF LABELED AMOUNT DISSOLVED							
	15 Minutes		30 Minutes		45 Minutes		60 Minutes	
	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978
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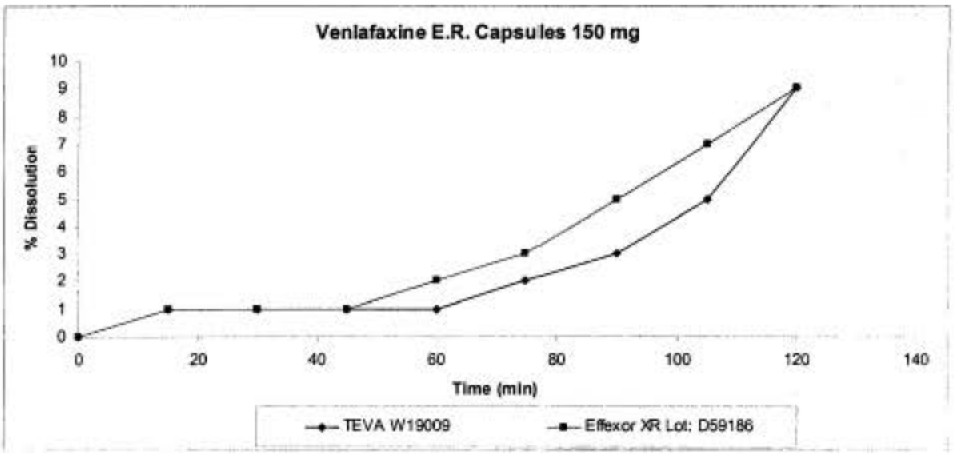
12								
Mean	1	1	1	4	1	12	5	23
RSD%	69.8	61.8	61.7	53.9	71.8	49.7	64.8	45.0

TAB#	% OF LABELED AMOUNT DISSOLVED							
	75 Minutes		90 Minutes		105 Minutes		120 Minutes	
	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978	TEVA W24012	Effexor XR Lot: E06978
1	[redacted] (b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	14	36	27	44	36	49	39	54
RSD%	59.6	43.6	47.6	38.9	43.4	36.5	41.4	33.5

150 mg strength
0.1 N HCl

		% OF LABELED AMOUNT DISSOLVED							
Batch No.	Parameters	15 Minutes	30 Minutes	45 Minutes	60 Minutes	75 Minutes	90 Minutes	105 Minutes	120 Minutes
TEVA W19009	Mean of 12 tablets	1	1	1	1	2	3	5	9
	RSD%	55.4	56.5	55.4	67.4	50.1	24.9	16.0	10.4
Effexor XR Lot: D59186	Mean of 12 tablets	1	1	1	2	3	5	7	9
	RSD%	94.8	39.3	30.6	23.0	16.1	12.6	11.4	10.3

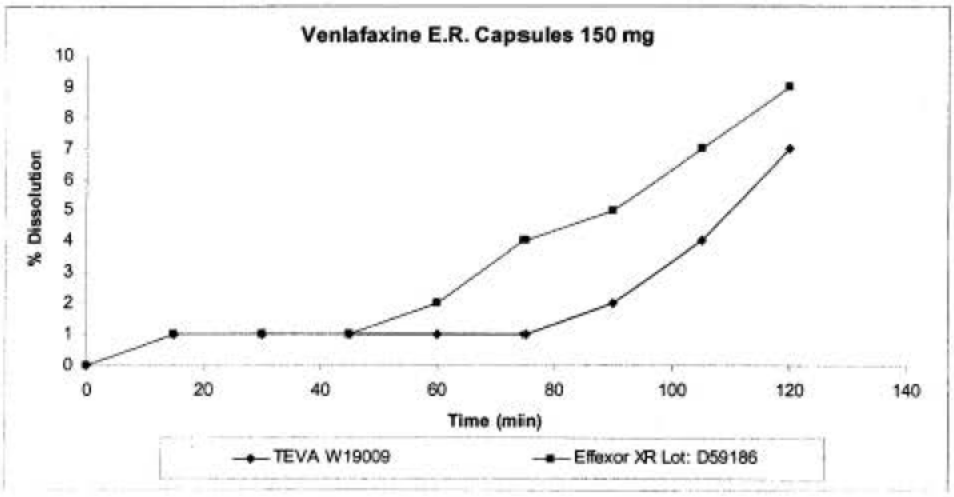


TAB#	% OF LABELED AMOUNT DISSOLVED							
	15 Minutes		30 Minutes		45 Minutes		60 Minutes	
	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	1	1	1	1	1	1	1	2
RSD%	55.4	94.8	56.5	39.3	55.4	30.6	67.4	23.0

TAB#	% OF LABELED AMOUNT DISSOLVED							
	75 Minutes		90 Minutes		105 Minutes		120 Minutes	
	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	2	3	3	5	5	7	9	9
RSD%	50.1	16.1	24.9	12.6	16.0	11.4	10.4	10.3

0.1 N HCl with 5% alcohol

		% OF LABELED AMOUNT DISSOLVED							
Batch No.	Parameters	15 Minutes	30 Minutes	45 Minutes	60 Minutes	75 Minutes	90 Minutes	105 Minutes	120 Minutes
TEVA W19009	Mean of 12 tablets	1	1	1	1	1	2	4	7
	RSD%	68.2	64.0	36.5	33.2	21.9	13.8	16.0	13.4
Effexor XR Lot: E59186	Mean of 12 tablets	1	1	1	2	4	5	7	9
	RSD%	33.9	27.5	18.6	11.9	10.3	9.0	8.8	8.1

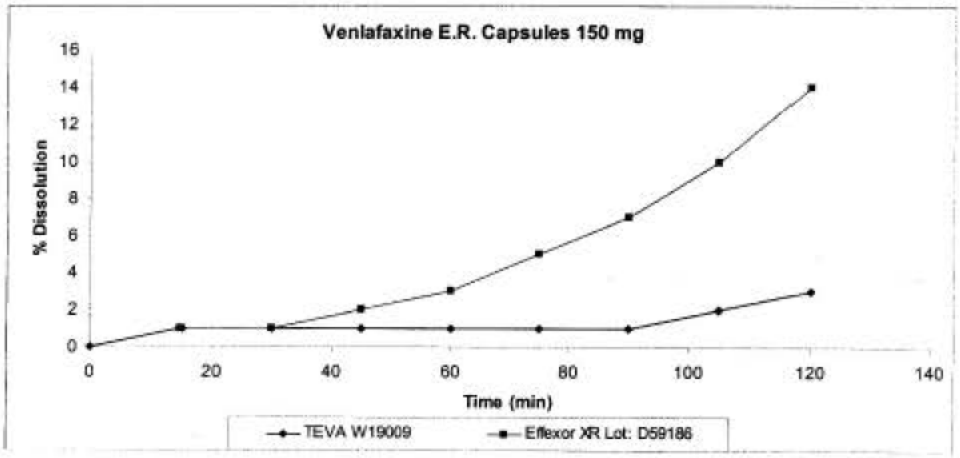


TAB#	% OF LABELED AMOUNT DISSOLVED							
	15 Minutes		30 Minutes		45 Minutes		60 Minutes	
	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	1	1	1	1	1	1	1	2
RSD%	68.2	33.9	64.0	27.5	36.5	18.6	33.2	11.9

TAB#	% OF LABELED AMOUNT DISSOLVED							
	75 Minutes		90 Minutes		105 Minutes		120 Minutes	
	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	1	4	2	5	4	7	7	9
RSD%	21.9	10.3	13.8	9.0	16.0	8.8	13.4	8.1

0.1N HCl with 20% alcohol

Batch No.	Parameters	% OF LABELED AMOUNT DISSOLVED							
		15 Minutes	30 Minutes	45 Minutes	60 Minutes	75 Minutes	90 Minutes	105 Minutes	120 Minutes
TEVA W19009	Mean of 12 tablets	1	1	1	1	1	1	2	3
	RSD%	74.1	77.4	37.7	36.5	44.4	44.8	30.9	21.4
Effexor XR Lot: E59186	Mean of 12 tablets	1	1	2	3	5	7	10	14
	RSD%	88.5	59.5	33.6	22.7	17.7	17.2	15.2	14.7

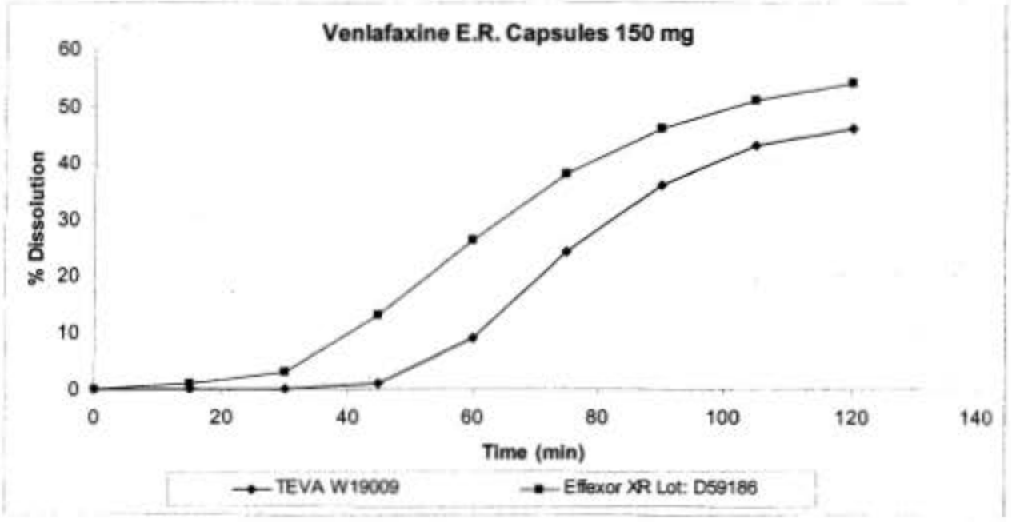


TAB#	% OF LABELED AMOUNT DISSOLVED							
	15 Minutes		30 Minutes		45 Minutes		60 Minutes	
	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	1	1	1	1	1	2	1	3
RSD%	74.1	88.5	77.4	59.5	37.7	33.6	36.5	22.7

TAB#	% OF LABELED AMOUNT DISSOLVED							
	75 Minutes		90 Minutes		105 Minutes		120 Minutes	
	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	1	5	1	7	2	10	3	14
RSD%	44.4	17.7	44.8	17.2	30.9	15.2	21.4	14.7

0.1 N HCl with 40% alcohol

Batch No.	Parameters	% OF LABELED AMOUNT DISSOLVED							
		15 Minutes	30 Minutes	45 Minutes	60 Minutes	75 Minutes	90 Minutes	105 Minutes	120 Minutes
TEVA W19009	Mean of 12 tablets	0	0	1	9	24	36	43	46
	RSD%	161.3	106.4	69.1	28.8	12.3	8.0	6.0	7.7
Effexor XR Lot: E59186	Mean of 12 tablets	1	3	13	26	38	46	51	54
	RSD%	44.7	28.3	17.4	11.0	8.2	6.4	6.9	4.1



TAB#	% OF LABELED AMOUNT DISSOLVED							
	15 Minutes		30 Minutes		45 Minutes		60 Minutes	
	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	1	0	3	1	13	9	26
RSD%	161.3	44.7	106.4	28.3	69.1	17.4	28.8	11.0

TAB#	% OF LABELED AMOUNT DISSOLVED							
	75 Minutes		90 Minutes		105 Minutes		120 Minutes	
	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186	TEVA W19009	Effexor XR Lot: D59186
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	24	38	36	46	43	51	46	54
RSD%	12.3	8.2	8.0	6.4	6.0	6.9	7.7	4.1

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)	8 6-10%, 16.8%	5 4-7%, 19.3%	6 0-8%, 23.9%	59 50-70%, 11.9%
Reference Mean (Range, RSD)	11 9-15%, 17.0%	9 7-11%, 13.6%	13 8-22%, 30.4%	56 14-71%, 34.8%
75 mg capsule	Mean % Drug Release (At 2 hours)			
Test Mean (Range, RSD)	5 3-6%, 25.0%	4 2-7%, 42.7%	2 0-4%, 66.0%	39 6-54%, 41.4%
Reference Mean (Range, RSD)	11 9-13%, 9.0%	10 6-12%, 15.2%	13 10-16%, 11.6%	54 15-69%, 33.5%
150 mg capsule	Mean % Drug Release (At 2 hours)			
Test Mean (Range, RSD)	9 8-10%, 10.4%	7 6-9%, 13.4%	3 2-4%, 21.4%	46 40-50%, 7.7%
Reference Mean (Range, RSD)	9 8-11%, 10.3%	9 8-10%, 8.1%	14 10-18%, 14.7%	54 52-58%, 4.1%

Reviewer's Comments:
Dissolution testing was conducted in 0.1 N HCl in the absence and presence of various concentrations of alcohol (5, 20, and 40%). The results of comparative dissolution testing on the 37.5 mg, 75 mg and 150 mg strengths of venlafaxine hydrochloride extended-release capsules and the RLD using various concentrations of ethanol in the dissolution medium show similar drug release at 2 hours in 40% ethanol. Therefore, Teva' Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg, 75 mg and 150 mg are comparable to the reference product Effexor XR® (venlafaxine hydrochloride) Capsules, 37.5 mg, 75 mg and 150 mg. The firm's response is acceptable.

3.2 Deficiency Comments

None

3.3 Recommendations

The in vitro alcohol dose dumping testing conducted by Teva Pharmaceuticals USA on Venlafaxine Hydrochloride Extended Release Capsules, 150 mg, lot #W19009, 75 mg, lot # W24012 and 37.5 mg, lot # W17005 comparing to the reference product, Effexor XR® Capsules, 150 mg, lot # D59186, 75 mg, lot # E06978 and 37.5 mg, lot # E07067, respectively, manufactured by Wyeth, is acceptable.

The previous DBE recommendations remain unchanged (v:/firmsnz/Teva/ltrs&rev/ 76565A0604.doc).

3.4 Additional Attachments

None

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 076565

APPLICANT: Teva Pharmaceuticals USA

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: 076565

4 *COMPLETED ASSIGNMENT FOR 76565 ID: 11076*

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
11076	4/23/2010	Other	In-vitro dose-dumping in alcohol	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Amendment (s)	
In-vitro dose-dumping in alcohol	1
Study Amendment Total	*1*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-76565	ORIG-1	TEVA PHARMACEUTICALS USA INC	VENLAFAXINE HYDROCHLORIDE

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
05/06/2010

MOHEB H MAKARY
05/06/2010

ETHAN M STIER on behalf of BARBARA M DAVIT
05/06/2010

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-565	SPONSOR : Teva Pharmaceutical
DRUG AND DOSAGE FORM:	Venlafaxine Oral Extended Release Capsules
STRENGTH(S):	37.5 mg, 75mg & 150mg
TYPES OF STUDIES:	Fasting, fasting (sprinkled) and Fed
CLINICAL STUDY SITE(S):	Anapharm Inc., Canada
ANALYTICAL SITE(S):	(b) (4)

STUDY SUMMARY : Fasting, fasting (sprinkled) and fed studies on 150 mg Extended Release Capsules are acceptable.
DISSOLUTION: Acceptable
WIVER REQUEST: A waiver of in vivo bioequivalence study requirements for 37.5mg, and 75mg strengths Extended Release Capsules is acceptable.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic: Yes New facility: No For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

Proposed Dissolution Method and Spec from Original Submission Acceptable: Yes___ No X
(If No, Project Manager (PM) should verify and sign below when acknowledgement amendment is received)
DBE Dissolution Method and Spec acknowledged by firm: Date___X_____
Amendment Date: March 25, 2005
PROJECT MANAGER: ___Keri Suh_____ DATE:__04/06/05_____

PRIMARY REVIEWER : Nhan L. Tran, Ph.D. BRANCH : III
INITIAL : _____ DATE : 4-6-05

TEAM LEADER : Yih Chain Huang, Ph.D. BRANCH : III
INITIAL : _____ DATE : 4/6/2005

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
INITIAL : _____ DATE : 4/6/05

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-565
Drug Product Name	Venlafaxine Hydrochloride Extended Release Capsules
Strengths	150 mg, 37.5, 75mg
Applicant Name	Teva Pharmaceuticals USA
Address	1090 Horsham Road, North Wales, Pennsylvania, USA 19454
Submission Date	December 10, 2002
Amendment Dates	February 13, 2003: Adding 37.5 mg & 75 mg strengths April 10, 2003: Additional fasting study (mixed with apple sauce)
Reviewer	Nhan L. Tran
First Generic	Yes
File Location	V:\firmsnz\Teva\ltrs&rev\76565 N1202

I. Executive Summary

Teva is referencing Wyeth's Effexor® XR Capsules, 150 mg. The sponsor has conducted three (3) bioequivalence studies a) a single-dose fasting, b) a single dose non-fasting and c) a single dose fasting with the content of the capsule mixed with applesauce. The results (point estimate, 90% CI) of the fasting study of 22 male and female normal healthy volunteers (24 enrolled, 22 completed) are: For the parent drug: LAUCt 105.3, 100.4-110.5%; LAUCi 103.1, 97.8-108.7%; and LCmax 106.8, 100.5-113.5% and for the metabolite (O-desmethylvenlafaxine): LAUCt 108.2, 104.8-111.8%; LAUCi 97.7, 92.9-102.8%; and LCmax 114.2, 109.29-119.35%. For the fed study, the firm stated that, since the fed study was conducted before the Food Guidance was published (the fed study started on 09/26/2002, the Food Guidance was published on 1/30/2003), point estimates instead of 90% C.I. limits were used for equivalence determination. The results (18 enrolled, 17 completed) are: For the parent drug: LAUCt 98.07; LAUCi 100.41; and LCmax 85.88 and for the metabolite: LAUCt 98.21; LAUCi 97.44; and LCmax 97.15. For the fasting (sprinkled) study (24 enrolled, 18 completed), the results (point estimate, 90% CI) are: For the parent drug: LAUCt 111.14, 104.67-118.02%; LAUCi 107.51, 102.42-112.84%; and LCmax 116.22, 108.33-124.68%. Sine no results of the metabolite were reported, this study is incomplete.

The firm conducted comparative dissolution testing using the FDA recommended dissolution method (900 mL water, USP Apparatus I (basket) at 100 rpm) on 37.5 mg, 75 mg and 150 mg Extended Release Capsules. In addition, comparative dissolution testing using the FDA recommended dissolution method (Basket at 100 rpm, 900 ml) on 150 mg capsule strength in different media (0.1 N HCl, phosphate buffer pH 4.5 and 6.8) was performed. Since the submission is incomplete, the waivers of *in vivo* bioequivalence study requirements for 37.5 mg, and 75 mg capsules are not considered at this time.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Venlafaxine Hydrochloride Extended Release Capsules, 150mg
Reference Product	Effexor^{R} XR Capsule, 150 mg
RLD Manufacturer	Wyeth Laboratories Inc.
NDA No.	20-699
RLD Approval Date	October 20, 1997
Indication	For the treatment of depression

B. PK/PD Information

Bioavailability	Venlafaxine is well absorbed after oral administration, and about 92% of a single dose of venlafaxine is absorbed. The relative bioavailability of venlafaxine from an immediate release (IR) capsule was 100% when compared to an oral solution.
Food Effect	Bioavailability is not affected by food.
Metabolism	Venlafaxine is extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the only major active metabolite.
Excretion	Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours.
Half-life	5±2 hours for venlafaxine and 11±2 hours for ODV.
Relevant OGD or DBE History	The RLD for Venlafaxine Extended Release Capsules is Effexor[R] XR Capsule, 150 mg by Wyeth (Orange Book). There are several Control Documents (CD) on Venlafaxine ER Capsules: 02-051, 02-259, 02-628, 02-724, 03-182, 03-290, and 03-883. In those CDs, the Division of Bioequivalence (DBE) has recommended the following (original text in *italic*): 1. *The following studies are recommended to establish bioequivalence of Venlafaxine Hydrochloride ER Capsules:* a. *A single-dose fed bioequivalence study comparing Venlafaxine HCl ER Capsules, 150 mg, to the reference listed drug (RLD), Effexor® XR (Venlafaxine HCl) Extended-Release Capsules, 150 mg. Please apply the 90 % confidence intervals criteria to your fed bioequivalence study.* b. *A single-dose fed bioequivalence study comparing Venlafaxine HCl ER Capsules, 150 mg, to the RLD, Effexor® XR (Venlafaxine HCl) Extended-Release Capsules, 150 mg. The contents of the capsules should be sprinkled over a teaspoonful of applesauce.* c. *The significant occurrence of nausea and vomiting with both the 75 mg and 37.5 mg dose under fasting conditions makes it difficult to perform bioequivalence studies under fasting conditions. The approved labeling of the RLD recommends administration with food. Administration of a single dose of 150 mg under fed conditions is well tolerated.* 2. *Both venlafaxine and its active metabolite, O-desmethyl venlafaxine, should be measured for the bioequivalence studies.* 3. *Waivers of in-vivo bioequivalence study requirements may be granted for the lower strengths of the drug product based on acceptable in-vivo bioequivalence studies on the higher strength, formulation proportionality of all strengths, and acceptable comparative dissolution profiles on all strengths.* 4. *Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using USP apparatus I (basket) at 100 rpm in 900 mL of water at 37°C, and USP apparatus I (basket) at 75, and/or 100 rpm in aqueous media of the following pHs: 1.2, 4.5, and 6.8. In order to detect premature release of the drug (dose dumping) from the formulation, please include early sampling times of 1, 2, and 4 hours and continue until at least (b) (4) % of the drug is released.* It should be noted that although the DBE recommended a fed single dose study and a fed single dose study with the content of the capsule mixed with applesauce, TEVA conducted 3 separate studies a) a fasting b) a non-fasting and c) a fasting study with the content of the capsule mixed with applesauce. Since this will be the first generic, the DBE was asked to examine the submission, which was examined on January 2, 2003 and March 5, 2003. The DBE has determined that the application was complete for filing.
Agency Guidance	None.
Drug Specific Issues (if any)	Adverse reactions including tremor, myoclonus, diaphoresis, nausea, vomiting, seizures, and death.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	2
Single-dose fed	Yes	1
Steady-state	No	
In vitro dissolution	Yes	5
Waiver requests	Yes	2
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

D. Pre-Study Bioanalytical Method Validation

	Parent	Metabolite
Analyte name	Venlafaxine	O-desmethylvenlafaxine (ODV)
Internal Standard	(b) (4)	(b) (4)
Method description	HPLC with MS Detection	HPLC with MS Detection
QC range	15. ng/mL To 140 ng/mL	15.0 ng/mL To 280.0 ng/mL
Standard curve range	5.05 ng/mL To 200 ng/mL	5.0 ng/mL To 400.0 ng/mL
Limit of quantitation	5.0 ng/mL	5.0 ng/mL
Average recovery of Drug (%)	83.47 to 92.36	84.42 to 92.66
Average Recovery of Int. Std (%)	93.19	93.19
Intraday precision range (%CV)	4.15 to 13.39	3.4 to 13.61
Intraday accuracy range (%)	93.56 To 109.35	93.12 to 106.95
Interday precision range (%CV)	4.51 To 12.06	3.79 to 12.83
Interday accuracy range (%)	95.68 To 106.65	95.03 to 108.54
Bench-top stability (hrs)	42 at room temp.	42 at room temp.
Freeze-thaw stability (cycles)	5	5
Long-term storage stability (days)	95 @ -20^{0}C	95 @ -20^{0}C
Dilution integrity	Accuracy 95.80%	Accuracy 97.25%
Specificity	No significant Interference	No significant interference
SOPs submitted	Yes	Yes
Bioanalytical method is acceptable	Yes	Yes
20% Chromatograms included (Y/N)	Yes	Yes
Random or Serial Selection of Chrom	Yes (serially)	Yes (serially)

A. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	02204
Study Design	Randomized, 2-way Crossover, single-dose
No. of subjects enrolled	24
No. of subjects completing	22
No. of subjects analyzed	22
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 16 Female: 6
Test product	Venlafaxine Extended Release Capsule
Reference product	Effexor^{R} XR Capsule
Strength tested	150 mg
Dose	1 x 150 mg

Summary of Statistical Analysis of Venlafaxine		
Parameter	**Point Estimate**	**90% Confidence Interval (Log transformed)**
AUC0-t	1.05	100.37 – 110.55
AUC∞	1.03	97.80 – 108.73
Cmax	1.06	100.54 – 113.54
Summary of Statistical Analysis of O-desmethylvenlafaxine		
Parameter	**Point Estimate**	**90% Confidence Interval (Log transformed)**
AUC0-t	1.08	104.84 – 111.79
AUC∞	0.97	92.92 – 102.85
Cmax	1.14	109.29 – 119.35

Reanalysis of Study Samples, Fasting Bioequivalence Study—Venlafaxine								
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**
Unacceptable internal std. Response	4	1	0.43	0.11	4	1	0.43	0.11
Incomplete analysis	3	10	0.32	1.08	3	10	0.32	1.08
Above upper limit of quantitation	18	7	1.95	0.76	18	7	1.95	0.76
Pharmacokinetic repeats	0	2	0	0.22	0	2	0	0.22
Sample reanalyzed to obtain confirming value	9	4	0.98	0.43	9	4	0.98	0.43
Rejected sample dilution	56	20	6.07	2.17	56	20	6.07	2.17
Total	**90**	**44**	**9.76**	**4.77**	**90**	**44**	**9.76**	**4.77**

- Total number of study samples = 922
- Total number of samples not available or unacceptable = 2
- According to the analytical firm's SOP (Refer to SOP (b) (4) 7000, Addendum IV), two samples were subjected to pharmacokinetic repeat. Those 2 samples were from subject #16, Period 2 (Reference product). The repeats were not involved Cmax.
- The reviewer has verified that the use of recalculated plasma concentration data does not change the study outcome.
- According to reviewer's opinion, the analytical study and selection of samples are acceptable.

Reanalysis of Study Samples, Fasting Bioequivalence Study—O-desmethylvenlafaxine								
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
Unacceptable internal std. Response	3	1	0.32	0.10	3	1	0.32	0.10
Incomplete analysis	2	2	0.22	0.22	2	2	0.22	0.22
Sample reanalyzed to obtain confirming value	3	1	0.32	0.10	3	1	0.32	0.10
Rejected sample dilution	34	12	3.68	1.30	34	12	3.68	1.30
Total	**42**	**16**	**4.55**	**1.73**	**42**	**16**	**4.55**	**1.73**

- Total number of study samples = 922
- Total number of samples not available or unacceptable = 2
- No reanalyzed samples were involving Cmax values.

The reviewer confirmed that the use of recalculated plasma concentration data does not change the study outcome.

2. Single-dose Fed Bioequivalence Study

Study No.	02205
Study Design	Randomized, 2-way crossover, single-dose
No. of subjects enrolled	18
No. of subjects completing	17
No. of subjects analyzed	17
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male 12 Female 5
Test product	Venlafaxine Extended Release Capsule
Reference product	Effexor^{R} XR Capsule
Strength tested	150 mg
Dose	1 x 150 mg

Summary of Statistical Analysis of Venlafaxine & O-Desmethylvenlafaxine		
Parameter	**Point Estimate**	
(Log transformed data)	**Venlafaxine**	**O-Desmethylvenlafaxine**
AUC_{0-t}	0.98	0.98
AUC_{∞}	1.00	0.97
Cmax	0.86	0.97

Reanalysis of Study Samples, Fed Bioequivalence Study—Venlafaxine								
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
Unacceptable internal std. Response	1	4	0.14	0.56	1	4	0.14	0.56
Incomplete analysis	3	0	0.42	0	3	0	0.42	0
Pharmacokinetic repeats	1	3	0.13	0.42	1	3	0.13	0.42
Sample reanalyzed to obtain confirming value	2	6	0.28	0.84	2	6	0.28	0.84
Total	**7**	**13**	**0.98**	**1.82**	**7**	**13**	**0.98**	**1.82**

- Total number of study samples = 712

- Total number of samples not available or unacceptable = 2
- According to the analytical firm's SOP (Refer to SOP (b) (4) 7000, Addendum IV), 4 samples were subjected to pharmacokinetic repeat. Those 4 samples were: 1 from subject #8, Period 1 (Reference product), 1 from subject #9, Period 1 (Test product), 2 from subject #9, Period 2 (Reference product). The repeats were not involved Cmax.
- Using both values in the analysis, the reviewer confirmed that the use of recalculated plasma concentration data does not change the study outcome.
- According to reviewer's opinion, the analytical study and selection of samples are acceptable.

The use of recalculated plasma concentration data does not change the study outcome.

Reanalysis of Study Samples, Fed Bioequivalence Study----O-Desmethylvenlafaxine								
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**
Unacceptable internal std. Response	1	4	0.14	0.56	1	4	0.14	0.56
Incomplete analysis	3	0	0.42	0	3	0	0.42	0
Pharmacokinetic repeats	3	1	0.42	0.14	3	1	0.42	0.14
Sample reanalyzed to obtain confirming value	3	5	0.42	0.70	3	5	0.42	0.70
Total	**10**	**10**	**1.4**	**1.4**	**10**	**10**	**1.4**	**1.4**

- Total number of study samples = 712
- Total number of samples not available or unacceptable = 2
- According to the analytical firm's SOP (Refer to SOP (b) (4) 7000, Addendum IV), 4 samples were subjected to pharmacokinetic repeat. Those 4 samples were: 1 from subject #4, Period 2 (Test product), 1 from subject #8, Period 1 (Reference product), 1 from subject #8, Period 2 (Test product) and 1 from subject #9, Period 1 (Test product). The repeats were not involved Cmax.
- The use of recalculated plasma concentration data does not change the study outcome.
- According to reviewer's opinion, the analytical study and selection of samples are acceptable.

The use of recalculated plasma concentration data does not change the study outcome.

3. Fasting Study with the drug mixed with applesauce.

Study Summary	
Study No.	30024
Study Design	Randomized, 2-way Crossover, single-dose
No. of subjects enrolled	24
No. of subjects completing	19
No. of subjects analyzed	19
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 14 Female: 5
Test product	Venlafaxine Extended Release Capsule
Reference product	Effexor^{R} XR Capsule
Strength tested	150 mg
Dose	1 x 150 mg. Content of the capsule mixed with applesauce

Summary of Statistical Analysis of Venlafaxine		
Parameter	**Point Estimate**	**90% Confidence Interval (Log transformed)**
AUC0-t	1.11	104.67 – 118.02
AUC∞	1.07	102.42 – 112.84
Cmax	1.16	108.33 – 124.68

Summary of Statistical Analysis of O-desmethylvenlafaxine		
Parameter	**Point Estimate**	**90% Confidence Interval (Log transformed)**
AUC0-t	Not provided	Not provided
AUC∞	Not provided	Not provided
Cmax	Not provided	Not provided

Reanalysis of Study Samples, Fasting Bioequivalence Study (Sprinkled)								
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**
Unacceptable internal std. Response	1	1	0.12	0.12	1	1	0.12	0.12
Above upper limit of quantitation	7	0	0.84	0	7	0	0.84	0
Above or below modified calibration range	33	28	3.95	3.35	33	28	3.95	3.35
Repeated or reinjected by error	0	1	0	0.12	0	1	0	0.12
Pharmacokinetic repeats	1	1	0.12	0.12	1	1	0.12	0.12
Sample reanalyzed to obtain confirming value	3	1	0.36	0.12	3	1	0.36	0.12
Total	**45**	**32**	**5.39**	**3.83**	**45**	**32**	**5.39**	**3.83**

- Total number of study samples = 835
- Total number of samples not available or unacceptable = 1
- According to the analytical firm's SOP (Refer to SOP (b) (4) 7000, Addendum IV), two samples were subjected to pharmacokinetic repeat. Those 2 samples were from subject #16, Period 2 (Reference product). The repeats were not involved Cmax.
- The use of recalculated plasma concentration data does not change the study outcome.
- According to reviewer's opinion, the analytical study and selection of samples are acceptable.

The use of recalculated plasma concentration data does not change the study outcome.

Reanalysis of Study Samples, Fasting Bioequivalence Study for O-desmethylvenlafaxine (Sprinkled)								
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**
Unacceptable internal std. Response	1	1	0.12	0.12	1	1	0.12	0.12
Above upper limit of quantitation	0	1	0	0.12	0	1	0	0.12
Sample reanalyzed to obtain confirming value	1	2	0.12	0.24	1	2	0.12	0.24
Total	**2**	**4**	**0.24**	**0.48**	**2**	**4**	**0.24**	**0.48**

- Total number of study samples = 835
- Total number of samples not available or unacceptable = 1
- No reassay samples were Cmax.

F. Formulation

Location in appendix	Section Formulation Data
Inactive ingredients within IIG Limits (yes or no)	**Yes**
If no, list ingredients outside of limits	**N/A**
If a tablet, is the product scored? (yes or no)	**N/A**
If yes, which strengths are scored?	**N/A**
Is scoring of RLD the same as test? (yes or no)	**N/A**
Formulation is acceptable (yes or no)	**Yes**
If not acceptable, why?	**N/A**

G. In Vitro Dissolution

Source of Method	FDA
Medium	Water
Volume (mL)	900
USP Apparatus type	I (Basket)
Rotation (rpm)	100
Firm's proposed specifications	(b) (4)
FDA-recommended specifications:	
F2 metric calculated (yes or no)	Yes
If no, reason why F2 not calculated	N/A
Method is acceptable (yes or no)	Yes

H. Waiver Request(s)

Strengths for which waivers requested	37.5mg and 75mg
Regulation cited	No
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	Yes
Waiver granted (yes or no)	No (See Deficiencies)

I. Deficiency Comment

1. For the fasting (sprinkled) study, the firm is requested to submit pharmacokinetic data of venlafaxine metabolite (ODV) along with the statistical analysis for evaluation.
2. For the fasting study, it is noted that Subject #1 vomited at 4 hrs 54 minutes after dosing in Period 1 (Test formulation). However this subject was allowed to continue the study. Please note that data from subjects who experience emesis any time during the labeled dosing interval should be deleted (as subjects #2 and #24 in the study). The firm is requested to re-calculate pharmacokinetic parameters and statistically re-analyze the data without subject # 1.
3. The firm indicated that Phosphate buffer pH 4.5 was used. However, normally pH of acetate buffer ranges from 4.1 to 5.5 and pH of phosphate buffer from 5.8 to 8. The firm is requested to clarify this matter.

J. Recommendations

1. The *in vivo* bioequivalence studies conducted under fasting and fasting (sprinkled) conditions by Teva Pharmaceuticals on its Venlafaxine Hydrochloride 150 mg Extended Release Capsules, lot #K30455, comparing it to the reference product Effexor® XR 150 mg Capsule (Wyeth), lot #9010767, are incomplete.

2. The dissolution testing conducted by Teva Pharmaceuticals on its Venlafaxine Hydrochloride 150 mg, 37.5 mg, 50 mg, 75 mg and 100 mg Extended Release Capsules is acknowledged.

3. The waiver request for 37.5 mg and 75 mg capsules is not considered at this time due to Deficiencies above.

4. Hence, the application is incomplete.

5/27/04

Nhan L. Tran, Ph.D., Review Branch III

5/27/2004

Y.C. Huang, Ph.D., Team Leader, Review Branch III

Barbara M Davit 5/27/04

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

I. Appendix

K. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information	
Study Number	02204
Study Title	Randomized, 2-way crossover, bioequivalence study of Venlafaxine 150 mg Extended Release Capsules and Effexor® XR 150 mg Extended Release Capsules administered as 1x150 mg capsule in healthy subject under fasting conditions.
Clinical Site	Anapharm Inc., Sainte-Foy, Quebec, Canada
Principal Investigator	Eric Masson, Pharm.D.
Study/Dosing Dates	Period I: 09-21-2002; Period II: 09-28-2002
Analytical Site	(b) (4)
Analytical Director	Not provided
Analysis Dates	10-02-2002 to 10-28-2002
Storage Period (no. of days from first sample to final analysis)	37 Days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Venlafaxine HCl	Effexor[R] XR
Manufacturer	Teva Pharmaceuticals	Wyeth Laboratories
Batch/Lot No.	Lot K-30455	9010767
Manufacture Date	8-27-2002	N/A
Expiration Date	N/A	March 2003
Strength	150 mg	150 mg
Dosage Form	Capsule	Capsule
Batch Size	(b) (4)	N/A
Potency	(b) (4) %	N/A
Content Uniformity	101%	100%
Formulation	See Formulation	
Dose Administered	1x150 mg	1x150 mg
Route of Administration	Oral	Oral
No. of Sequences	2	
No. of Periods	2	
No. of Treatments	2	
No. of Groups	1	
Washout Period	7 days	
Randomization Scheme	AB: 1, 2, 4, 7, 8, 10, 14, 15, 16, 20, 21, 24 BA: 3, 5, 6, 9, 11, 12, 13, 17, 18, 19, 22, 23	
Blood Sampling Times (hrs)	0, 1, 2, 3, 4, 5, 5.5, 6, 6.33, 6.67, 8, 8.5, 9, 10, 12,16,24,36	
Blood Volume Collected/Sample	1x7 mL	
Blood Sample Processing/Storage	-20±5^{0}C	
IRB Approval	Yes	
Informed Consent	Yes	
Subjects Demographics	See Table1	
Length of Fasting	10 hours	
Length of Confinement	34 hours	
Safety Monitoring	Yes	

Table 1 Demographics of Study Subjects (N=22)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	100
Mean	41	Mean	73.2	18-40	50	Male	71	Afr. Amer.	0
SD	12	SD	9.7	41-64	50	Female	29	Hispanic	0
Range	23-57	Range	57-95	65-75	0			Asian	0

Study Results

Dropout Information

Subject No	2	24
Reason	Vomited 4 hrs after dosing	Vomited 4 hrs after dosing
Period	1	1
Replacement	No	No

It is noted that Subject #1 also vomited at 4 hrs 54 minutes after dosing in Period 1 (Test formulation). However this subject was allowed to continue the study. There was no explanation why this subject was not withdrawn from the study as Subjects #2 and 24.

Study Adverse Events (that were possibly/probably related to the study drugs)

Adverse Event Description*	# in Test Group	# in Reference Group
Vomiting	3	
Heartburn	2	
High blood pressure	4	5
Nausea	6	4
Headache	3	3
Hot flushes	1	1
Dizziness	2	3
Fatigue	2	1
Loose stool	3	3
Lost appetite	4	6
Total:	30	26

* All were mild or moderate in intensity.

Protocol Deviations

No significant protocol deviations were reported.

Comments:
As judged by the investigator the adverse events and protocol deviations did not compromise the integrity of the study.

Assay Validation – Within Study (Vol. 1.2, pages 309-321)

	Parent	Metabolite
QC Conc. (ng /mL)	14.81, 29.62, 59.24, 138.24	14.75, 59.02, 118.03, 275.41
Inter day Precision (%CV)	4.89 - 7.43	4.81 - 7.15
Inter day Accuracy (%)	102.88 - 108.97	101.90 – 110.02
Cal. Standards Conc. (ng/mL)	5, 10, 20, 40, 80, 120, 160, 200	5, 10, 40, 80, 160, 240, 320, 400
Inter day Precision (%CV)	2.81 – 5.38	3.61 – 5.59
Inter day Accuracy (%)	93.50 – 107.40	92.96 – 107.87
Linearity Range (R^2 values range)	0.9947 – 0.9985	0.9958 – 0.9981

Chromatograms:
There were no significant interfering peaks. Twenty percent of the chromatograms were included. All chromatograms were serially selected.

SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
(b) (4) 167.04	2002-25-10	Chromatographic Acceptance Criteria and Verification of Chromatograms

(b) (4) 7000.05	2002-07-22	Pharmacokinetic Repeats
(b) (4) 156.07	2001-04-26	Samples Reassay & Reporting of Final Concentrations

Comments on repeat assays.

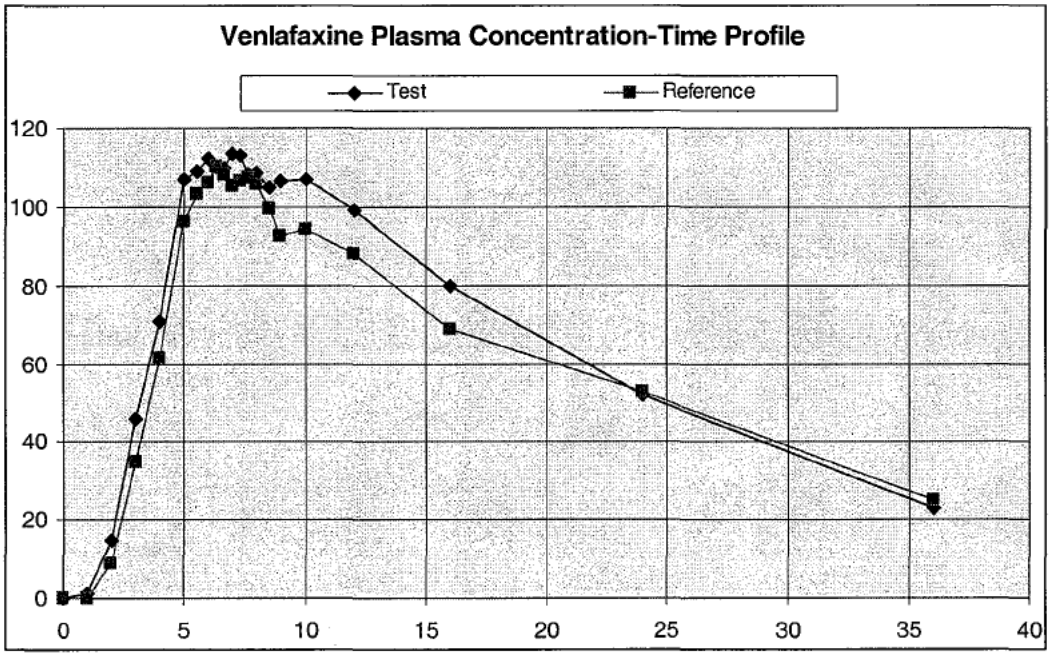
- All SOPs' were followed. There were no significant SOP or protocol deviations.
- Did recalculation of plasma concentrations change the study outcome? N/A
- Does the reviewer agree with the outcome of the repeat assays? Yes
- Provide any other comments about repeat assays. None
- QC concentrations are appropriate comparing to standard concentrations.

Conclusion: Analytical method is acceptable.

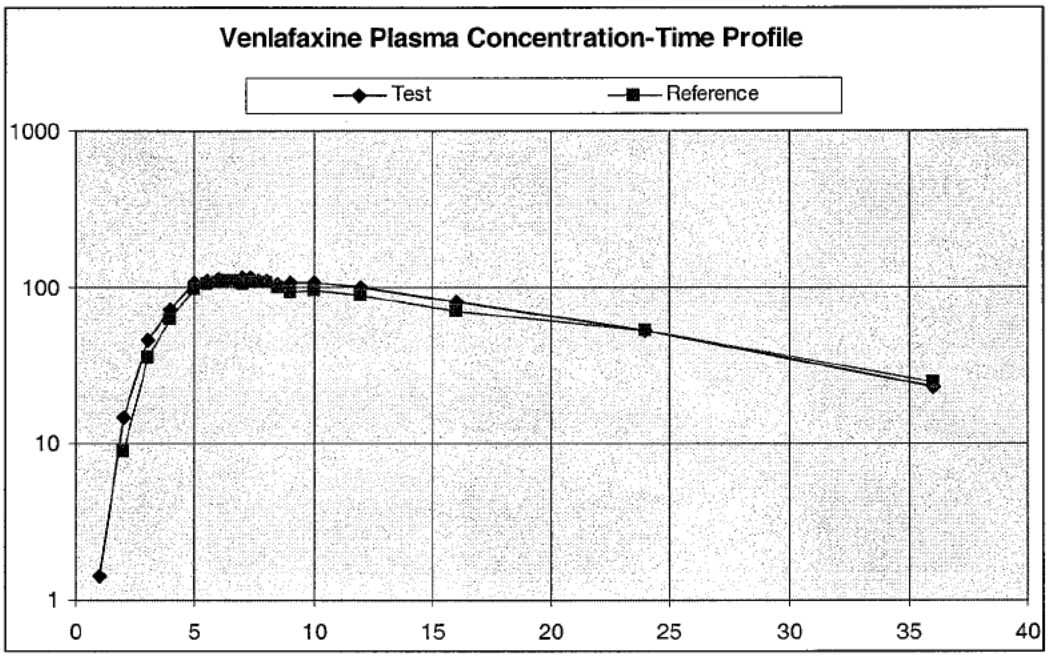
Mean plasma concentrations of Venlafaxine and O-Desmethylvenlafaxine (ODV)

Time	Test (T)	%CV	Ref (R)	%CV	T/R		Test (T)	%CV	Ref (R)	%CV	T/R
(hrs)	Venlafaxine						O-Desmethylvenlafaxine (ODV)				
0	0	0	0	0	0		0	0	0	0	0
1	1.41	228.9	0	0	0		2.75	223.9	0	0	0
2	14.56	65.71	8.89	84.08	1.63		18.96	92.61	11.93	81.31	1.59
3	46.05	48.34	34.77	42.41	1.32		51.23	56.11	43.24	56.85	1.18
4	71.0	45.13	61.35	44.32	1.15		81.80	60.51	73.47	55.32	1.11
5	106.72	39.47	96.41	38.49	1.10		114.78	59.55	107.24	54.33	1.07
5.5	109.02	37.42	103.19	39.63	1.05		124.52	55.83	113.90	54.98	1.09
6	112.12	38.08	105.98	41.60	1.05		137.56	54.39	124.84	54.41	1.10
6.33	109.97	38.65	110.07	40.02	1.00		138.45	54.39	132.88	51.35	1.04
6.67	109.93	39.62	107.95	45.20	1.01		145.17	54.28	134.61	52.76	1.08
7	113.35	38.45	105.19	43.14	1.08		151.10	52.05	140.21	51.88	1.08
7.33	113.13	39.79	106.34	43.55	1.06		155.60	54.05	141.94	50.27	1.09
7.67	108.31	39.31	107.40	46.47	1.00		154.92	52.61	146.28	51.87	1.06
8	108.33	40.25	105.56	46.84	1.03		162.39	51.84	146.50	49.23	1.10
8.5	104.76	41.99	99.66	48.00	1.05		160.50	52.26	149.26	49.31	1.07
9	106.53	44.13	92.74	48.59	1.15		168.51	50.77	150.52	49.74	1.12
10	106.90	47.92	94.32	54.00	1.13		176.91	50.71	153.28	46.84	1.15
12	99.21	52.82	87.86	60.06	1.13		181.35	50.32	158.58	47.20	1.14
16	79.78	67.80	68.92	68.75	1.16		174.48	48.70	149.70	45.29	1.16
24	52.12	91.13	52.94	83.11	0.98		135.68	44.27	131.05	46.62	1.03
36	22.91	123.3	24.78	104.1	0.92		73.61	45.02	76.40	43.91	0.96

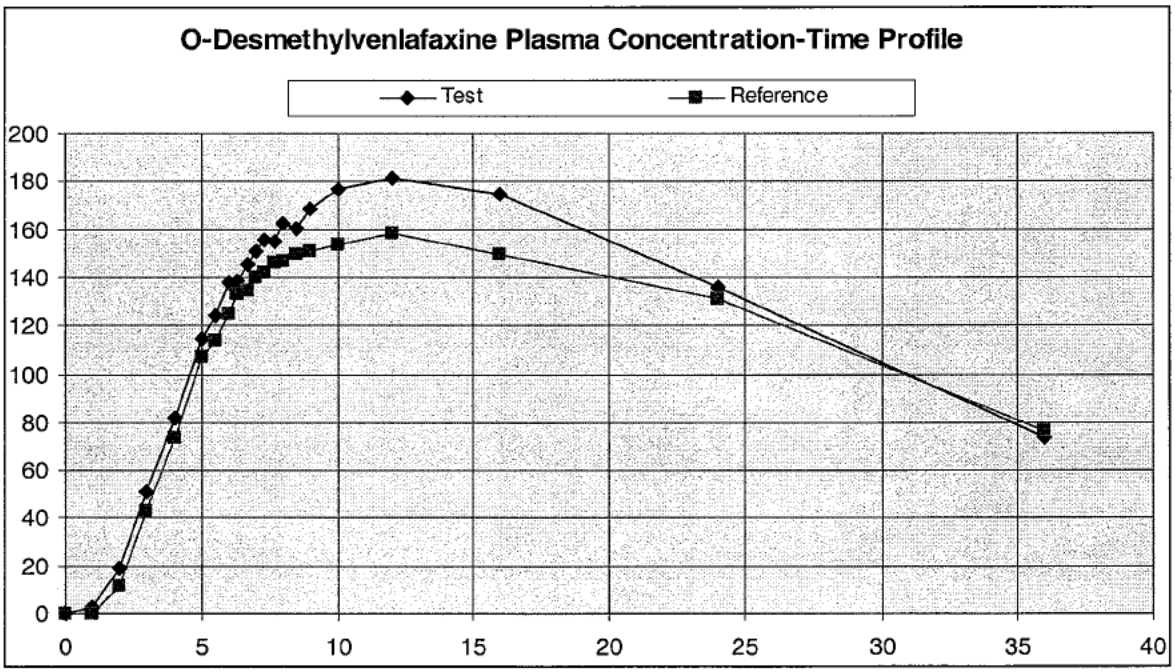
Linear Plot



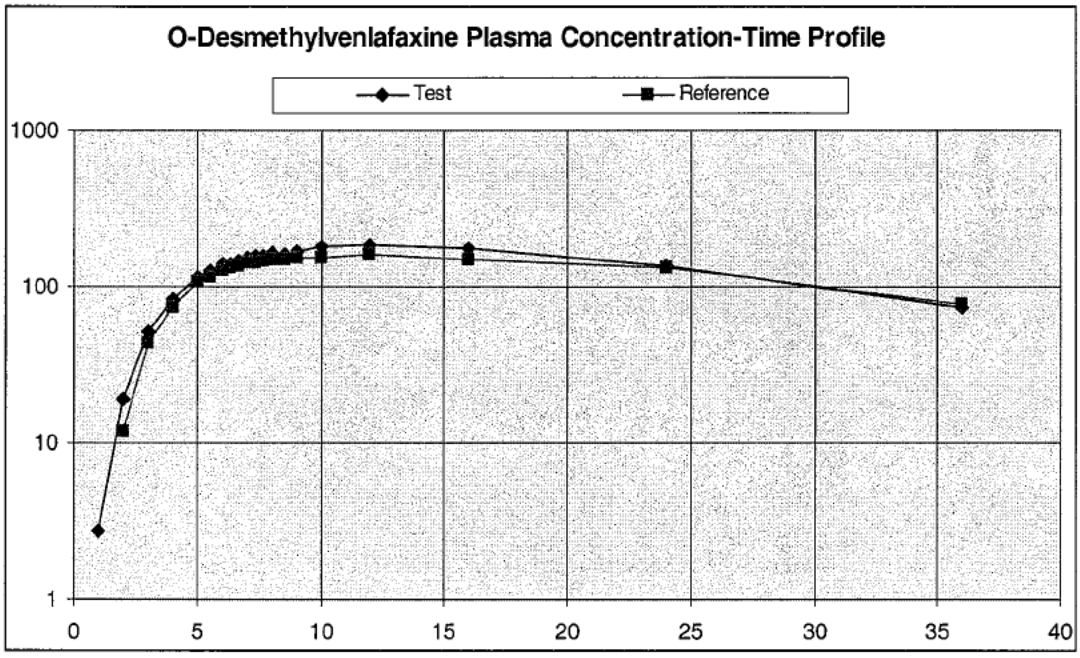
Semi-Log Plot



Metabolite Linear Plot:



Metabolite Semi-Log Plot



Mean Pharmacokinetic Parameters

Venlafaxine:

PARAMETERS	TEST MEAN	TEST %CV	REF. MEAN	REF %CV	RATIO TEST/REF	90% C.I (Log trans)
AUCt (ng.h/ml)	2257.53	64.65	2110.79	64.58	1.07	100.4-110.5
AUCI (ng.h/ml)	2811.08	79.68	2700.62	78.00	1.04	97.8-108.7
CMAX (ng/ml)	124.75	37.68	117.69	41.83	1.06	100.5-113.5
KE (1/h)	0.082	39.56	0.063	28.33	1.30	
THALF (h)	10.11	48.66	12.05	35.79	0.84	
TMAX (h)	7.29	23.18	6.99	19.21	1.04	

Additional Study Information

Root mean square error, AUC	0.092560
Root mean square error, Cmax	0.116380
Mean ratio AUC0-t/AUC∞	Test: 0.80 ; Ref. 0.78
Range of values, ratio AUC0-t/AUC∞	Test: 0.60-0.96; Ref.: 0.64 – 0.93

Comments: (on pharmacokinetic analysis)

- Ke and AUCi were determined for all 22 subjects.
- Indicate the number of subjects with the following:
  a. Measurable drug concentrations at 0 hr, None

b. First scheduled post-dose sampling time as Tmax, None
c. First measurable drug concentration as Cmax. None

- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? Yes
- Were there statistically significant sequence or period effects? No.
- Are the 90% confidence intervals for AUCt, AUCi, Cmax within the acceptable limits of 80-125%. Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect N/A
- Based on ratio AUCt/AUCinf (Test 0.80 and Ref 0.78), sampling time of 36 hours is not long enough.

Metabolite (O-desmethylvenlafaxine):

PARAMETERS	TEST MEAN	TEST %CV	REF. MEAN	REF %CV	RATIO T/R	90% C.I (Log transf.)
AUCt (ng.h/ml)	4539.33	46.74	4174.60	45.66	1.08	104.84-111.79
AUCI (ng.h/ml)	6797.15	37.65	6927.66	38.40	0.98	92.92-102.85
CMAX (ng/ml)	192.33	47.23	167.42	46.93	1.15	109.29-119.35
KE (1/h)	0.0432	28.59	0.0339	25.11	1.27	
THALF (h)	17.53	35.93	21.57	23.35	0.81	
TMAX (h)	13.14	33.25	12.70	42.43	1.03	

Additional Study Information

Root mean square error, AUC	0.061497
Root mean square error, Cmax	0.084325
Mean ratio AUC0-t/AUC∞	Test: 0.66 ; Ref. 0.60
Range of values, ratio AUC0-t/AUC∞	Test: 0.39-0.91; Ref.: 0.50 – 0.83

Comments: (on pharmacokinetic analysis)

- Ke and AUCi were determined for 19 subjects. Cannot determine Kel for subjects #8, 10 and 12 due to irregular terminal phases.
- Indicate the number of subjects with the following:
  a. Measurable drug concentrations at 0 hr, None
  b. First scheduled post-dose sampling time as Tmax, None
  c. First measurable drug concentration as Cmax. None
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? Yes
- Were there statistically significant sequence or period effects? No
- Are the 90% confidence intervals for AUCt, AUCi, Cmax within the acceptable limits of 80-125%. Yes

- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect N/A
- Based on ratio AUCt/AUCinf (Test 0.66, Ref 0.60), sampling time of 36 hours is too short.

Conclusion: The single-dose fasting bioequivalence study is incomplete. Since subject #1 experienced emesis during the labeled dosing interval (at 4 hrs 54 minutes after dosing in Period 1--Test formulation) this subject should be deleted from the study. The firm should re-analyze the data without this subject.

2. Single-dose Fed Bioequivalence Study

Study Information	
Study Number	02205
Study Title	Randomized, 2-way crossover, bioequivalence study of Venlafaxine 150mg ER Capsules and Effexor^{R} XR 150mg Capsules administered as 1x150 mg capsule in healthy subject under fed conditions
Clinical Site	Anapharm Inc., Sainte-Foy, Quebec, Canada
Principal Investigator	Eric Masson, Pharm.D.
Study/Dosing Dates	Period I: 09-26-2002; Period II: 10-03-2002
Analytical Site	(b) (4)
Analytical Director	Not provided
Analysis Dates	10-12-2002 to 11-01-2002
Storage Period (first sample to final analysis)	37 Days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Venlafaxine HCl Extended Release	Effexor^{R} XR
Manufacturer	Teva Pharmaceuticals	Wyeth Laboratories
Batch/Lot No.	Lot K-30455	9010767
Manufacture Date	Not provided	N/A
Expiration Date	N/A	March 2003
Strength	150 mg	150 mg
Dosage Form	Capsule	Capsule
Batch Size	(b) (4)	N/A
Potency	(b) (4) %	N/A
Content Uniformity	101%	100%
Formulation	Formulation (page 31)	
Dose Administered	1x150 mg	1x150 mg
Route of Administration	Oral	Oral
No. of Sequences	2	
No. of Periods	2	
No. of Treatments	2	
No. of Groups	1	
Washout Period (days)	7	
Randomization Scheme	AB: 2, 5, 7, 9, 11, 12, 13, 15, 18 BA: 1, 3, 4, 6, 8, 10, 14, 16, 17	
Blood Sampling Times (hrs)	0, 1, 2, 3, 4, 5, 5.5, 6, 6.33, 6.67, 8, 8.5, 9, 10, 12,16,24,36	
Volume Collected/Sample	1x7 mL	
IRB Approval	Yes	
Informed Consent	Yes	
Subjects Demographics	See Table2	
Length of Fasting	10 hours before the breakfast	
Length of Confinement	34 hours	
Safety Monitoring	Yes	

Table 2 Demographics of Study Subjects (N=17)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
Mean	41	Mean	72.8	<18	0	Male	72%	Caucasian	100
SD	12	SD	**12**	18-40	61%	Female	28%	Afr. Amer.	
Range	**20-63**	**Range**	**52-97**	41-64	39%			Hispanic	
				65-75	0			Asian	

Study Results

Dropout Information

Subject No	3
Reason	Vomited
Period	1
Replacement	No

Study Adverse Events

Adverse Event Description*	# in Test Group	# in Reference Group
Nausea	**4**	**8**
Headache	**1**	**1**
Hot flushes	**1**	**0**
Drowsiness	**1**	**2**
Loose stools	**1**	**1**
Dizziness	**1**	**1**
Flatulence	**1**	**1**
Vomiting	**0**	**1**
High blood pressure	**6**	**4**
Total:	**16**	**19**

* All were mild or moderate in intensity.

Protocol Deviations

No significant protocol deviations were reported.

Comments: As judged by the investigator the adverse events did not compromise the integrity of the study.

Assay Validation – Within Study

	Parent	Metabolite
QC Conc. (ng, /mL)	14.81, 29.92, 59.24, 138.24	14.75, 59.02, 118.03, 275.41
Inter day Precision (%CV)	5.13 –9.31	5.15 – 7.97
Inter day Accuracy (%)	102.04 – 107.15	100.21 – 107.99
Cal. Standards Conc. (ng/mL)	4.99, 9.99, 19.98, 39.95, 79.90, 119.86, 159.81, 199.76	4.93, 9.89, 39.42, 78.85, 157.70, 236.54, 315.39, 394.24
Inter day Precision (%CV)	4.26 –6.18	4.53 – 8.19
Inter day Accuracy (%)	95.16 – 108.46	94.52 – 106.44
Linearity Range (range of R^2)	0.9949 – 0.9981	0.9957 – 0.9987

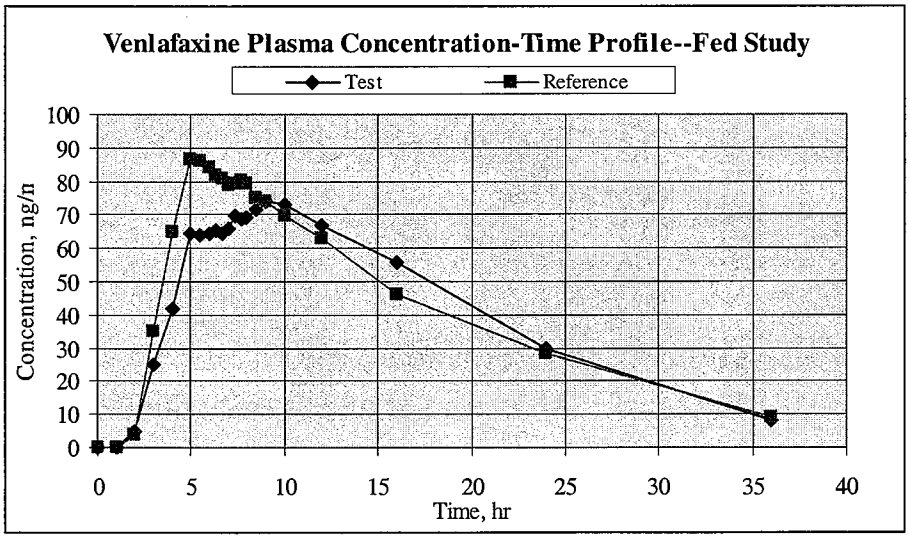
Chromatograms: No interfering peaks were observed.
SOP's dealing with analytical repeats: Same as that of the fasting study.
Comments on repeat assays.

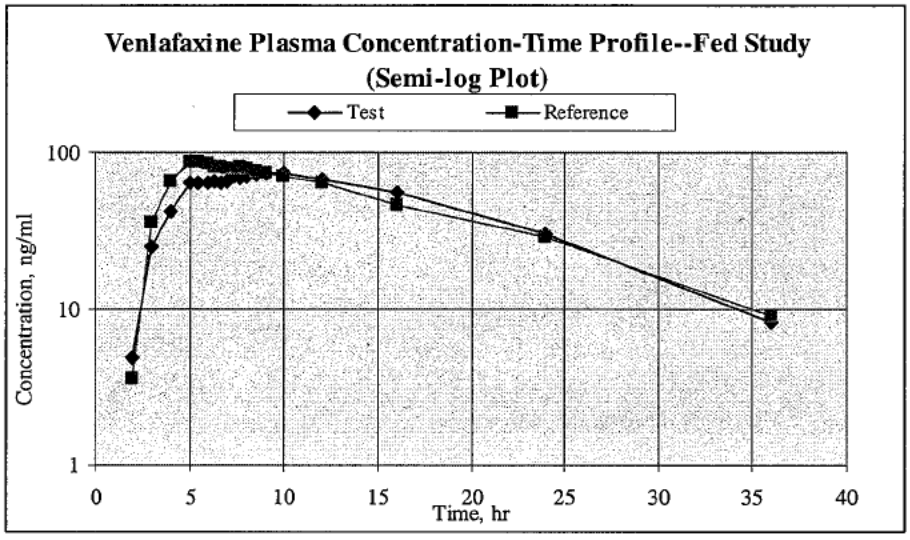
- All SOPs' were followed.
- Did recalculation of plasma concentrations change the study outcome? N/A
- Does the reviewer agree with the outcome of the repeat assays? Yes
- Provide any other comments about repeat assays. None

Conclusion: Analytical method is acceptable.

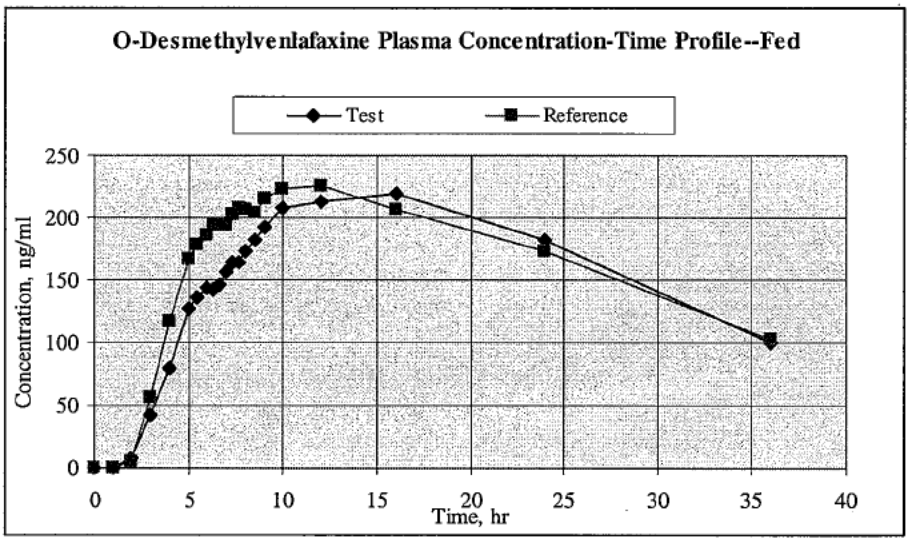
Mean plasma concentrations of Venlafaxine and O-desmethylvenlafaxine (ODV)

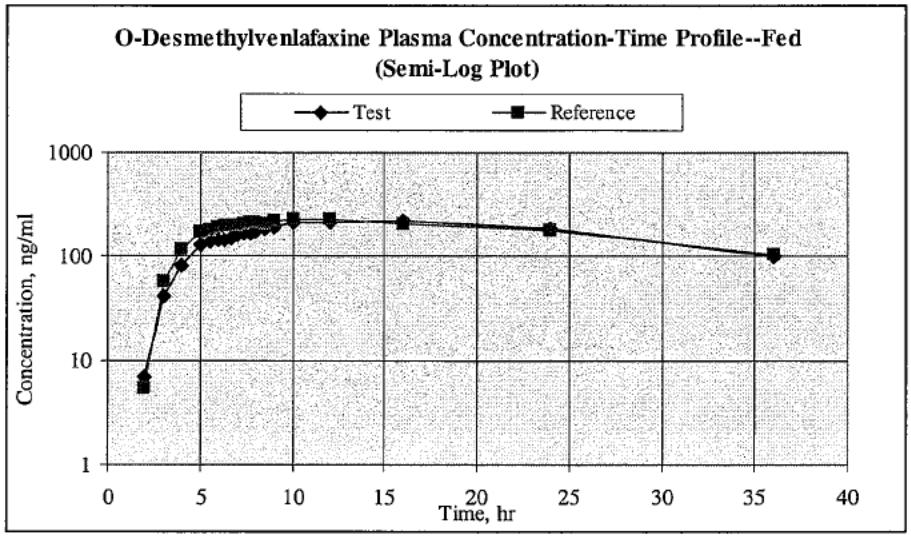
Time	Test (T)	%CV	Ref (R)	%CV	T/R		Test (T)	%CV	Ref (R)	%CV	T/R
(hrs)	Venlafaxine						O-Desmethylvenlafaxine (ODV)				
0	0	0	0	0	0		0	0	0	0	0
1	0	0	0	0	0		0	0	0	0	0
2	4.89	119.88	3.62	157.8	1.35		7.08	116.6	5.47	98.01	1.3
3	24.82	50.47	35.27	64.78	0.70		41.84	44.22	55.85	47.00	0.7
4	41.59	47.00	64.75	45.56	0.64		79.64	33.66	116.97	35.73	0.6
5	64.60	35.25	86.40	39.48	0.75		126.59	31.47	167.26	33.10	0.7
5.5	63.91	39.30	86.07	40.59	0.74		135.36	30.52	178.66	26.05	0.7
6	64.47	41.16	84.12	39.76	0.77		143.13	29.71	185.90	28.90	0.7
6.33	65.15	43.06	81.79	39.70	0.80		142.08	28.95	193.34	27.23	0.7
6.67	64.45	43.80	80.66	41.53	0.80		146.07	29.44	194.01	22.59	0.7
7	66.02	44.25	78.92	41.60	0.84		156.50	31.50	193.89	28.15	0.8
7.33	69.90	45.64	79.46	41.34	0.88		163.95	28.25	202.03	24.01	0.8
7.67	68.54	48.22	80.34	42.10	0.85		164.59	26.63	207.96	24.19	0.7
8	69.37	45.98	79.42	43.73	0.87		172.80	26.89	206.90	26.49	0.8
8.5	71.76	50.66	75.20	46.74	0.95		182.42	23.53	204.41	24.79	0.8
9	74.07	48.23	73.86	42.98	1.00		192.23	23.40	214.89	23.39	0.8
10	73.11	51.88	69.93	44.12	1.05		207.79	22.54	223.17	24.71	0.9
12	67.00	48.33	63.12	49.89	1.06		213.38	22.40	225.70	25.22	0.9
16	55.78	50.88	45.99	56.10	1.21		218.94	22.35	206.33	26.29	1.0
24	29.93	72.08	28.37	70.23	1.05		181.65	29.55	173.36	32.56	1.0
36	8.23	128.92	8.92	114.4	0.92		100.59	45.58	102.45	42.85	0.9





Metabolite (O-Desmethylvenlafaxine)





Mean Pharmacokinetic Parameters

Venlafaxine

PARAMETERS	TEST	%CV	REF	%CV	T/R (arith)	T/R (LS)
AUCt (ng.h/ml)	1358.37	56.43	1383.57	55.60	0.98	0.98
AUCI (ng.h/ml)	1596.83	56.54	1605.29	56.74	0.99	1.00
CMAX (ng/ml)	81.84	45.93	93.50	40.35	0.87	0.86
KE (1/h)	0.0859	21.03	0.0805	19.18	1.06	
THALF (h)	8.51	27.33	8.92	20.29	0.95	
TMAX (h)	8.28	27.28	5.62	18.22	1.47	

Additional Study Information

Root mean square error, AUC	0.127773
Root mean square error, Cmax	0.162972
Mean ratio AUC0-t/AUC∞	Test: 0.85 ; Ref. 0.86
Range of values, ratio AUC0-t/AUC∞	Test: 0.76-0.96; Ref.: 0.80 – 0.95

Comments: (on pharmacokinetic analysis)

- Ke and AUCi were determined for 16 subjects. Cannot determine Kel for subject #9 due to irregular terminal phases.
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr, None
  b. first scheduled post-dose sampling time as Tmax, None
  c. first measurable drug concentration as Cmax. None
- The ratios calculated by the reviewer agree with firm's calculations.

- Were there statistically significant sequence or period effects? If so, did these affect the integrity of the study? No
- Are the 90% confidence intervals for AUCt, AUCi, Cmax within the acceptable limits of 80-125%. N/A, as the fed study was conducted before the Food Guidance was published.
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect N/A

O-Desmethylvenlafaxine

PARAMETERS	TEST	%CV	REF	%CV	T/R (arith)	T/R (LS)
AUCt (ng.h/ml)	5591.56	25.27	5748.06	27.46	0.97	0.98
AUCI (ng.h/ml)	7945.58	33.19	8102.12	34.18	0.98	0.97
CMAX (ng/ml)	227.02	21.18	236.21	24.29	0.96	0.97
KE (1/h)	0.0426	34.61	0.0389	22.35	1.09	
THALF (h)	18.56	40.89	18.64	21.88	0.99	
TMAX (h)	13.8	26.82	11.3	34.89	1.22	

Additional Study Information

Root mean square error, AUC	0.085134
Root mean square error, Cmax	0.085361
Mean ratio AUC0-t/AUC∞	Test: 0.70 ; Ref. 0.71
Range of values, ratio AUC0-t/AUC∞	Test: 0.46-0.85; Ref.: 0.58 – 0.82

Comments: (on pharmacokinetic analysis)

- Ke and AUCi were determined for 15 subjects. Cannot determine Kel for subjects #11 and 13 due to irregular terminal phases.
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr, None
  b. first scheduled post-dose sampling time as Tmax, None
  c. first measurable drug concentration as Cmax. None
- The ratios calculated by the reviewer agree with firm's calculations
- Were there statistically significant sequence or period effects? If so, did these affect the integrity of the study? No
- Are the 90% confidence intervals for AUCt, AUCi, Cmax within the acceptable limits of 80-125%. N/A, as the fed study was conducted before the Food Guidance was published.
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect N/A

Conclusion: The single-dose fed bioequivalence study is acceptable.

3. Fasting single-dose sprinkled study: Content of the capsule mixed with applesauce.

Study Information		
Study Number	30024	
Study Title	Randomized, 2-way crossover, bioequivalence study of Venlafaxine 150mg ER Capsules and Effexor^{R} XR 150mg Capsules administered as 1x150 mg capsule in healthy subject administered as the content of the capsule mixed with applesauce in healthy subjects under fasting condition.	
Clinical Site	Anapharm Inc., Sainte-Foy, Quebec, Canada	
Principal Investigator	Eric Masson, Pharm.D.	
Study/Dosing Dates	Period I: 02-09-2003; Period II: 02-16-2003	
Analytical Site	(b) (4)	
Analytical Director	Not provided	
Analysis Dates	02-20-2003 to 03-06-2003	
Storage Period (first sample to final analysis)	27 Days	
Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Venlafaxine HCl Extended Release	Effexor^{R} XR
Manufacturer	Teva Pharmaceuticals	Wyeth Laboratories
Batch/Lot No.	Lot K-30455	9010767
Manufacture Date	Not provided	N/A
Expiration Date	N/A	March 2003
Strength	150 mg	150 mg
Dosage Form	Capsule	Capsule
Batch Size	(b) (4)	N/A
Potency	99.2%	N/A
Content Uniformity	101%	100%
Formulation	See Formulation (page 31)	
Dose Administered	1x150 mg	1x150 mg
Route of Administration	Oral	Oral
No. of Sequences	2	
No. of Periods	2	
No. of Treatments	2	
No. of Groups	1	
Washout Period (days)	7	
Randomization Scheme	AB: 2, 3, 4, 6, 9, 12, 13, 16, 17, 19, 21, 24 BA: 1, 5, 7, 8, 10, 11, 14, 15, 18, 20, 22, 23	
Blood Sampling Times (hrs)	0, 1, 2, 3, 4, 5, 5.5, 6, 6.33, 6.67, 8, 8.5, 9, 10, 12,16,24,36	
Volume Collected/Sample	1x7 mL	
IRB Approval	Yes	
Informed Consent	Yes	
Subjects Demographics	See Table3	
Length of Fasting	10 hours before the breakfast	
Length of Confinement	34 hours	
Safety Monitoring	Yes	

Table 3 Demographics of Study Subjects (N= 18)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
Mean	37	Mean	73.3	<18	0	Male	80%	Caucasian	96%
SD	12	SD	**10.9**	18-40	63%	Fem.	28%	Afr. Amer.	0%
Range	**19-58**	**Range**	**53.2-97.8**	41-64	37%			Asian	4%

Study Results

Dropout Information

Subject No	14	18	20	21	23	24
Reason	Vomiting	Vomiting	Vomiting	Adverse reaction	Vomiting	Adverse reaction
Period	1	1	1	1	1	1
Replacement	No	No	No	No	No	No

Study Adverse Events

Adverse Event Description	**# in Test Group**	**# in Reference Group**
Nausea	**6**	**5**
Vomiting	**0**	**4**
Hot flushes	**0**	**1**
Drowsiness	**0**	**2**
Loose stools	**2**	**2**
Dizziness	**3**	**1**
Headache	**0**	**2**
Tachycardia	**4**	**1**
Bradycardia	**2**	**1**
High blood pressure	**4**	**0**
Total:	**21**	**19**

Protocol Deviations: No significant protocol deviations were reported.

Comments: As judged by the investigator the adverse events did not compromise the integrity of the study. With the exception of vomiting, all side effects are mild as judged by the clinician. The adverse events are comparable between T (21) and R (19) treatments

Assay Validation – Within Study

	Parent	Metabolite
QC Conc. (ng, /mL)	14.99, 59.96, 139.92	15.08, 120.60, 281.40
Inter day Precision (%CV)	2.49 – 4.95	2.45 – 4.98
Inter day Accuracy (%)	105.73 – 111.34	108.96 – 114.69
Cal. Standards Conc. (ng/mL)	5.01, 10.01, 20.02, 40.04, 80.08, 120.12, 160.16, 200.20	4.96, 9.92, 39.66, 79.33, 158.66, 237.98, 317.31, 396.64
Inter day Precision (%CV)	2.06 – 4.50	2.96 – 5.76
Inter day Accuracy (%)	98.37 – 101.70	98.37 – 101.84
Linearity Range (range of R^2)	0.9981 – 0.9994	0.9980 – 0.9993

Chromatograms: No interfering peaks were observed.
SOP's dealing with analytical repeats: Same as that of the fasting study.

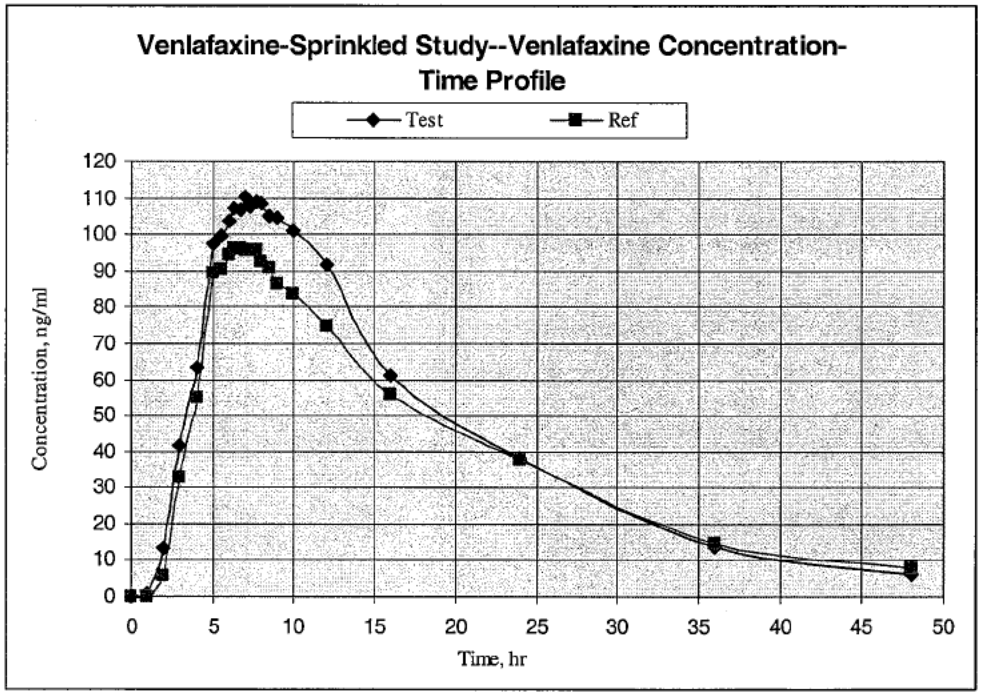
Comments on repeat assays.

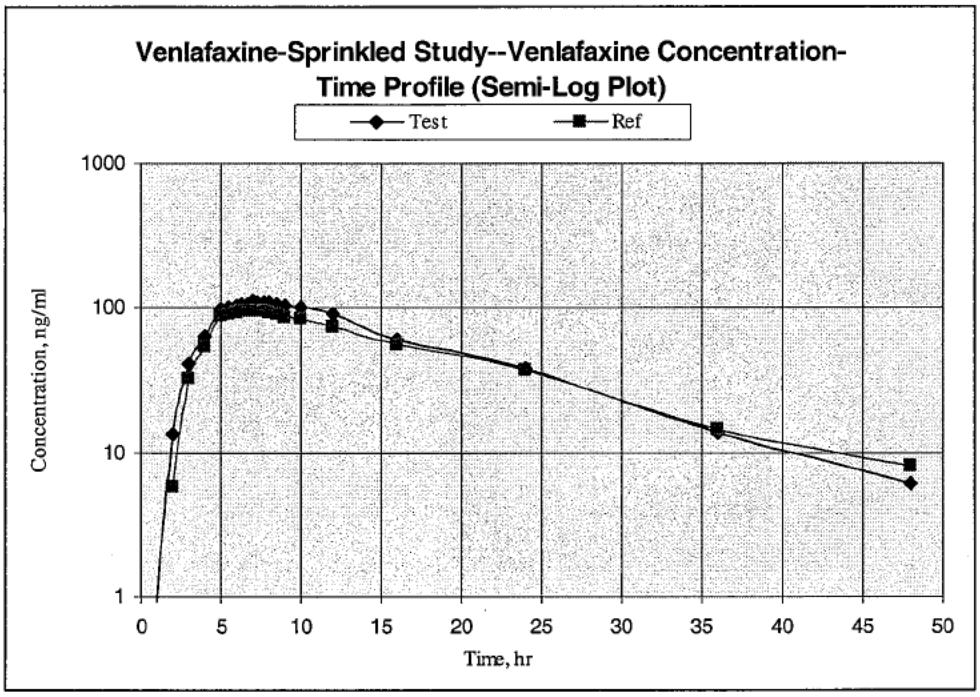
- All SOPs' were followed.
- Did recalculation of plasma concentrations change the study outcome? N/A
- Does the reviewer agree with the outcome of the repeat assays? Yes

Provide any other comments about repeat assays. None
Conclusion: Analytical method is acceptable.

Mean plasma concentrations of Venlafaxine are presented below.

Time	Test (T)	%CV	Ref (R)	%CV	T/R		Test (T)	%CV	Ref (R)	%CV	T/R
(hrs)	**Venlafaxine**						**O-Desmethylvenlafaxine (ODV)**				
0	0	0	0	0	---		**NO**		**NO**		
1	0.92	237.85	0	0	---		**DATA**		**DATA**		
2	13.37	43.58	5.78	100.0	2.31						
3	41.76	40.87	32.56	38.02	1.28						
4	63.42	37.63	54.78	41.91	1.15						
5	97.24	32.98	89.64	36.97	1.08						
5.5	99.74	32.58	90.43	38.74	1.10						
6	103.47	34.59	94.27	38.74	1.09						
6.33	107.25	33.78	95.91	38.39	1.11						
6.67	106.89	35.90	96.23	38.56	1.11						
7	110.32	38.67	95.61	38.76	1.15						
7.33	107.73	38.50	95.85	40.99	1.12						
7.67	109.03	40.50	95.64	42.30	1.14						
8	108.49	42.32	92.43	41.23	1.17						
8.5	104.79	43.98	90.76	43.99	1.15						
9	104.59	45.20	86.53	46.64	1.20						
10	101.07	47.47	83.66	49.03	1.20						
12	91.55	54.95	74.73	57.84	1.22						
16	61.24	72.75	55.91	67.87	1.09						
24	37.91	101.83	37.57	87.62	1.00						
36	13.65	151.04	14.56	130.6	0.93						
48	6.13	208.78	8.11	185.5	0.75						





Mean Pharmacokinetic Parameters (N=18)

Venlafaxine:

PARAMETERS	TEST MEAN	TEST %CV	REF. MEAN	REF %CV	RATIO (Arith. Mean) T/R	RATIO (LS Mean) T/R	90% C.I (Log transform.)
AUCt (ng.h/ml)	1954.72	74.93	1771.22	73.46	1.10	1.11	104.67 – 118.02
AUCI (ng.h/ml)	2149.75	78.80	2039.56	81.86	1.05	1.07	102.42 – 112.84
CMAX (ng/ml)	119.31	39.12	102.91	39.36	1.16	1.16	108.33 – 124.68
KE (1/h)	0.0891	25.11	0.0715	23.56	1.25		
THALF (h)	8.43	33.93	10.45	34.22	0.80		
TMAX (h)	7.19	25.57	6.83	22.72	1.05		

Additional Study Information

Root mean square error, AUC	0.104139
Root mean square error, Cmax	0.116757
Mean ratio AUC0-t/AUC∞	Test: 0.91 ; Ref. 0.87
Range of values, ratio AUC0-t/AUC∞	Test: 0.78-0.98; Ref.: 0.75 – 0.94

Comments: (on pharmacokinetic analysis)

- Ke and AUCi were determined for 18 subjects.
- Indicate the number of subjects with the following:

a. measurable drug concentrations at 0 hr, None
b. first scheduled post-dose sampling time as Tmax, None
c. first measurable drug concentration as Cmax. None

- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? Yes
- Were there statistically significant sequence or period effects? No
- Are the 90% confidence intervals for AUCt, AUCi, Cmax within the acceptable limits of 80-125%. Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect N/A

O-Desmethylvenlafaxine: No data were reported.

PARAMETERS	TEST MEAN	TEST %CV	REF. MEAN	REF %CV	RATIO TEST/REF	90% C.I (Log trans)
AUCt (ng.h/ml)						
AUCI (ng.h/ml)						
CMAX (ng/ml)						
KE (1/h)						
THALF (h)						
TMAX (h)						

Additional Study Information

Root mean square error, AUC	Not reported
Root mean square error, Cmax	Not reported
Mean ratio AUC0-t/AUC∞	Not reported
Range of values, ratio AUC0-t/AUC∞	Not reported

Conclusion: The single-dose fasting (sprinkled) Bioequivalence study is incomplete. The firm is requested to submit data on the metabolite.

L. Formulation Data

Ingredients	Amount (mg) per Capsule/ Strength					
	37.5 mg	(%)/Tab	75 mg	(%)/Tab	150 mg	(%)/Tab
[redacted]						

(b) (4)

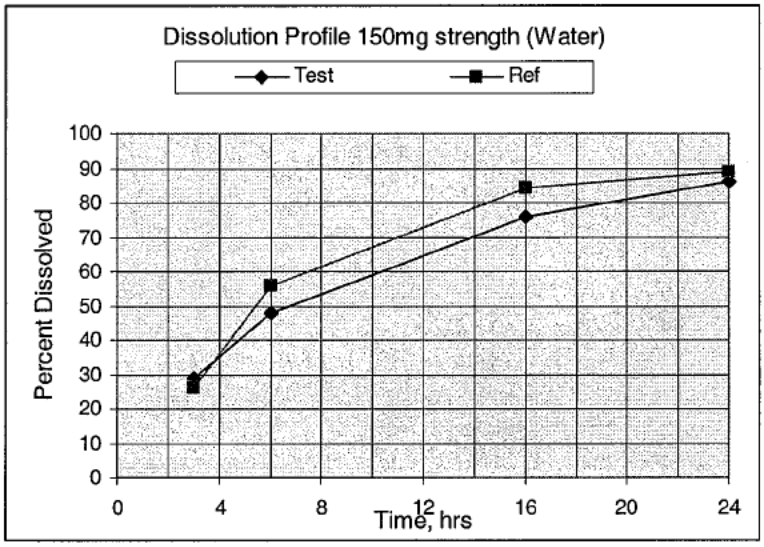
(b) (4)

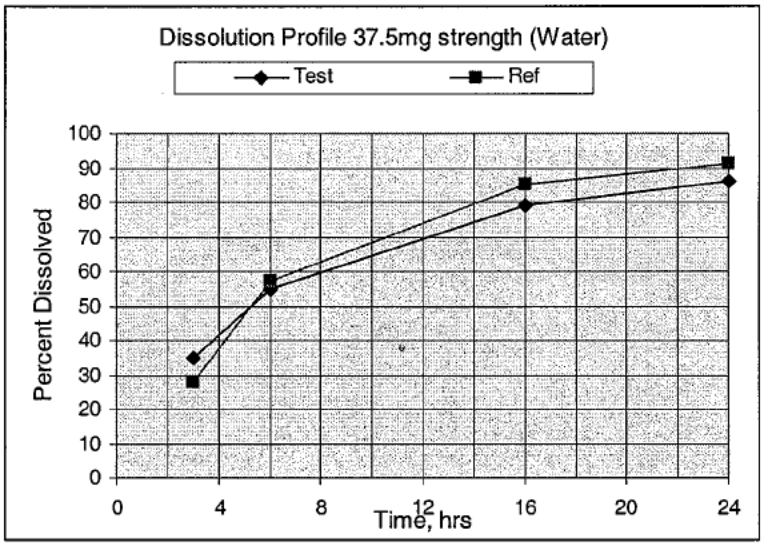
M. Dissolution Data

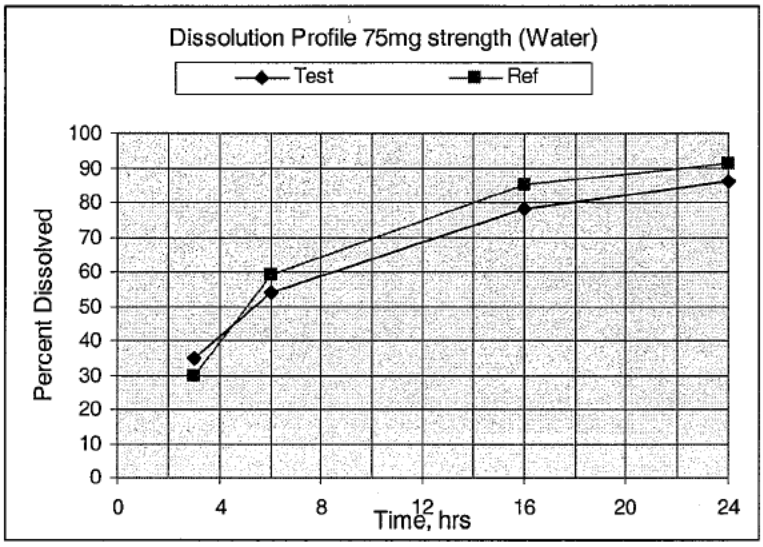
The firm conducted dissolution testing using the following FDA recommended method:
USP Apparatus I (Basket)
Speed: 100 RPM
Medium: Water, 900 ml
Results are shown in tables below:

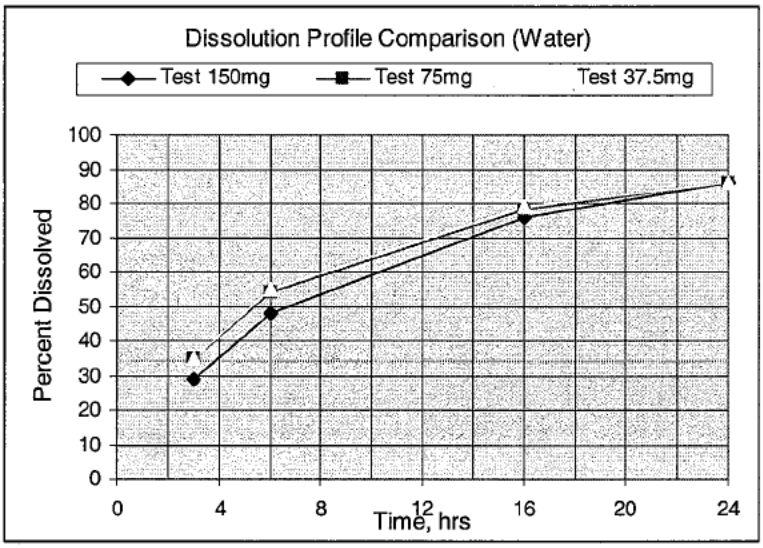
Sampling Time (hrs)	Test Product, strength 150 mg Lot No. K-30455 (Biolot)			Reference Product, Strength 150 mg Lot No. 9010767 (Biolot)		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
3	29	4.8	(b) (4)	26	3.8	(b) (4)
6	48	4.0		56	2.2	
16	76	4.4		84	1.6	
24	86	4.5		89	3.0	
F2	**60.65**					
Sampling Time (hrs)	**Test Product, Strength 37.5 mg Lot No. K-30703**			**Reference Product, Strength 37.5 mg Lot No. A13238**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
3	35	8.8	(b) (4)	28	7.0	(b) (4)
6	55	7.2		57	4.1	
16	79	6.6		85	3.3	
24	86	6.4		91	3.2	
F2	**63.25**					
Sampling Time (hrs)	**Test Product, Strength 75 mg Lot No. K-30702**			**Reference Product, Strength 75 mg Lot No. A14492**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
3	35	4.9	32 – 38	30	7.0	26 – 35
6	54	4.5	51 – 59	59	5.1	53 – 65
16	78	4.1	73 – 84	85	4.7	78 – 94

24	86	3.9	83 - 93	91	3.8	85 – 99
F2	**62.37**					









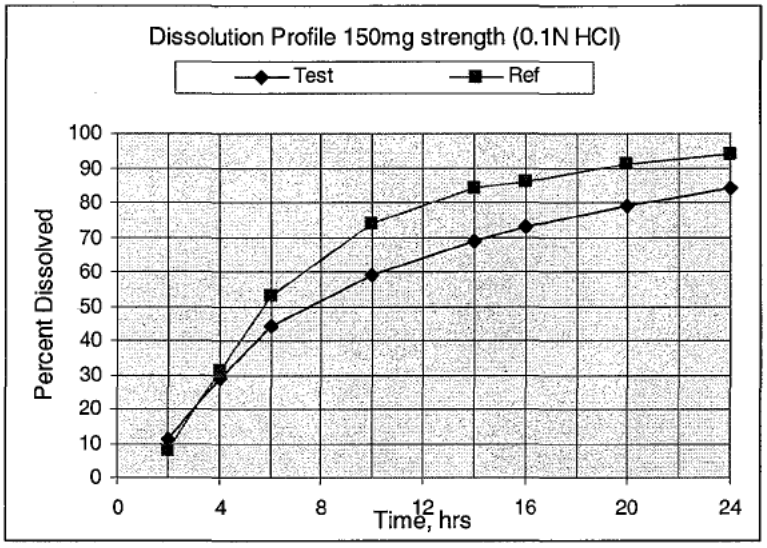
The firm proposed the following specifications:

(b) (4)

In addition, dissolution testing was conducted in various conditions such as 0.1 N HCl, 4.5 and 6.8 buffers using the same method above.
Results are shown in tables below:

USP Apparatus I (Basket)
Speed: 100 RPM
Medium: 0.1 N HCl, 900 ml

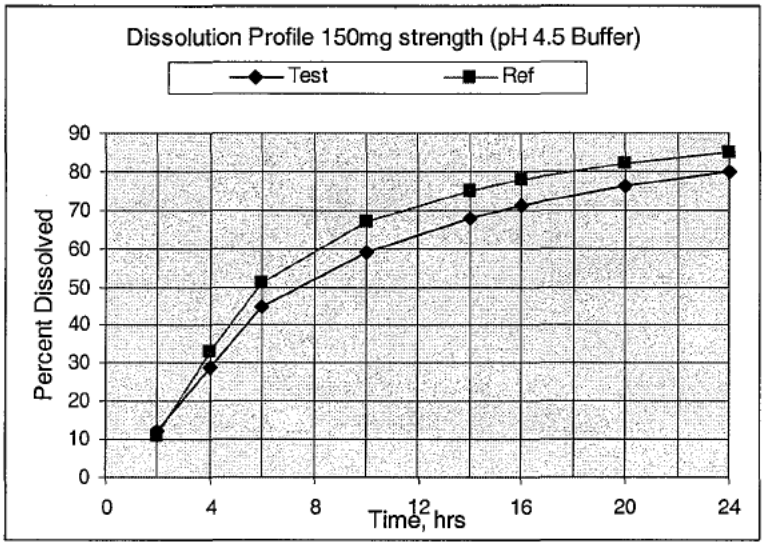
Sampling Time (hrs)	Test Product, strength 150 mg Lot No. K-30455			Reference Product, Strength 150 mg Lot No. 9010767		
	Mean	%CV	Range	Mean	%CV	Range
2	11	11.0	8 – 13	8	17.1	6 – 10
4	29	7.1	27 – 33	31	7.7	27 – 36
6	44	6.6	41 – 51	53	11.1	48 – 66
10	59	10.1	55 – 73	74	13.8	65 – 94
14	69	10.4	64 – 86	84	13.5	73 – 103
16	73	10.4	67 – 90	86	12.5	76 – 106
20	79	10.7	73 – 96	91	12.2	80 – 112
24	84	10.2	79 – 101	94	12.5	83 – 117
F2	**47.96**					



USP Apparatus I (Basket)
Speed: 100 RPM
Medium: Phosphate buffer, pH 4.5, 900 ml

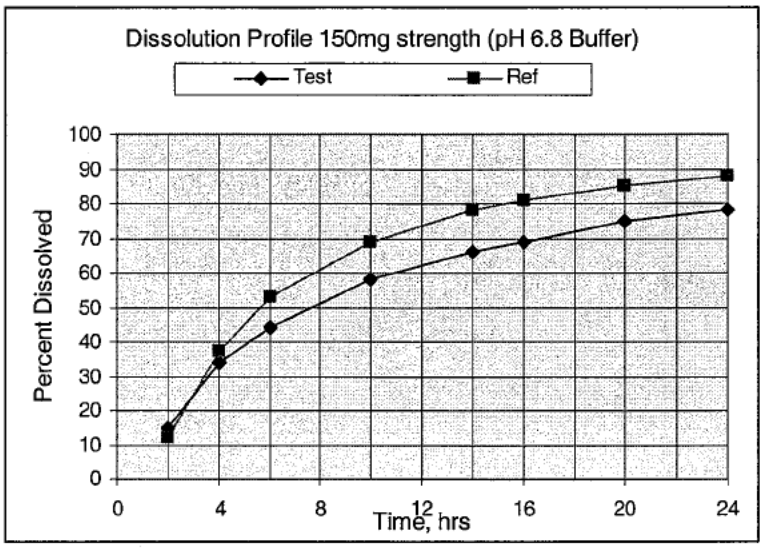
Sampling Time (hrs)	Test Product, strength 150 mg Lot No. K-30455			Reference Product, Strength 150 mg Lot No. 9010767		
	Mean	%CV	Range	Mean	%CV	Range
2	12	23.3	10 – 13	11	13.5	8 – 13
4	29	10.4	29 – 35	33	9.8	27 – 37
6	45	5.5	43 – 52	51	3.5	47 – 53
10	59	3.7	58 – 65	67	3.1	64 – 70
14	68	2.7	66 – 73	75	2.8	72 – 78
16	71	2.3	69 – 75	78	2.7	75 – 81
20	76	2.1	74 – 80	82	2.7	79 – 85
24	80	2.4	79 – 85	85	2.2	82 – 87
F2	**61.24**					

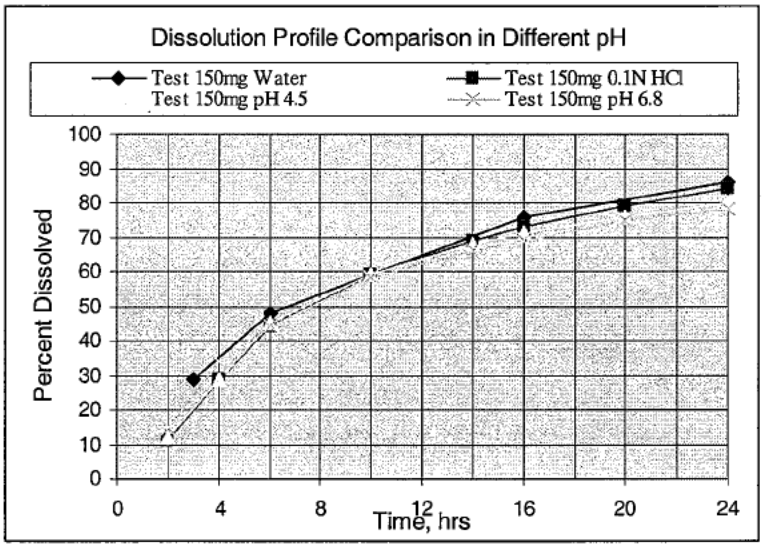
Note: The firm indicated that Phosphate buffer pH 4.5 was used. However, normally pH of acetate buffer ranges from 4.1 to 5.5 and pH of phosphate buffer from 5.8 to 8. The firm is requested to clarify this matter.



USP Apparatus I (Basket)
Speed: 100 RPM
Medium: Phosphate buffer, pH 6.8, 900 ml

Sampling Time (hrs)	Test Product, strength 150 mg Lot No. K-30455			Reference Product, Strength 150 mg Lot No. 9010767		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	15	6.5	14 – 17	12	6.2	10 – 13
4	34	4.5	31 – 36	37	3.0	34 – 37
6	44	4.6	41 – 48	53	2.2	50 – 54
10	58	3.8	55 – 62	69	1.9	68 – 71
14	66	3.4	62 – 69	78	1.8	77 – 80
16	69	3.4	65 – 73	81	1.7	79 – 83
20	75	2.9	71 – 78	85	1.8	83 – 88
24	78	3.2	74 - 82	88	2.0	87 – 92
F2	**51.2**					





Similar dissolution profiles were observed in different dissolution media as shown in the graph above.

N. Consult Reviews

None

O. SAS Outputs

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-565 APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Venlafaxine Extended Release Capsules 37.5mg,75mg & 150mg.

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. For the fasting (sprinkled) study (Study No. 30024), please submit pharmacokinetic data of venlafaxine metabolite (O-Desmethylvenlafaxine) along with summary statistical analysis for evaluation.

2. For the fasting study (Study No. 02204), it is noted that Subject #1 vomited at 4 hrs 54 minutes after dosing in Period 1 (Test formulation). However this subject was allowed to continue the study. Please note that data from subjects who experience emesis any time during the labeled dosing interval should be deleted. Please re-calculate pharmacokinetic parameters and statistically re-analyze the data without subject # 1.

3. You indicated that Phosphate buffer pH 4.5 was used in dissolution testing. However, normally pH of acetate buffer ranges from 4.1 to 5.5 and pH of phosphate buffer from 5.8 to 8. Please clarify why phosphate buffer pH 4.5 was used instead of acetate buffer pH 4.5.

Sincerely yours,

for Barbara M. Davit

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-565
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Final with Dates)
HFD-658/N. Tran
HFD-658/Y. Huang 4/15/27/2004
HFD-650/D. Conner 5/27/04

BIOEQUIVALENCY - INCOMPLETE

Submission dates:
12/10/2002
02/13/2003
04/10/2003

1. **FASTING STUDY** (STF) o/c — Strength: 150 mg
Outcome: IC

Clinical: Anapharm, Quebec, Canada
Analytical: [redacted] (b) (4)

2. **FOOD STUDY** (STP) o/c — Strength: 150 mg
Outcome: AC

Clinical: Anapharm, Quebec, Canada
Analytical: [redacted] (b) (4)

3. **FASTING STUDY** (STF)(Sprinkled) o/c — Strength: 150 mg
Outcome: IC

Clinical: Anapharm, Quebec, Canada
Analytical: [redacted] (b) (4)

4. **DISSOLUTION WAIVER** (DIW) o/c — Strength: 37.5 mg
Outcome: IC

Testing site: Teva Pharmaceutical

5. **DISSOLUTION WAIVER** (DIW) o/c — Strength: 75 mg
Outcome: IC

Testing site: Teva Pharmaceutical

Outcome Decisions: **IC** - Incomplete

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076565

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

June 30, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING/SPL FINAL FOR APPROVED ANDA 076565

ANDA # 076565
VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, 37.5 mg, 75 mg, and 150 mg

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a Labeling/SPL Final for Approved ANDA 076565 to the above-referenced Abbreviated New Drug Application to provide our package insert in SPL format. This labeling is provided in accord with the Agency's requirement to provide labeling in SPL format within 14 days of receiving final approval of an ANDA. ANDA #076565 was approved on June 28, 2010.

Please find enclosed herein a disk containing our updated final print package insert Rev. A 2/2010 in Word and PDF formats. Also provided is a comparison to the previously approved version (Iss. 2/2010) in PDF format. Please note that the changes to the PI are in the HOW SUPPLIED section, which was revised to include only the package sizes we intend to market. Additionally, please note that we have submitted the SPL file with drug listing; it can be found in the following location: http://www.accessdata.fda.gov/spl/data/9a30e1b5-272b-4109-ad6c-a3c9a895822f/9a30e1b5-272b-4109-ad6c-a3c9a895822f.xml.

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 2 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

This information is submitted for your review and approval. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

Sincerely,

{see appended signature page}

PE/hm
Enclosures

Philip Erickson / SA

Philip Erickson
Senior Director, Regulatory Affairs

30 June 2010

Date

M E M O R A N D U M

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

DATE:

FROM: Robert Lionberger, Ph.D.
Science Staff
Office of Generic Drugs

THROUGH: Barbara Davit, Ph.D., J.D.
Acting Director, Division of Bioequivalence II
Office of Generic Drugs

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

TO: ANDA 076565 – Teva Pharmaceuticals USA
Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg, 75 mg, 150 mg

SUBJECT: Decision to approve Teva's ANDA for Venlafaxine Hydrochloride Extended-release Capsules

A citizen petition (Docket No. FDA-2010-P-0255) dated May 20, 2010 was submitted by Osmotica Pharmaceutical Corp. (Osmotica) requesting that FDA require ANDA applicants for Venlafaxine Hydrochloride Extended-release Tablets to show bioequivalence to Osmotica's Venlafaxine Hydrochloride Extended-release Tablets under both fed and fasting conditions.

The citizen petition describes concerns regarding bioequivalence for Venlafaxine Hydrochloride Extended-release Tablets that may also pertain to the bioequivalence for Venlafaxine Hydrochloride Extended-release Capsules. Teva's ANDA for Venlafaxine Hydrochloride Extended-release Capsules is undergoing final review to determine whether it may be approved. As part of this review, we have considered whether the scientific issues raised in the citizen petition apply to this application.

The petition is subject to section 505(q) of the Act. In accordance with section 505(q)(1)(A)(ii), FDA is obligated not to delay the approval of a 505(b)(2) NDA or an ANDA based on a citizen petition seeking such a delay unless it concludes, "upon reviewing the petition, that a delay is necessary to protect the public health." Our draft guidance states that, unless the petition may be summarily denied because we conclude that the primary purpose of the petition is to delay approval and it does not on its face raise valid scientific or regulatory issues, we determine whether a delay is necessary to protect the public health based on our preliminary evaluation of

the issues raised in the petition. In making this determination, we consider whether the allegations in the petition, if we were to accept them, are such that approval of the pending application could negatively affect the public health. Neither the statute nor our draft guidance, however, requires us to delay the approval of a pending application until we respond to the petition, so long as we have reviewed the issues described in the petition and determined that they do not require the agency to delay approval of the application to protect the public health. We have now completed that review and, as summarized in this memorandum, determined that a delay of approval of ANDA 076565 is not necessary to protect the public health.

Analysis

Osmotica's Venlafaxine Hydrochloride Extended-release Tablets

Osmotica's Venlafaxine Hydrochloride Extended-release Tablet was approved on May 20, 2008 in a 505(b)(2) application (NDA 22-104). The product was approved in 37.5 mg, 75 mg, 150 mg, and 225 mg strengths for treatment of major depressive disorder and social anxiety disorder. Osmotica's product was approved based on FDA's findings of safety and effectiveness for Wyeth's Effexor XR Extended-release Capsules and was supported by comparative bioavailability data.

Osmotica claims that important information may be overlooked if fasted bioequivalence studies are not performed. Osmotica notes that their product met the bioequivalence criteria for the 37.5 mg strength in the fasted state but not for the 75 mg strength (Petition at 5). Osmotica states that the 75 mg tablet resulted in higher blood levels, which was consistent with the fed state (Petition at 5). The following bioequivalence studies were performed by Osmotica: a single-dose fed study of the 225 mg strength, a fed and fasting study of the 37.5 mg strength, and a fed and fasting study of the 75 mg strength (Clinical Pharmacology and Biopharmaceutics Review, 9/25/07). All strengths were determined to be bioequivalent under fed conditions. The 37.5 mg strength was bioequivalent under fasting conditions; however, the 75 mg strength was not bioequivalent under fasting conditions. A waiver of bioequivalence for the 150 mg strength was granted because the 75 mg, 150 mg, and 225 mg strengths are compositionally proportional.

Osmotica also claims that there are no serious safety concerns for bioequivalence studies under the fasted state. They claim that there was "very little difference" in the rates of nausea and vomiting in the fasted studies of the 37.5 mg and 75 mg strengths (Petition at 5).

OGD's Bioequivalence Recommendations for Venlafaxine Hydrochloride Extended-release Products

For the tablet dosage form, OGD currently recommends a single-dose, two-treatment, two-period crossover *in-vivo* fed study with the 150 mg strength (Draft Guidance on Venlafaxine Hydrochloride Extended-release Tablets, recommended February 2010, revised March 2010). The bioequivalence recommendations also state that "[d]ue to safety concerns, bioequivalence studies under fasting conditions are not recommended."

The current recommendations for the capsule dosage form are the same as the tablet, with the addition of a single-dose, two-treatment, two-period crossover *in-vivo* fed sprinkle study with the 150 mg strength (Draft Guidance on Venlafaxine Hydrochloride Extended-release Capsules, recommended February 2006, revised May 2007, revised December 2008). The bioequivalence recommendations for the capsule dosage form contain the same warning against performing studies under fasting conditions.

Generally, for extended release drug products, OGD recommends bioequivalence studies under fed and fasted conditions. However, there may be instances where studies under both fed and fasted conditions are not recommended, such as when there are safety concerns.

Prior to the Draft Guidance on Venlafaxine Hydrochloride Extended-release Capsules, OGD provided bioequivalence recommendations to sponsors through controlled correspondence. In a controlled correspondence to (b) (4) in 2002, the Division of Bioequivalence recommended a single-dose fasting study and a single-dose fed study with the 75 mg strength (control document 02-051). In 2003, the recommendations were changed after issues of nausea and vomiting during the fasted bioequivalence studies were brought to OGD's attention. The Division of Bioequivalence recommended a single-dose fed study and a single-dose fed study with the contents of the capsule sprinkled over a teaspoonful of applesauce with the 150 mg strength (control documents 02-259, 02-628, 02-724, 03-182, 03-290, and 03-883). The recommendations also noted that the

> significant occurrence of nausea and vomiting with both the 75 mg and 37.5 mg dose under fasting conditions makes it difficult to perform bioequivalence studies under fasting conditions. The approved labeling of the RLD recommends administration with food. Administration of a single dose of 150 mg under fed conditions is well tolerated.

Teva's Venlafaxine Hydrochloride Extended-release Capsules

Teva's proposed drug product, submitted in 2002, is Venlafaxine Hydrochloride Extended-release Capsules, 37.5 mg, 75 mg, and 150 mg, referencing Wyeth's Effexor XR Capsules, not Osmotica's Venlafaxine Extended-release Tablets. As noted, although Osmotica's petition specifically only references the tablet dosage form, and not the capsules, we are reviewing whether we should delay approval of Teva's ANDA on the basis of the issues raised in the petition because the issues raised by Osmotica could apply to both dosage forms.

Teva conducted three bioequivalence studies: a single dose fasting, a single dose fed, and a single dose fasting sprinkle, comparing their Venlafaxine Hydrochloride Extended-release Capsules, 150 mg, to Wyeth's Effexor XR Capsules, 150 mg. The bioequivalence studies were found to be acceptable and a waiver was granted for the 37.5 mg and 75 mg strengths.

Conclusion

OGD has carefully considered the issues raised by the petitioner. Although the petitioner does not specifically request fasting bioequivalence studies for the capsule dosage form, we have reviewed whether we should delay approval of Teva's ANDA on the basis of the bioequivalence issues raised in the petition because they could apply to the extended-release capsule dosage form. Teva performed a single-dose fasting bioequivalence study with the 150 mg strength and the Division of Bioequivalence determined that the study was acceptable. Because Teva has conducted the fasting bioequivalence study described in the petition, we need not determine whether such a study is necessary for approval of a venlafaxine hydrochloride extended-release drug product. Therefore, after reviewing the petition and Teva's ANDA, we have determined that Teva's ANDA may be approved, and delaying approval of ANDA 076565 is not necessary to protect the public health.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-76565	ORIG-1	TEVA PHARMACEUTICALS USA INC	VENLAFAXINE HYDROCHLORIDE

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

/s/

ROBERT A LIONBERGER
06/28/2010

ROUTING SHEET

☒ **APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **CGMP**

Division: IV	**Team: 10**	**PM: Thomas Hinchliffe**

Electronic ANDA: Yes ☐ No ☒

ANDA #:076565
Firm Name:TEVA Pharmaceuticals USA
ANDA Name:Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg, 75 mg and 150 mg
RLD Name:020699, Effexor XR, Wyeth Pharmaceuticals, Inc.

Electronic AP Routing Summary Located:
V:\Chemistry Division II\Team 10\Electronic AP Summaries

AP/TA Letter Located:
V:\Chemistry Division II\Team 10\Final Version For DARRTS

Project Manager Evaluation: **Date: 6/18/10 Initials:** toh

☐ Previously reviewed and tentatively approved --- Date _____
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec′d date 12/11/2002	Date of Application 12/10/2002	Date Acceptable for Filing 12/11/2002
Patent Certification (type) 4	Date Patent/Excl. expires	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: 6/28/10* ☐ 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) 6/18/10 Addendum Needed: Yes ☐ No ☐ Comment:
Date of Acceptable Bio 05/06/2010 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 04/13/2010 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: Ext-Rel

Modified-release dosage form: Yes ☒ No ☐ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 6/18/10 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 6/18/10

☒ 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: 6/28/10**

Chief, Reg. Support Branch **Initials:** rlw/for

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 Date Checked Granted Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
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:1/12/2006 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:
☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP
☐ OTHER:

Comments:ANDA submitted for the 150 mg strength on 12/11/2002, BOS=Effexor XR NDA 20699, PIII to '186, MOU to '923(Tx of GAD), PIV to '708, '171, '120 and '958. On 1/21/2003 the firm submitted revised patent certs: PIII to '186, MOU in totality to '923(Tx of GAD), MOU partially to the '120 and '958 as each of these patents relates to Tx of GAD, PIV to '708 and '171 in totality, PIV to '120 and '958 partially as related to Tx of Depression. ANDA ack for filing with a PIV on 12/11/2002 for the 150 mg(LO dated 1/22/2003). On February 13, 2003 the sponsor submitted a NSA for inclusion of the 37.5 and 75 mg strengths, Same BOS, same certifications as the 150 mg. New Strength Amendment filing review satisfactory and complete on 3/24/2003. Letter from counsel for the innovator rec'd on 3/26/2003-CA 03-CV-1293(KSH) filed on 3/24/2003 in the D of NJ for infringment of the '171, '120, and '958 patents on all three strengths. 30 month stay of approval expires 8/13/2005. Patent Amendment rec'd on 4/2/2003-RR from Wyeth-Ayerst in Madison NJ signed and dated 2/10/2003, Fed Ex notice to WA in Madison NJ signed and dated 2/13/2003, copy of CA 03-CV-1293(KSH) provided. Minor amendment submitted 4/2/2004-firm addressed the I-261 exclusivity. Patent Amendment submitted on 1/30/2008-CA 03-1293 was dismissed on 1/12/2006 pursuant to a settlement and license agreement. Patent Amendment submitted 4/28/2009: MOU to the '120 and '958 with respect to GAD and SAD claims, MOU to '101 with respect to Tx of Panic Disorder, Carving out I-561(Long term Tx of Social Anxiety Disorder). Letter from Pfizer submitted on 6/4/2010 stating that Pfizer does not object to approval of ANDA 76565 on or after 7/1/2010.

TEVA's cover letter for the 1/30/2008 submission states: "…pursuant to that agreement, Wyeth will send to the Agency in due course, under separate cover, a letter stating that Wyeth has no objection to FDA approving TEVA's ANDA 76-565

for Venlafaxine HCL Extended-release Capsules on or after July 1, 2010 but not as of any earlier date until Wyeth informs FDA separately in writing of such earlier date." OGD rec'd the referenced letter on 6/4/2010.

Despite the wording of the letter from Pfizer there is no documentation in the ANDA file that would preclude the approval of this ANDA(CA has been dismissed and the Agency is not aware of a PI which precludes approval of this ANDA). ANDA is eligible for immediate Full Approval with 180 day exclusivity governed by pre-MMA exclusivity standards.

2. ***Labeling Endorsement***

Reviewer, Hoppes, Charles V:
Date6/18/10
InitialsCH

Labeling Team Leader, Grace, John F:
Date6/18/10
InitialsJG

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☐n/a

Comments:
From: Grace, John F
Sent: Friday, June 18, 2010 1:55 PM
To: Hoppes, Charles V; Hinchliffe, Thomas
Subject: RE: 76565 AP Endorsement needed

concur.

From: Hoppes, Charles V
Sent: Friday, June 18, 2010 1:52 PM
To: Hinchliffe, Thomas
Cc: Grace, John F
Subject: RE: 76565 AP Endorsement needed

Tom,

No new changes for the RLD, the approval summary should still be OK.

Charlie.

3. ***Paragraph IV Evaluation*** **PIV's Only**

David Read
OGD Regulatory Counsel
Pre-MMA Language included ☐

Date 25Jun10
InitialsDTR

Post-MMA Language Included ☐
Comments:Changes to AP letter saved to V drive.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 6/23/2010**
Chemistry Div. **IV (Iser)** **InitialsRLI**
Comments:Acting Director, CMC OK

5. ***First Generic Evaluation*** **First Generics Only**
Frank Holcombe **Date 6/28/10**
Assoc. Dir. For Chemistry **Initials rlw/for**
Comments: (First generic drug review)
N/A. Tentative approvals for this drug product have been issued to Impax ANDA 78-057 and Mylan ANDA 78-789 on October 16, 2007 and November 13, 2008, respectively,

OGD Office Management Evaluation

6. Peter Rickman **Date 6/28/10**
Director, DLPS **Initials rlw/for**
Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes ☐ No ☐
Petition: Yes☐ No☐
Comments:Bioequivalence studies (fasting, non-fasting and fasting sprinkle) on the 150 mg capsule strength found acceptable. In-vitro dissolution testing for all three capsule strengths also found acceptable. Waivers granted to the 37.5 mg, 75 mg and 150 mg capsule strengths under 21 CFR 320.22(d)(2). Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 8/27/09, 1/22/10. In-vitro dissolution studies performed using various concentrations of ethanol also found acceptable 5/6/10.

Final-printed labeling (FPL) found acceptable for approval 4/13/10, as endorsed 6/18/10. Teva has provided method-of-use statements and elected to "carve-out" information pertaining to the use of the product for generalized anxiety disorder, treatment of panic disorder, and treatment of social anxiety disorder. This is acceptable.

CMC found acceptable for approval (Chemistry Review #6).

AND/OR

7. Robert L. West **Date 6/28/10**
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 6/25/10 (Verified 6/28/10). No "OAI" Alerts noted.

Refer to the summary provided above by M.Shimer for the legal/regulatory basis for approval of this first-generic ANDA.

This ANDA is recommended for approval.

8. ***OGD Director Evaluation***
Keith Webber
Deputy Director, OPS
Comments: rlw/for 6/28/10
First Generic Approval ☒
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments:

9. Project Manager
Date 6/28/10
Initials TOH

Check Communication and Routing Summary into DARRTS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-76565	ORIG-1	TEVA PHARMACEUTICALS USA INC	VENLAFAXINE HYDROCHLORIDE

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/s/

THOMAS O HINCHLIFFE
06/28/2010

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

June 21, 2010

VIA FEDERAL EXPRESS AND ELECTRONIC MAIL

Keith Webber, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: FINAL APPROVAL OF ANDA # 076565 -- VENLAFAXINE HCl EXTENDED-RELEASE CAPSULES, 37.5 mg, 75 mg, and 150 mg

Dear Dr. Webber:

This letter is in reference to a June 18, 2010 telephone call from Mr. Bob West of the Office of Generic Drugs requesting information regarding the approvability of the above-referenced ANDA prior to July 1, 2010. As the attached court order makes clear, Judge Martini's dismissal of Wyeth's patent suit against Teva does not bar FDA from granting final approval to Teva's ANDA prior to July 1, 2010, under 35 U.S.C. § 271(e)(4)(A) (authorizing the patent court to order "the effective date of any approval ... to be a date which is not earlier than the date of the expiration of the patent") or any other authority. Instead, the court's dismissal order merely bars Teva from marketing its Venlafaxine HCl ER products--whether they are approved or not--"except as licensed under the License Agreement." Order at 1 (attached as **Exhibit A**). Accordingly, nothing in the court's order remotely prohibits FDA from granting final approval to Teva's ANDA at this time.

In addition, while we do not believe it is necessary--or, given the burdens it would impose on the Agency, advisable--for FDA to examine the settlement agreements underlying such court orders, we nonetheless note that section 4.1.2 of the License Agreement specifically contemplates FDA approval of Teva's ANDA prior to July 1, 2010.[1] This provision is notable because the district court expressly incorporated that provision of the agreement into its judgment--meaning that the court expressly contemplated FDA granting final approval to Teva's ANDA prior to the July 1, 2010 market entry date elsewhere provided by that agreement. Order

[1] As the court's order notes, the parties' agreement was filed under seal in the district court. Order at 1. Due to the parties' ongoing confidentiality obligations, Teva is not able to furnish the Agency with a complete copy of the unredacted License Agreement at this time.

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

at 1 ("[T]he License Agreement entered into between the parties [is] adopted by the Court as part of this Order.").

As for Teva's January 28, 2008 letter, nothing in it was intended to suggest that Teva cannot obtain final approval prior to the license date. It was merely an effort to apprise FDA as a courtesy of the possibility that the license date itself might be accelerated, and that Wyeth might be notifying FDA of same.

If you have any further questions, I can be reached at (215) 591-3141.

Sincerely,

Philip Erideson/gp

PE/

Enclosure

cc: Martin Shimer
Bob West
David Read
Susan Levine

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

WYETH, Plaintiff, v. TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES LTD., Defendants.	Civil Action No.: 03-1293 (WJM)

DISMISSAL ORDER

As a result of the parties having executed the Settlement and Release Agreement dated November 2, 2005 and the License Agreement (as defined in the Settlement and Release Agreement), the Court hereby Orders:

1) Until the expiration of United States Patent Nos. 6,274,171 B1; 6,403,120 B1; and 6,419,958 B2; or the termination of the License Agreement, Defendants shall not make, use, sell, offer for sale, or import XR Product, as that term is defined in the License Agreement, for use in the Territory, except as licensed under the License Agreement.

2) Defendants' Counterclaim(s) of patent invalidity and unenforceability are dismissed with prejudice. Defendants' Counterclaim(s) of non-infringement are dismissed without prejudice.

3) The Settlement and Release Agreement and the License Agreement entered into between the parties, which have been filed with this Court under seal, are adopted by the Court as part of this Order.

4) This Court retains jurisdiction to enforce this Order and the parties' Settlement and Release Agreement and License Agreement.

SO ORDERED.

William J. Martini, U.S.D.J.

Jan 12, 2006

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

June 15, 2010

Keith Webber, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

QUALITY TELEPHONE AMENDMENT/RESPONSE TO INFORMATION REQUEST

ANDA # 076565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES, 37.5 mg, 75 mg, and 150 mg

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA in response to a telephone request received from Ashley Jung of the Office of Generic Drugs on June 14, 2010. Specifically, Teva was asked to further tighten our in-process and drug product release criteria for PSD of the pellets. We were also asked to clarify the type of (b) (4) being used for this testing during manufacture and release ((b) (4)). Finally, due to concern regarding our ability to consistently meet L1 dissolution testing, we are to commit to submit a CBE-0 containing a summary of all dissolution data accrued for our validation batches when 12-month CRT stability testing is complete. These requests are addressed below in the order presented in the telephone contact.

1. Per your request to further tighten the in-process limits for PSD testing of the ER-coated pellets, as well as the drug product release criteria for PSD of the pellets, we have reviewed all data accrued for the validation batches as well as batches intended for commercial launch. Presented in **Attachment 1** are PSD data for three lots of (b) (4) coated pellets made to encapsulate three commercial batches. These lots were specifically chosen as they present PSD results for the various (b) (4) that are within our previously-proposed limits, but where there was slightly more variation in the results obtained for the (b) (4) than for the validation batches presented in our June 7, 2010 amendment.

   We then assessed the dissolution results for the three finished product batches resultant from the pellet batches noted above. Finally, we performed f2 calculations on the dissolution data for these three drug product batches, comparing the results to those of Teva's ANDA batch for the 150 mg strength. The data demonstrate that the PSD limits proposed herein yield product with dissolution results that are comparable to those of our ANDA batch, which was used to demonstrate bioequivalence to the RLD. Please refer to

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
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Attachment 1 for the dissolution data and f2 results discussed herein. Based on these results, we have further revised the limits as follows:

Please refer to the revised in-process control summaries and revised finished product release and shelf life specifications in **Attachment 2** which reflect these tighter limits. Finally, revised manufacturing procedures which state the revised in-process limits for the ER-coated pellets are provided in **Attachment 3**.

2. The (b) (4) used for testing the in-process samples, as well for performing the PSD on the finished product samples, are the (b) (4) type.

3. As requested, we hereby commit to submit a CBE-0 post-approval to provide dissolution data for all validation batches through the twelve-month controlled-room temperature stability station.

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 21 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

It is our understanding that sponsors submitting electronic submissions to CDER do not need to submit an electronic submission or paper submission to the ORA District Office, as District Offices are able to access electronic Chemistry Manufacturing and Control submissions through CDER's Electronic Document Room. Therefore, Teva Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable office of the FDA certifying that an electronic amendment has been submitted to CDER.

We believe the information provided herein appropriately addresses all questions presented in the June 14, 2010 request. Should you have any additional questions or require any further

clarification, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

PE/jbp
Enclosures

Philip Erickson/gp
Philip Erickson
Senior Director, Regulatory Affairs

6/15/10
Date

Record of Telephone Conversation

Please further tighten the particle size controls for both the in-process and release testing to set meaning specification. We note that your limits remain too wide based on the observed data. Also, please clarity which (b) (4) are being used for the testing and manufacturing (i.e. (b) (4)

Based on the previously provided dissolution data we are concerned about your ability to consistently meet the dissolution at L1. Please commit to provide a CBE-0 with a summary of the dissolution data when your 12 months stability data become available for your validation batches.

FYI, please note that your request for fulfillment of the CBE-0 for the addition of an alternate manufacturing site is still under review. If any deficiency is found we will communicate it to you at that time.

Date:
6/14/10

ANDA Number:
76565

Product Name:
Venlafaxine HCl ER Capsules

Firm Name:
Teva

Firm Representative:
Philip Erickson

Phone Number:
(215) 591-3141

FDA Representative:
H. Ashley Jung

Endorsements:

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-76565	ORIG-1	TEVA PHARMACEUTICALS USA INC	VENLAFAXINE HYDROCHLORIDE

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/s/

HUIJEONG A JUNG
06/14/2010

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

June 11, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

ANDA # 076565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES, 37.5 mg, 75 mg, and 150 mg

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a telephone amendment to the above-referenced, pending Abbreviated New Drug Application in response to a June 10, 2010 telephone contact from Ashley Jung of the Office of Generic Drugs. Specifically, we were requested to provide the drug substance certificates of analysis for the lots used in the manufacture of the executed batches referenced in our May 17, 2010 quality telephone amendment / response to information request.

Please find provided herein (**Attachment 1**), the Teva and supplier certificates of analysis for the requested lots of drug substance. The following table identifies the executed batches and the corresponding drug substance lot numbers.

Drug Product Strength	Executed Batch (Lot #)	Drug Substance (Teva Lot #)	Drug Substance (Supplier Lot #)
37.5 mg	W17003	094K1254	350601809
75 mg	W24010	094K1254 & 094K0863	350601809 & 350601509
150 mg	W26004	094K0863	350601509

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 2 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
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www.tevausa.com

It is our understanding that sponsors submitting electronic submissions to CDER do not need to submit an electronic submission or paper submission to the ORA District Office. District Offices are able to access electronic Chemistry, Manufacturing, and Control submissions through CDER's Electronic Document Room. Therefore, Teva Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable office of the FDA certifying that an electronic submission has been submitted to CDER.

It is Teva Pharmaceuticals USA's belief that the information provided herein represents a complete response to the request presented in the June 10, 2010 telephone contact. This information is submitted toward the continued review and approval of this ANDA. If there are any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

PE/dad
Enclosures

Philip Erickson
Senior Director, Regulatory Affairs

6/11/10
Date

Record of Telephone Conversation

The CMC review of the 07-Jun-10 has not yet been completed. However, to facilitate the review please provide the following information as soon as possible as a telephone amendment: COA's (both API manufacturer's and in-house) of the API batches used for the validation batches submitted in the amendment dated 5/17/10.	**Date:** 6/10/10
	ANDA Number: 76565
	Product Name: Venlafaxine HCl ER Capsules
	Firm Name: Teva
	Firm Representative: Jill Pastore
	Phone Number: (215) 591-3141
	FDA Representative: H. Ashley Jung
	Endorsements:

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-76565	ORIG-1	TEVA PHARMACEUTICALS USA INC	VENLAFAXINE HYDROCHLORIDE

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/s/

HUIJEONG A JUNG
06/10/2010

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

June 7, 2010

Keith Webber, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

QUALITY TELEPHONE AMENDMENT/RESPONSE TO INFORMATION REQUEST

ANDA # 076565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES, 37.5 mg, 75 mg, and 150 mg

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA in response to a review letter received from the Office of Generic Drugs dated June 1, 2010, a copy of which is provided in **Attachment 1** for reference. Comments are addressed in the order presented in the June 1, 2010 letter.

1. In accord with Teva's internal SOPs, in-process controls are performed throughout the encapsulation run. To begin an encapsulation run, set-up tests are in place to ensure proper equipment functioning. Capsules are checked for physical parameters (description, imprinting, size and lock). The following table outlines set-up testing:

Stage	Test	Sample Size
		(b) (4)

(b) (4) The tests, sample size and sample frequency are detailed below:

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

Stage	Test	Sample Size	Minimum Frequency Per Batch
[redacted] (b) (4)			

Samples times are recorded on the printouts of the in-process testing, as well as in the batch record on the "implementation follow up" table. As such, the "implementation follow up tables" showing the in-process sample times which occurred during the validation batches of Venlafaxine HCl ER Capsules, presented in our May 17, 2010 amendment (W17003, W24010 and W26004), are provided for review in **Attachment 2**.

In addition to the in-process control testing discussed above, Teva's manufacturing procedures for Venlafaxine HCl ER Capsules include [redacted] (b) (4)

Please refer to the revised manufacturing procedures in **Attachment 3** (Step [redacted] (b) (4)). All future batches of Venlafaxine HCl ER Capsules will be tested in accord with the requirements outlined above.

2. We hereby confirm that in-process limits for uniformity testing of the coated pellets are based on the theoretical target value. Further, as recommended, the sample size for the uniformity testing of ER coated pellets, for the combined sublots, has been revised to a [redacted] (b) (4) mg sample (equivalent to the weight of one 37.5 mg capsule). Please refer to the revised manufacturing procedures in **Attachment 3** (see Step [redacted] (b) (4) page 56).

3. As requested, multi media dissolution data are provided in **Attachment 4** for the 75 mg (W24010) and 150 mg (W26004) validation batches. In addition, Certificates of Analysis for the first three validation batches for each strength are provided in **Attachment 5**. All

dissolution data are well within the defined limits for this product, and show comparable drug release from batch to batch. Also provided in **Attachment 5** are f2 calculations which further demonstrate consistency of batch-to-batch dissolution for testing conducted using the official medium (water), where the f2s meet the generally accepted criteria of ≥ 50 (as noted in the *Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products- General Considerations*). Calculations are also provided for the 75 mg and 150 mg strengths in the various media used to support multi media testing. Specifically, the following are provided:

Strength	Comparison	Dissolution Medium	f2 Result
37.5 mg	W17003 vs W17004	Water	66
37.5 mg	W17003 vs. W17005	Water	62
37.5 mg	W17004 vs. W17005	Water	86
75 mg	W24010 vs. W24011	Water	84
75 mg	W24010 vs. W24012	Water	58
75 mg	W24011 vs. W24012	Water	60
75 mg	W24010 vs. K-30455^	Water	58
75 mg	W24010 vs. K-30455	0.1N HCl	80*
75 mg	W24010 vs. K-30455	pH 4.5 buffer	68*
75 mg	W24010 vs. K-30455	pH 6.8 buffer	63*
150 mg	W26004 vs. W26005	Water	92
150 mg	W26004 vs. W26006	Water	85
150 mg	W26005 vs. W26006	Water	85
150 mg	W26004 vs. K-30455	Water	57*
150 mg	W26004 vs. K-30455	0.1N HCl	51*
150 mg	W26004 vs. K-30455	pH 4.5 buffer	52 (48*)
150 mg	W26004 vs. K-30455	pH 6.8 buffer	51 (49*)

^K-30455 is the 150 mg ANDA batch

*Calculations include sampling times not required by the drug product specification recommended by the Agency in an August 11, 2004 bioequivalence review letter. Recalculation using only the FDA-specified time points all yielded acceptable f2 results.

4. As requested, the particle size limits for both in-process testing as well as finished product release have been tightened as follows (expressed as % retained on the (b) (4)):

(b) (4)

ER Coated Pellets (sublots 1 and 2)::

Size	Previous limit	Proposed limit
		(b) (4)

Finished Product Release:

Size	Previous limit	Proposed limit
		(b) (4)

Please refer to the manufacturing procedures in **Attachment 3** for the in-process limits. In addition, **Attachment 6** contains Teva's updated summary of in-process controls, as well as Teva's revised drug product release specifications which reflect the tightened finished product PSD criteria. Further, please refer to **Attachment 5** for the certificates of analysis for three commercial scale batches of each strength, which include PSD data for release of the batches. The data demonstrate that our product is in accord with the tightened limits herein.

5. In accord with your request, all deviation reports generated during validation of Teva's Venlafaxine HCl ER Capsules are provided in **Attachment 7**. It is important to note that all incidents occurred during early validation batches which were rejected due to the issues reported therein. Based on the experience gained during the manufacture of these batches and optimization that occurred as a result, Teva went on to successfully validate this product at the commercial scale.

   Please note stability data for the validation batches, beyond Time Zero, are not yet available. We commit to provide the stability data for these batches in the first annual report submitted toward this ANDA. For your review, please find in **Attachment 8** the Time Zero testing for all configurations.

In addition to the responses above, we wish to provide clarification regarding the site of manufacture of the API used to manufacture the validation batches discussed herein. As noted in Teva's August 19, 2008 minor amendment, (b) (4) Therefore, we believe the data herein fulfill that commitment and fully support

manufacture of the intermediate by (b) (4). Thus, a CBE-0 to supply such data is no longer required.

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 60 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

It is our understanding that sponsors submitting electronic submissions to CDER do not need to submit an electronic submission or paper submission to the ORA District Office, as District Offices are able to access electronic Chemistry Manufacturing and Control submissions through CDER's Electronic Document Room. Therefore, Teva Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable office of the FDA certifying that an electronic sequence has been submitted to CDER.

We believe the information provided herein appropriately addresses all concerns expressed in the June 1, 2010 review letter. Should you have any additional questions or require any further clarification, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

PE/jbp
Enclosures

Philip Erickson
Senior Director, Regulatory Affairs

6/7/2010
Date

Pfizer Inc
235 East 42nd Street
New York, NY 10017

June 1, 2010

SD-31
ORIG-1

By FEDEX

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 Teva Pharmaceuticals Inc. (Teva) for venlafaxine HCl extended release capsules authorizing Teva to market and distribute that product in the United States on and after July 1, 2010 and, as such, that the FDA may make approval of Teva's ANDA No. 76-565 for generic venlafaxine extended release capsules effective on or after July 1, 2010, assuming such ANDA is otherwise approvable.

Sincerely,

Geoffrey M. Levitt
Senior Vice President & Associate General Counsel

FDA FAX

ANDA 076565

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)

TO: Teva Pharmaceuticals USA

TEL: (215) 591-3141

ATTN: Phillip Erickson, R. Ph.

FAX: (215) 591-8812

FROM: H. Ashley Jung, Pharm.D., Ph.D.

PROJECT MANAGER: Thomas Hinchliffe, Pharm.D.

This facsimile is in reference to your abbreviated new drug application 076565.

Pages (including cover): 2

SPECIAL INSTRUCTIONS:

*The deficiencies presented below represent MINOR deficiencies and the current review cycle will remain open. You should respond to these deficiencies with a "**Telephone Amendment**" within ten (10) days. If you have questions regarding these deficiencies or are unable to respond within the ten (10) days please contact the Project Manager, Tom Hinchliffe, at 240-276-8536. Please submit documentation by fax to the attention of the Project Manager at 240-276-8582. Please also submit official hard copies of any faxed documentation to the Document Room.*

ANDA: 076565 APPLICANT: Teva Pharmaceuticals USA

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

The deficiencies presented below represent MINOR deficiencies and the current review cycle will remain open. You should respond to these deficiencies with a "Telephone Amendment" within ten days. If you have questions regarding these deficiencies please contact the Project Manager, Tom Hinchliffe, at 240-276-8536. Please submit documentation by fax to the attention of the Project Manager at 240-276-8582. Please also submit official hard copies of any faxed documentation to the Document Room.

A. Deficiencies:

(b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-76565	ORIG-1	TEVA PHARMACEUTICALS USA INC	VENLAFAXINE HYDROCHLORIDE

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/s/

HUIJEONG A JUNG
06/01/2010

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

May 19, 2010

Thomas Hinchliffe
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPONDENCE/ SUBMISSION OF REQUESTED SAMPLES

ANDA # 076565
VENLAFAXINE HCL EXTENDED RELEASE CAPSULES, 37.5 mg, 75 mg, and 150 mg

Dear Dr. Hinchliffe:

Teva Pharmaceuticals USA submits herewith correspondence to the above-referenced pending ANDA to provide drug product samples which were requested in a May 11, 2010 review letter. Specifically, Teva was asked to submit samples of product from batches manufactured at a commercial scale. As such, please find enclosed three bottles of each of the following:

- Venlafaxine HCl ER Capsules, 37.5 mg, Lot W17003
- Venlafaxine HCl ER Capsules, 75 mg, Lot W24010
- Venlafaxine HCl ER Capsules, 150 mg, Lot W26004

Please note that the executed batch records, in-process data and finished product certificates of analysis for each of these three lots were provided in Teva's May 17, 2010 telephone amendment. Hard copies of the certificates of analysis for each of these lots are provided herein for reference.

The submission which accompanies the requested samples is presented in electronic format, while those documents with a handwritten signature are also provided in paper. The electronic submission is provided on one CDROM comprised of approximately one megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812 should you have any questions about the samples provided herein.

Sincerely,
{see appended signature page}

PE/jbp
Enclosures

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

Philip Erickson

Philip Erickson
Senior Director, Regulatory Affairs

May 19, 2010
Date

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

May 17, 2010

Keith Webber, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
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7500 Standish Place, Room 150
Rockville, MD 20855-2773

QUALITY TELEPHONE AMENDMENT/RESPONSE TO INFORMATION REQUEST

ANDA # 076565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES, 37.5 mg, 75 mg, and 150 mg

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA in response to a review letter received from the Office of Generic Drugs dated May 11, 2010, a copy of which is provided in **Attachment 1** for reference. Comments are addressed in the order presented in the May 11, 2010 letter. While on its face, the May 11, 2010 letter requests a major amendment, the Agency verbally agreed to accept this response as a telephone amendment in light of our ability to respond within ten days of receipt of the review letter.

1. [redacted] (b) (4) As such, in accord with the USP General Chapter <1225> on Validation of Analytical Methods, neither the Limit of Quantitation nor Precision tests are applicable to this method's validation requirements. Additionally, one should note that the proposed (b) (4) limit associated with this method represents (b) (4)% of that contained in the official monograph for this compendial article as well as only (b) (4)% of the limit set forth in *FDA Guidance for Industry: Q3C: Impurities: Residual Solvents*.

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

However, in deference to your request for additional method validation data, Teva provides herein as **Attachment 2** data to establish both the Limit of Quantitation and the Precision of the proposed (b) (4) method for the determination of (b) (4) .

2. As requested, a table providing batch sizes (ANDA scale versus commercial scale), and equipment used in these batches is provided in **Attachment 3** to aid your review.

3. Teva's proposed packaging configurations are those that were presented in our 8/15/08 amendment containing Kfar Saba batches. A summary of the package sizes and proposed package components is provided in **Attachment 4**. Changes that are within brackets created by the configurations contained in the 8/15/08 amendment which are deemed annual-reportable in accord with the April 2004 *Guidance for Industry- Changes to an NDA or ANDA* will be submitted in the first annual report.

4. As requested, the theoretical minimum and maximum fill weights, expressed in milligrams, have been added to our Master Formula sheets. Said fill weights are based on the in-process criteria contained within this application. Revised Master Formulae and Manufacturing Procedures (English and Hebrew) for Teva's proposed commercial batches are presented in **Attachment 5** for each strength of drug product. The calculations used to determine the fill weights are also provided on the Master Formulae sheets.

5. The correct theoretical fill weight value to be used in the calculation for Teva's 150 mg strength is "(b) (4)". Further, we assure the Agency that (b) (4) testing will be assessed at (b) (4) in the manufacturing process in all future batches to be manufactured by Teva. Please refer to the summary of in-process controls, as well as in-process specification sheets, which are provided in **Attachment 6**.

6. Teva's original ANDA batch for the 37.5 mg strength was manufactured in 2002, and therefore has been expired for over seven years. In response to your request for comparative dissolution data for this strength, please find in **Attachment 7** a report comparing Teva's original 150 mg ANDA batch (K-30455) versus a recently manufactured 37.5 mg batch (W17003, made with the proposed capsule shells), which contains comparative dissolution test data in various media. Because Teva's 37.5 mg and 150 mg strengths are (b) (4), we believe the data herein demonstrate the equivalence of dissolution in the media tested.

7. We acknowledge your concerns regarding (b) (4) . As such, Teva has implemented in-process (b) (4) from the manufacturing process. A representative sample of the remaining (b) (4) s and subjected to PSD limits, as noted on the in-process control summary located in **Attachment 6**. In order to further ensure quality of this product, we

propose addition of a drug product test, whereby (b) (4) and the sample will be subject to the following criteria:

(b) (4)

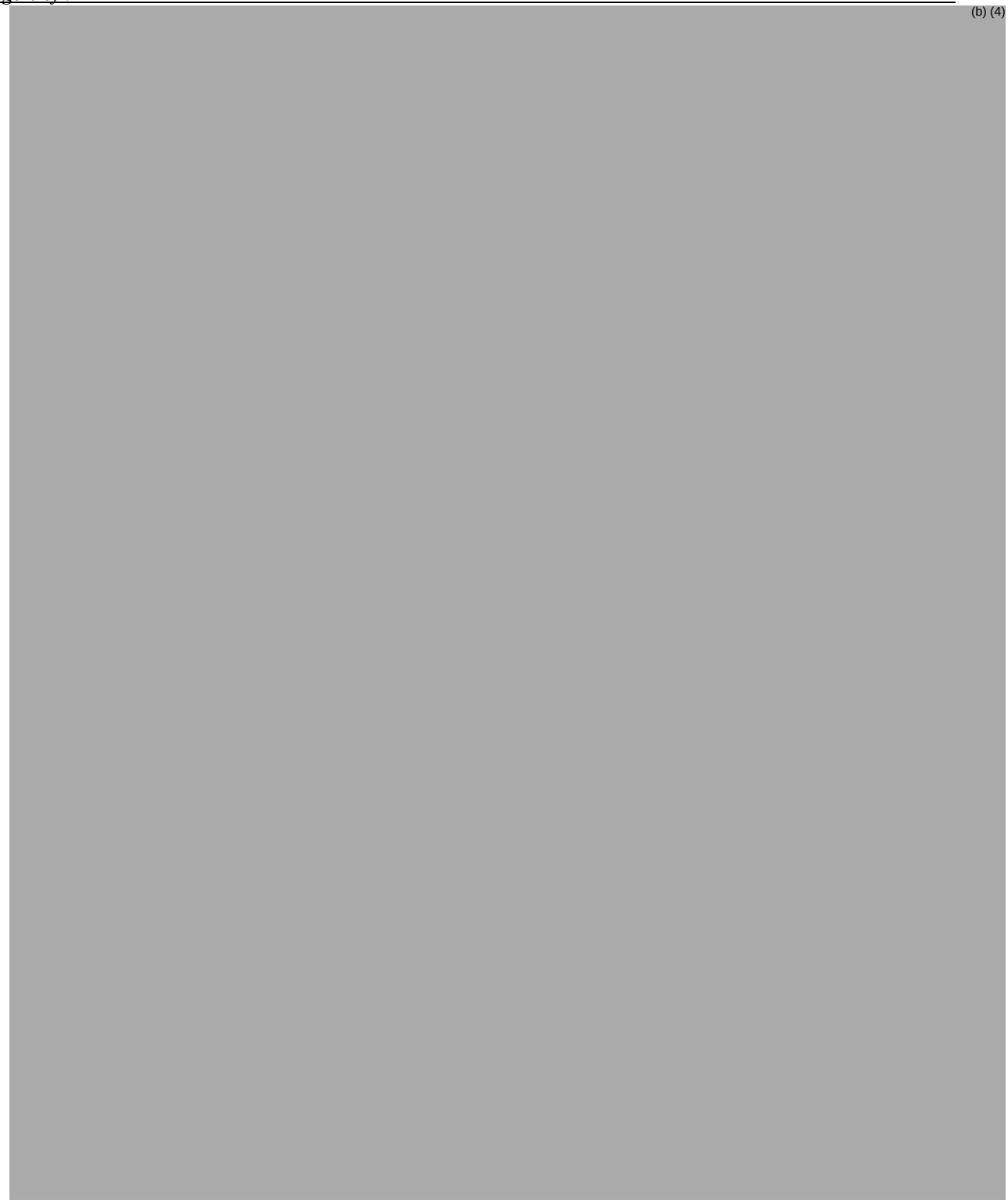
Please refer to the revised Drug Product Specifications document in **Attachment 8**. The methods used for the PSD testing of these pellets (QDP0018141 and QGM0000002) are provided in **Attachment 9**.

8. Per your request, executed batch records for each drug product strength, manufactured at the commercial scale, are presented in **Attachment 10**. In addition, a summary of all in-process data obtained during the manufacture of these batches is provided in tabular form in **Attachment 11**. Please note that the batches contained in Attachment 10 were manufactured prior to the inclusion of some of the in-process tests noted herein. However, the batches were indeed tested for all aforementioned IPCs as presented in the summary. Finished product certificates of analysis for the executed batches provided herein are located in **Attachment 12**.

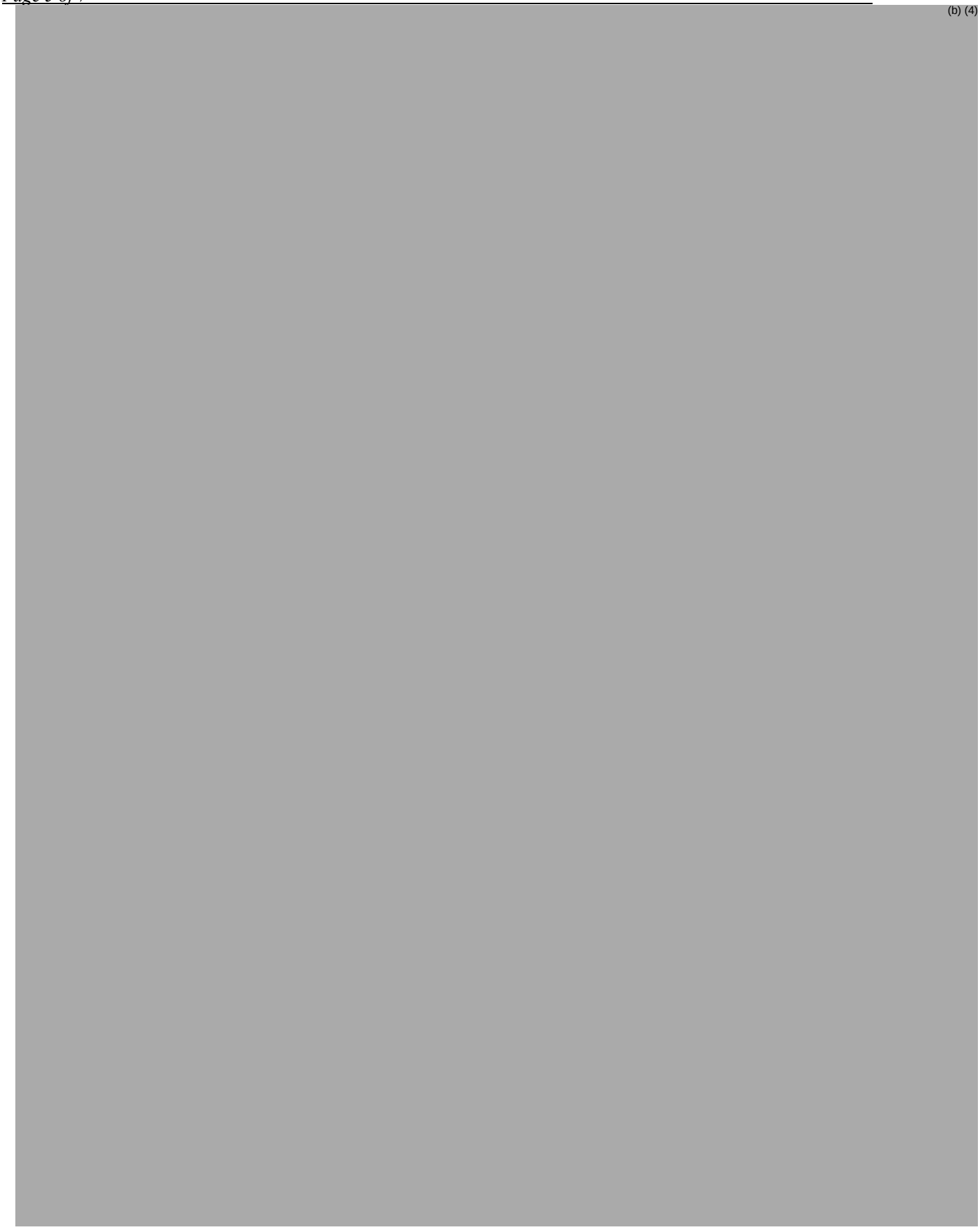
   Additionally, samples of each of these commercial scale batches will be submitted under separate cover upon their receipt in the US from the Kfar Saba, Israel manufacturing facility. Samples will be directed to the attention of the project manager, Thomas Hinchliffe.

(b) (4)

(b) (4)



(b) (4)



The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 108 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

It is our understanding that sponsors submitting electronic submissions to CDER do not need to submit an electronic submission or paper submission to the ORA District Office, as District Offices are able to access electronic Chemistry Manufacturing and Control submissions through CDER's Electronic Document Room. Therefore, Teva Pharmaceuticals USA hereby certifies that **a** letter has been forwarded to the applicable office of the FDA certifying that an electronic sequence has been submitted to CDER.

We believe the information provided herein appropriately addresses all concerns expressed in the May 11, 2010 review letter. Should you have any additional questions or require any further clarification, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

PE/jbp/rsv
Enclosures

Philip Erickson
Senior Director, Regulatory Affairs

May 17, 2010
Date

QUALITY DEFICIENCY - MAJOR

ANDA 076565

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Teva Pharmaceuticals USA TEL: (215) 591-3141

ATTN: Philip Erickson FAX: (215) 591-8812

FROM: Thomas Hinchliffe FDA CONTACT PHONE: (240) 276-8536

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 10, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Venlafaxine Extended Release Capsules, 37.5 mg, 75 mg, and 150 mg.

Reference is also made to your amendment dated September 24, and September 28, 2009.

The Division of Chemistry has completed its review of the submission(s) 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.

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 MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MAJOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20857

*After the effective date, **01-Aug-2010**, ANDAs will only be accepted at the new mailing address listed above. **DO NOT submit your ANDA Regulatory documents to this address prior to 01-Aug-2010.** 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/*

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-565 APPLICANT: TEVA Pharmaceuticals USA

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

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.

6. (b) (4)

7.

8.

Sincerely,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-76565	ORIG-1	TEVA PHARMACEUTICALS USA INC	VENLAFAXINE HYDROCHLORIDE

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
05/11/2010
for Florence S. Fang

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

April 23, 2010

Keith Webber, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT: ALCOHOL DOSE DUMPING STUDIES

ANDA # 076565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES, 37.5 mg, 75 mg, and 150 mg

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a bioequivalence amendment to the above-referenced, pending Abbreviated New Drug Application for the purpose of providing *in vitro* dissolution studies conducted using various concentrations of ethanol in the dissolution medium, in accord with requirements currently posted on the Agency's Bioequivalence Recommendations website. Confirmation was received April 21, 2010 from Dr. Diane Nhu of the Division of Bioequivalence that generic applicants are required to submit such alcohol dose dumping studies for Venlafaxine HCl ER Capsules.

Please find the following documentation herein:

Attachment 1: Alcohol dose-dumping studies conducted on all three strengths of drug product. Testing was conducted using a recently manufactured batch of each strength of Teva's product versus the respective strengths of the RLD, using 0.1N HCl as the medium, and media in which 5%, 20% and 40%, respectively, of the 0.1N HCl medium was substituted with Alcohol USP. The data demonstrate that Teva's product behaves similarly to the reference product in all media tested.

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately one megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

This information is submitted toward the continued review and approval of this ANDA on July 1, 2010. If there are any questions on the information provided herein, please do not hesitate to

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

PE/jbp
Enclosures

Philip Erickson

Philip Erickson
Senior Director, Regulatory Affairs

April 23, 2010
Date

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

April 7, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

ANDA # 076565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES,
37.5 mg, 75 mg, and 150 mg

Dear Dr. Webber:

We submit herewith a labeling amendment to the above-referenced, pending Abbreviated New Drug Application to provide an updated package insert in accord with the most current labeling of the reference-listed drug Effexor XR® Extended-Release Capsules, approved on January 6, 2010.

Please find enclosed in **Attachment 1** Teva's final print package insert (Iss. 2/2010) in Word and PDF formats and a comparison to the last submitted package insert (Iss. 4/2009) in PDF format.

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 2 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

This information is submitted toward the continued review and approval of this ANDA. If there are any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

PE/do
Enclosures

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

Philip Erickson
Senior Director, Regulatory Affairs

April 7, 2010
Date

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

September 29, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT
(ELECTRONIC FORMAT)

ANDA # 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES,
37.5 mg, 75 mg, and 150 mg
BIOEQUIVALENCE AMENDMENT – RESPONSE TO AUGUST 28, 2009 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a Bioequivalence Amendment to the above-referenced pending ANDA in response to an August 28, 2009 review letter. For ease of your review, a copy of the letter is provided in **Attachment 1**.

(b) (4)

In accord with the Agency's request to provide submissions in electronic format, the entire submission is presented electronically on the enclosed disk. Please note that an originally signed paper certification or declaration accompanies this submission wherever an original handwritten signature is currently provided. The electronic bioequivalence amendment is provided on one CDROM comprised of approximately 1 megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

Should there be any questions regarding the information contained herein, please do not hesitate to contact me by telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Eriksen Jr.

PE/do
Enclosure

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

September 24, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT
(CONTAINS REQUEST FOR RECLASSIFICATION TO A MINOR AMENDMENT)

ANDA # 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES,
37.5 mg, 75 mg, and 150 mg
MAJOR AMENDMENT – RESPONSE TO JUNE 11, 2009 REVIEW LETTER

Dear Mr. Buehler:

Prior to addressing the individual review comments conveyed in the June 11, 2009 review letter, Teva hereby requests reclassification of this amendment to that of (b) (4)

Please note that we maintain the proposal to use the (b) (4)) as stated in our January 28, 2009 Unsolicited Amendment. For clarification, the following table summarizes the sites that are pertinent to this ANDA:

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19. [redacted] (b) (4)

Per your request for samples, please note that samples of the Kfar Saba batches as submitted in Teva's August 19, 2008 amendment have been forwarded under separate cover to Tom Hinchliffe of the Office of Generic Drugs.

In accord with the Agency's request to provide our response in electronic format, the entire submission is presented electronically on the enclosed disk. Please note that an originally signed paper certification or declaration accompanies this submission wherever an original handwritten signature is currently provided. The electronic amendment is provided on one CDROM comprised of approximately 42 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Sponsors submitting electronic submissions to CDER do not need to submit an electronic submission or paper submission to the ORA District Office. District Offices are able to access electronic Chemistry Manufacturing and Control submissions through CDER's Electronic Document Room.

TEVA Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable office of the FDA certifying that an electronic unsolicited amendment has been submitted to CDER

This information is submitted for your continued review and approval of this pending application. We bring to your attention that, as stated in our Patent Amendment of January 29, 2008, pursuant to a licensing agreement with Wyeth, this application may be eligible for final approval on or after July 1, 2010 or some earlier date if the Agency is so notified in writing by Wyeth. It is Teva's belief that the above is a complete response to the June 11, 2009 review letter. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Eriksson

PE/do
Enclosures

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

September 18, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT
(ELECTRONIC FORMAT)

ANDA # 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES,
37.5 mg, 75 mg, and 150 mg
LABELING AMENDMENT – RESPONSE TO JULY 9, 2009 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a labeling amendment to the above-referenced pending Abbreviated New Drug Application in response to a July 9, 2009 fax from Michelle Dillahunt of the Division of Labeling and Program Support. For ease of review, please find a copy of the aforementioned fax provided herein (**Attachment 1**).

Enclosed as **Attachment 2**, please find a folder containing Teva's final print package insert (Iss. 4/2009), Medication Guide (Rev. E 5/2008), and container labeling (Iss. 6/2008) in PDF format. There have been no changes to the labeling since it was last submitted in draft format in our April 27, 2009 Telephone Labeling Amendment. Please note that the prominence of the expression of strength and net quantity was not readily evident in the draft labeling previously provided. As requested, the drug product strength is more prominent and the net quantity is less prominent in the final print labeling provided herein.

In accord with the Agency's request to provide submissions in electronic format, the entire submission is presented electronically on the enclosed disk. Please note that an originally signed paper certification or declaration accompanies this submission wherever an original handwritten signature is currently provided. The electronic labeling amendment is provided on one CDROM comprised of approximately 1 megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

It is Teva Pharmaceuticals USA's belief that the information presented herein represents a complete response to the comments presented in the July 9, 2009 fax. This information is submitted for your continued review of this ANDA. Should you have any further questions, please do not hesitate to contact me by telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/pe

PE/do
Enclosures

BIOEQUIVALENCE AMENDMENT

ANDA 76-565

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Teva Pharmaceuticals USA TEL: (215) 591-3141

ATTN: Philip Erickson FAX: (215) 591-8812

FROM: Scott Vehovic FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on January 28, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Venlafaxine 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 __1__ 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.** 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:

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76565

APPLICANT: Teva Pharmaceuticals USA

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 the following deficiencies have been identified:

(b) (4)

2. Please submit dissolution data on the 37.5 mg and 75 mg strengths using the FDA-recommended method. The dissolution testing should be conducted in 900 mL of water at 37°C ± 0.5°C using USP apparatus 1 (basket) at 100 rpm.

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

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
08/28/2009

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

June 22, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

ORIG AMENDMENT
N-000-AF

ANDA # 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES,
37.5 mg, 75 mg, and 150 mg
LABELING AMENDMENT – RESPONSE TO MAY 19, 2009 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a labeling amendment to the above-referenced pending Abbreviated New Drug Application in response to a May 19, 2009 fax from the Division of Labeling and Program Support. For ease of review, please find a copy of the aforementioned fax provided herein in **Attachment 1**. Please note the deficiencies have been addressed in the order in which they were presented in the FDA correspondence.

1. CONTAINER LABELS – 15's, 100's, and 500's

   a. We hereby assure the Agency that we will differentiate the strengths of this drug product by use of contrasting colors in our labels. This will be apparent at the time of submission of the final print version of the labels.

   b. Please note that packaging component summary tables, DMF letters of authorization, technical information, USP data, permeation data, and accelerated and controlled room temperature stability in support of the 15 count packaging configuration were provided in TEVA's August 19, 2008 Major Amendment. An additional 15 count packaging configuration utilizing a bottle of a different size ((b) (4) cc) was proposed in a January 28, 2009 Unsolicited Amendment. All documentation for the new configuration as well as accelerated and controlled room temperature stability for both 15 count packaging configurations were provided in the Unsolicited Amendment.

RECEIVED
JUN 23 2009
OGD

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

2. PROFESSIONAL PACKAGE INSERT/MEDICATION GUIDE

At the time of submission of TEVA's original ANDA, U.S. Patent 6,444,708 was listed in FDA's electronic Orange Book without a use code. As such, TEVA filed a Paragraph IV certification. However, the '708 patent is now listed with the U-398 use code. Therefore, please find in **Attachment 2** a revised patent certification which provides revised certification to the '708 patent (changed from Paragraph IV to a method of use statement).

3. MEDICATION GUIDE

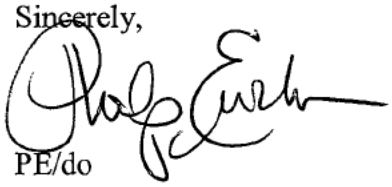
a. A sufficient quantity of Medication Guides will be provided with each bottle for each strength of the drug product such that there is one available per every 30 capsules to be dispensed. In addition, our existing agreement with the Hibbert Group to facilitate the distribution of the Medication Guides is applicable to this product. Medication guides will be provided to pharmacists through our participation in the Hibbert Group distribution program which provides pads of antidepressant Medication Guides to pharmacists, such that a Medication Guide may be provided with each presciption dispensed. Furthermore, to ensure proper distribution of the Medication Guides, the container labels for each strength and package size include the text "PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY".

b. We hereby assure the Agency that the Medication Guide for the drug product meets the general requirements for content and format as described in 21 CFR 208.20.

Please be informed that final print labeling will be provided closer to the anticipated final approval of this application.

It is Teva Pharmaceuticals USA's belief that the information presented herein represents a complete response to the comments presented in the May 19, 2009 fax. This information is submitted for your continued review of this ANDA. Should you have any further questions, please do not hesitate to contact me by telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/do
Enclosures

COMPLETE RESPONSE -- MAJOR

ANDA 76-565

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: TEVA Pharmaceuticals USA TEL: 215-591-3141

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Thomas Hinchliffe FDA CONTACT PHONE: (240) 276-8536

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 10, 2002, 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.

Reference is also made to your amendment dated August 19, 2008 and January 28, 2009.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (5 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 MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-565 APPLICANT: TEVA Pharmaceuticals USA

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

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

(b) (4)

In addition to responding to the deficiencies presented above please provide us samples for your batches submitted in your amendments dated 8/19/08 and 1/28/09.

Sincerely,

{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

6/11/2009 03:57:29 PM

for Florence S. Fang

Telephone Fax

ANDA76-565

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240 276 8991

TO: TEVA Pharmaceugicals USA

TEL: 215-591-3141

ATTN: Philip Erickson

FAX: 215-591-8812

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, 75 mg, & 150 mg

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING
(This review supersedes the review of the 4/6/06 submission)
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	76-565
Date of Submission:	April 27, 2009
Applicant's Name:	Teva Pharmaceuticals USA
Established Name:	Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg, 75 mg, & 150 mg
Proposed Proprietary Name:	None

Labeling Deficiencies

1. CONTAINER LABELS – 15s, 100s & 500s bottles for 37.5 mg, 75 mg, and 150 mg.

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

b. Please submit chemistry supporting data for your 15 count package size if you have not already done so.

2. PROFESSIONAL PACKAGE INSERT/MEDICATION GUIDE

General - You have not addressed the use code (U-398 treatment of GAD) associated with patent 6,444,708. Please clarify.

3. MEDICATION GUIDE

a. Please indicate in your labeling amendment how many patient information inserts will accompany each container size and how they will be presented.

b. Ensure that the medication guide that will be dispensed complies with 21 CFR 208.20.

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://service.govdelivery.com/service/subscribe.html?code=USFDA_17

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

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/s/

Lillie Golson
5/19/2009 11:30:04 AM
Lillie Golson for Wm. Peter Rickman

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

April 27, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE LABELING AMENDMENT

ANDA # 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES,
37.5 mg, 75 mg, and 150 mg
TELEPHONE LABELING AMENDMENT - REVISED LABELING, PATENT CERTIFICATION, AND EXCLUSIVITY STATEMENT

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced pending Abbreviated New Drug Application in response to a March 30, 2009 telephone request made by Michelle Dillahunt of the Division of Labeling and Program Support Branch. Specifically, TEVA was asked to provide updated product labeling as well to acknowledge any new patents or exclusivities listed in the FDA electronic Orange Book for which we had not yet certified.

TEVA's labeling has been updated in accord with SSRI-class label change relayed to TEVA in a February 4, 2009 e-mail correspondence from OGD's Division of Labeling and Program Support and in accord with the most current labeling for the reference listed drug product, Effexor XR® Extended-Release Capsules, approved on January 30, 2009. Furthermore, the Description section of the package insert has been updated to clarify the composition of sugar spheres, an excipient used in the formulation of the drug product, to note they are composed of sucrose and corn starch. Please note that a 15 count packaging configuration for each strength of the drug product was proposed in an August 19, 2008 Major Amendment. As a result, container labels for the new configuration are provided herein and the "How Supplied" section of the package insert was updated accordingly.

Provided in **Attachment 1**, please find a disk containing TEVA's draft package insert (Iss. 4/2009), draft container labeling (Iss. 6/2008), and Medication Guide (Rev. E 5/2008) in both

PDF and Word formats along with comparisons to that of our last submitted package insert (Iss. 4/2006) and container labeling (Iss. 4/2006).

In addition, TEVA's Patent Certification has been revised to provide certification to U.S. Patent 6,310,101 which recently listed in the electronic Orange Book for the reference drug product, Effexor XR® Extended-Release Capsules. The '101 patent is noted in the Orange Book with use code U-46 which is defined as "treatment of panic disorder". Please note that the indication protected by U-46 is not included in our proposed labeling as stated on the enclosed Patent Certification. Please find an updated patent certification statement provided in **Attachment 2**. Please note that U.S. Patent 4,535,186 and its associated Pediatric Exclusivity expired on June 13, 2008. As such, the revised Patent Certification reflects a change in certification to the '186 patent from Paragraph III to Paragraph II.

Additionally, TEVA's exclusivity statement has been revised to acknowledge the listing of exclusivity I-561, which is defined as "long-term treatment of social anxiety disorder". The indication protected by exclusivity I-561 has been omitted from TEVA's proposed labeling in accord with TEVA's "method of use" certifications to U.S. Patents 6,403,120 and 6,419,958. Please find an updated Exclusivity Statement provided in **Attachment 3**.

This information is submitted for your continued review and approval of this pending application. If there are any questions, please do not hesitate to contact me by telephone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/RY

PE/do
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

August 19, 2008

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT

ORIG AMENDMENT
N AC

ANDA # 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES, 37.5 mg, 75 mg, and 150 mg
MAJOR AMENDMENT – RESPONSE TO OCTOBER 12, 2006 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a major amendment to the above-referenced, pending ANDA in response to a review letter from the Division of Chemistry II dated October 12, 2006. A copy of the review letter is provided in **Attachment 1** for ease of your review. In accord with your request, new exhibit batches of drug product were manufactured and additional in-process controls of the drug (b) (4) process were added to provide additional assurance that we are able to produce drug product of consistent quality and potency. This submission is organized such that the new exhibit batches are presented first followed by our responses to the review letter comments. The review letter comments are addressed in the order in which they were presented.

In support of the new exhibit batches, the following are provided:

- Process flow diagrams for the executed and proposed manufacturing processes are provided in **Attachment 2**. Please note that other than the additional in-process controls (discussed in detail herein), no other changes were made to the manufacturing processes used to manufacture the pivotal batches of drug product. The scale of the new exhibit batches and the proposed commercial processes are also unchanged. For ease of your review, process flow diagrams of the originally submitted pivotal batches of drug product are also provided in **Attachment 2**.

- In process control summaries of the executed batches and the proposed commercial processes are provided in **Attachment 3**. The changes made to the in-process control of the drug (b) (4) process are discussed in detail in our responses to the deficiency comments herein.

statements of the manufacturers of the drug substance and excipients which compose Teva's drug product are provided in **Attachment 24**. The finished product release specifications were updated to include a (b) (4) specification in compliance with (b) (4)) and are provided in **Attachment 21**.

This information is submitted for your continued review and approval of this ANDA. Should there be any questions, please do not hesitate to contact me by telephone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/ps

PE/ws
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

January 29, 2008

PATENT AMENDMENT

N_000-XP

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ANDA # 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES,
37.5 mg, 75 mg, and 150 mg
PATENT AMENDMENT- STATUS OF PATENT LITIGATION

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending Abbreviated New Drug Application for the purpose of providing an update on the status of patent litigation related to this ANDA. Please note that TEVA was sued by Wyeth on March 24, 2003 (Civil Action No. 03-1293, (WJM) (DNJ)) regarding this application. As such, the following information is provided regarding the outcome of this Action.

On January 12, 2006, Civil Action No. 03-1293 (WJM) (DNJ) was dismissed. TEVA Pharmaceuticals USA has entered into a settlement and licensing agreement with Wyeth Pharmaceuticals Inc., the holder of NDA 20-699 for the reference listed drug Effexor® XR Capsules. Please be informed that, pursuant to that agreement, Wyeth will send to the Agency in due course, under separate cover, a letter stating that Wyeth has no objection to FDA approving TEVA's ANDA 76-565 for Venlafaxine HCl Extended-Release Capsules on or after July 1, 2010 but not as of any earlier date until Wyeth informs FDA separately in writing of such earlier date. Enclosed, please find a copy of the January 12, 2006 Dismissal Order for your records.

Should you have any questions concerning this information, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

MAJOR AMENDMENT

ANDA 76-565

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: TEVA Pharmaceuticals USA TEL: 215-591-3141

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Thomas Hinchliffe PROJECT MANAGER: (301) 827-5771

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 10, 2002, 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.

Reference is also made to your amendments dated June 1, 2005, December 22, 2005, July 6, 2006, and August 14, 2006.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__2__ 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 MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

See bellow comments.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-565 APPLICANT: TEVA Pharmaceuticals USA

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

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

We reviewed your telephone amendment faxed to us on August 14, 2006 and found that the currently proposed in-process specifications are not adequate due to lack of available data. Please manufacture another demonstration batch for the 150 mg strength capsule to establish an appropriate specification and to demonstrate that you are able to consistently produce quality drug product. Based on your submissions, we have identified the following problems:

e

In order to address all of the above issues please be sure to obtain as much in-process information as possible in the next demonstration batch. In addition to setting appropriate specifications, it is important to demonstrate that the batches can be manufactured consistently. Therefore, the new demonstration batch should use the same manufacturing procedures, including batch scale and equipment, as the bio-batch. In order to demonstrate that the new batch is the same as the bio-batch in regards to release we ask that you perform dissolution tests in multiple media.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

OGD is changing its CMC review process though our question based review (QbR) initiative, which is described in more detail on the OGD website: http://www.fda.gov/cder/ogd/QbR.htm.

OGD's QbR was designed with the expectation that ANDA applications would be organized according to the Common Technical Document (CTD), a submission format adopted by multiple regulatory bodies including the FDA. Generic firms are strongly recommended to submit their ANDAs in the CTD format (either eCTD or paper) to facilitate the implementation of the QbR and to avoid undue delays in the review of their applications.

Because of the increasing number of ANDA submissions OGD receives each year, the Quality Overall Summary (QOS) part of the CTD format is extremely important to making our new review process more efficient. Beginning in January 2007, all ANDA applicants are recommended to provide an electronic copy of a QOS that addresses OGD's QbR questions. The QbR-Quality Overall Summary Outline posted on our webpage http://www.fda.gov/cder/ogd/ contains all the questions to prepare the QOS. The QOS should be submitted in both MS Word and pdf format along with the paper or electronic submission. The QOS should be provided even if the remainder of the application is not in CTD format. OGD has prepared QOS models that can be found on the OGD web site. We ask you to use these as a guide for your submissions.

If you are already submitting QbR-based applications, we would like to take this opportunity to thank you for supporting this very important initiative.

Sincerely,

{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
10/12/2006 09:54:09 AM
for Florence S. Fang

113.1

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591-3141
Direct Fax: (215) 591-8812
philip.erickson@tevausa.com

August 14, 2006

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

TELEPHONE AMENDMENT

ORIG AMENDMENT

NIAM

ANDA # 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES,
37.5 mg, 75 mg, and 150 mg
TELEPHONE AMENDMENT – RESPONSE TO JULY 24, 2006 REQUEST

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced, pending ANDA in response to a July 24, 2006 review letter. Specifically, we have added additional in-process controls to our drug product manufacturing process to ensure the success and reproducibility of both the (b) (4) steps. A copy of the review letter is enclosed in **Attachment 1** for ease of your review.

Per your request, additional in-process controls have been added to both the (b) (4) steps of each strength of our drug product. (b) (4) . A summation of the changes are as follows:

In-Process Controls	Previously Proposed	Currently Proposed
[redacted] (b) (4)		

* To be performed on the three validation batches only

Please be informed that the executed batches for all three strengths are past their expiration (2004). As such, we are unable to provide data on the executed batches, other than [redacted] (b) (4) data that was generated at the time of manufacture. Teva Pharmaceuticals USA commits to provide additional data to support our in-process controls upon availability of the validation batches.

We note that the review letter also suggested tests [redacted] (b) (4).

The following is provided in support of the in-process controls proposed herein:

- In-process specifications for extended release coated pellets, for each strength, revised to add drug release testing are provided in **Attachment 2**.

- Manufacturing directions (English and Hebrew) for Venlafaxine Hydrochloride Extended Release Capsules, 37.5 mg, 75 mg, and 150 mg revised to include weight gain calculations and particle size distribution testing are provided in **Attachment 3**.

- Analytical methods for Particle Size Determination By Sonic Sifter (ARD-000003, Ver. 3.0) and Dissolution Testing (Method No. SI-19126, Ed. 01) are provided in **Attachment 4**. Additionally, the Content (b) (4) analytical procedure has been revised (Method No. SI-17223, Ed. No. 03) to include the theoretical capsule weight and is also provided in **Attachment 4**.

- (b) (4) testing results of the executed batches from the original ANDA are provided in **Attachment 5**. These data meet the proposed (b) (4) acceptance criteria.

It is Teva Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the July 24, 2006 review letter. This information is submitted for your continued review and approval of this ANDA. If there are any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/ws
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591-3141
Direct Fax: (215) 591-8812
philip.erickson@tevausa.com

July 6, 2006

ME

Ashley Hahm
Chemistry Reviewer
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

SUBJECT: VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES, 37.5 mg, 75 mg, and 150 mg – ANDA #76-565

(PHYSICAL SAMPLES)

Dear Ms. Hahm:

As requested in your June 26, 2006 telephone communication, please find enclosed samples of Venlafaxine Hydrochloride ER Capsules, 37.5 mg, 75 mg, and 150 mg. Specifically, the following samples are provided herein:

- Venlafaxine HCl ER Capsules, 37.5 mg: 500 count bottle of Batch No. K-30703, manufactured on November 5, 2002.
- Venlafaxine HCl ER Capsules, 75 mg: 500 count bottle of Batch No. K-30702, manufactured on November 5, 2002.
- Venlafaxine HCl ER Capsules, 150 mg: 500 count bottle of Batch No. K-30455, manufactured on August 27, 2002.

Please note that the smallest packaging configurations were unavailable. Therefore, 500 count sizes were sent for each strength. Due to availability, please note that the samples provided are past their expiration date (2004). Also, provided herein is a copy of the cover letter that accompanied the shipment of the samples from Teva Israel, as well as a statement regarding the material safety of the physical samples.

The remaining questions which were communicated to Teva on June 26, 2006 have been answered in a telephone amendment submitted toward this ANDA under separate cover. Should you have any additional questions or requests, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

Philip Ericson/jp

PE/ws
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591-3141
Direct Fax: (215) 591-8812
philip.erickson@tevausa.com

July 6, 2006

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

TELEPHONE AMENDMENT

ORIG AMENDMENT
N-000-AM

ANDA # 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES, 37.5 mg, 75 mg, and 150 mg
TELEPHONE AMENDMENT – RESPONSE TO JUNE 26, 2006 REQUEST

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced, pending ANDA in response to a June 26, 2006 telephone request made by Ashley Hahm, Chemistry Reviewer, of your office. Specifically, (1) We are to provide additional in-process controls to our drug product manufacturing process, (2) provide physical samples of our drug product for the purpose of visual inspection, and (3) clarify the status of Assia Chemical Industries, Ltd. as a source of drug substance. Comments are addressed in the order in which they are presented.

1. Per your request to provide additional in-process controls, [redacted] (b) (4) testing has been added to the in-process controls of all three strengths of our drug product. Provided in **Attachment 1** please find our in-process specifications for [redacted] (b) (4) which have been revised to add [redacted] (b) (4) testing. Also included in **Attachment 1**, please find the Content Uniformity of [redacted] (b) (4) analytical procedure (Method No. SI-17223, Ed. No. 02). Additionally, provided in **Attachment 2** please find the drug product manufacturing directions (English and Hebrew) which have been revised to add the sampling for [redacted] (b) (4) testing (see step numbers 4.5 and 5.1).

2. Per your request, we are providing physical samples of our Venlafaxine Hydrochloride ER Capsules, 37.5 mg, 75 mg, and 150 mg. Concurrent with this submission, these samples are being sent under separate cover to Ashley Hahm. Please note that, due to availability, the samples provided are past their expiration date.

3. As communicated to Ashley Hahm by telephone (subsequent to her June 26, 2006 telephone request), Teva Pharmaceuticals USA has not removed Assia Chemical Industries, Ltd. as a source of drug substance for this file, nor do we intend to do so. As committed in an April 1, 2004 minor amendment, we will submit the information necessary for approval of material supplied by Assia (the alternate facility) in a post-approval CBE-0 supplement.

It is Teva Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the June 26, 2006 telephone contact. This information is submitted for your continued review and approval of this ANDA. If there are any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson /jp

PE/ws
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591-3141
Direct Fax: (215) 591-8812
philip.erickson@tevausa.com

April 14, 2006

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

ANDA # 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES,
37.5 mg, 75 mg, and 150 mg
LABELING AMENDMENT – RESPONSE TO APRIL 3, 2006 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a labeling amendment to the above-referenced, pending ANDA in response to an April 3, 2006 review letter from the Labeling Review Branch of the Office of Generic Drugs. For ease of review, a copy of the review letter is provided in **Attachment 1**. Your comments are addressed in the order in which they were presented.

General:

- This product will be distributed with one package outsert attached to each bottle; each outsert will contain the text of the medication guide. Additional medication guides will be provided to pharmacists through our participation in the Hibbert Group distribution program which provides pads of antidepressant medication guides to pharmacists, such that a medication guide may be provided with each prescription dispensed.

Container:

- As requested, please find enclosed in **Attachment 2**, a CD-ROM containing electronic versions of our updated final print container labels (Iss. 4/2006) in both Word and PDF formats. Comparisons to the last submitted version our container labels in PDF format are also included on the disk. In accord with your recommendations, the container labels prominently display on the main panel the established name, strength, and the instruction "ATTENTION PHARMACIST: Each patient is required to receive a Medication Guide," and the strengths are differentiated from each other by color. In addition, the labels have been revised to clarify the country of origin to comply with U.S. Customs regulations.

Physician Insert/Medication Guide:

- We have revised our package insert in accord with your recommendations. Included on the CD-ROM enclosed in **Attachment 2,** please find an electronic version of our updated final print package insert (Iss. 4/2006), in both Word and PDF formats. A comparison to the last submitted version of our package insert in PDF format is also included on the disk. In addition, the final print medication guide (Rev. B 2/2005) is also included on the disk in PDF format. Though there have been no changes to the content of the medication guide since it was last submitted in draft, it is provided herein in final print for completeness of file.

It is Teva Pharmaceutical USA's opinion that the information presented herein represents a complete response to the requests presented in the April 3, 2006 review letter . This information is submitted for your continued review and approval of this ANDA. If there are any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/ws
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

February 7, 2006

Gary Buehler, Director
Food and Drug Administration
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UNSOLICITED AMENDMENT -
LABELING REVISION

ANDA# 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES,
37.5 mg, 75 mg, and 150 mg
UNSOLICITED AMENDMENT - LABELING REVISION

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced, pending Abbreviated New Drug Application. Specifically, package insert labeling has been revised in accord with the reference listed drug's labeling approved on November 29, 2005. Please find enclosed herein a CD-ROM containing an electronic version of our updated draft package insert and patient package insert (Iss. 12/2005) in both Word and PDF formats. A comparison to the last submitted version in PDF format is also included on the disk.

This information is submitted toward the continued review and approval of this ANDA. Should you have any questions on the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/ws
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591-3141
Direct Fax: (215) 591-8812
philip.erickson@tevausa.com

June 1, 2005

Gary Buehler, Director
Office of Generic Drug
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT
(Contains Labeling)

ANDA # 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES,
37.5 mg, 75 mg, and 150 mg
MINOR AMENDMENT – RESPONSE TO AUGUST 24, 2004 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced, pending Abbreviated New Drug Application in response to review letter dated August 24, 2004. For ease of review, please find attached a copy of this letter **(Attachment 1)**. We have addressed your comments in the order in which they were presented in your letter.

A. Deficiencies:

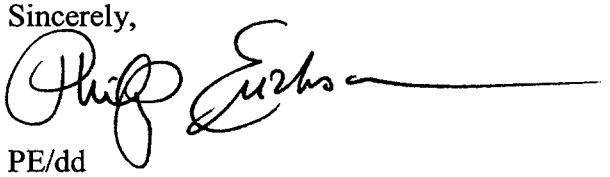
1. Please be informed that the drug substance manufacturer, Teva A.P.I. division (Teva Tech) responded to DMF #16281 deficiencies on April 13, 2005. Please find enclosed in **Attachment 2** a copy of the cover letter that accompanied the supplier's response.

2. Regarding the request to add an optical rotation test, the following data were received from the drug substance manufacturer, Teva Tech. The starting material in the drug substance synthesis, [redacted] (b) (4)) and the final product Venlafaxine Hydrochloride were tested for optical rotation. Test results are provided below:

2 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letter. This information is submitted for your continued review and approval of this ANDA. If there are any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/dd
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

ORIG AMENDMENT
N/AB

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591 3141
Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

March 25, 2005

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT - CMC DOCUMENTS INCLUDED

ANDA # 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES,
37.5 mg, 75 mg, and 150 mg
BIOEQUIVALENCE AMENDMENT – CMC DOCUMENTS INCLUDED
RESPONSE TO AUGUST 11, 2004 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a bioequivalence amendment to the above-referenced, pending Abbreviated New Drug Application in response to a review letter dated August 11, 2004. For ease of review, please find enclosed a copy of this letter in **Attachment 1**.

As requested, we have revised our dissolution specifications. Please find enclosed in **Attachment 2** revised Release Specifications and Finished Product Stability Protocols for Venlafaxine Extended-Release Capsules, 37.5 mg, 75 mg, and 150 mg. Please note that we have also tightened the proposed specification for [redacted] (b) (4)

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned bioequivalence review letter. This information is submitted for your continued review and approval of this ANDA. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/ws
Enclosures

RECEIVED
MAR 28 2005
OGD/CDER

MINOR AMENDMENT

AUG 2 4 2004

ANDA 76-565

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: TEVA Pharmaceuticals USA

TEL: 215-591-3141

ATTN: Philip Erickson

FAX: 215-591-8812

FROM: Thomas Hinchliffe

PROJECT MANAGER: (301) 827-5771

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 10, 2002, 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.

Reference is also made to your amendment dated April 1, 2004.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 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 have been 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.

AUG 24 2004

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	76-565
APPLICANT:	Teva Pharmaceuticals USA
DRUG PRODUCT:	Venlafaxine Hydrochloride Extended Release Capsules, 37.5mg, 75mg, and 150 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

[redacted]

Sincerely yours,

/s/ for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

********** -COMM. JOURNAL- ********** DATE AUG-25-2004 ***** TIME 17:25 ********

MODE = MEMORY TRANSMISSION START=AUG-25 17:23 END=AUG-25 17:25

FILE NO.=406

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-CDER OGD DOC RM -

********** - ***** - **********

MINOR AMENDMENT

AUG 2 4 2004

ANDA 76-565

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: TEVA Pharmaceuticals USA TEL: 215-591-3141

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Thomas Hinchliffe PROJECT MANAGER: (301) 827-5771

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 10, 2002, 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.

Reference is also made to your amendment dated April 1, 2004.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__1__ 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 have been 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.

CH

6.1

TEVA

ORIGINAL

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591 3141
Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

June 29, 2004

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT

ORIG AMENDMENT
N/AB

RECEIVED
JUN 30 2004
OGD / CDER

ANDA # 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES,
37.5 mg, 75 mg, and 150 mg
BIOEQUIVALENCE AMENDMENT – RESPONSE TO JUNE 4, 2004 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a bioequivalence amendment to the above-referenced, pending Abbreviated New Drug Application in response to a review letter dated June 4, 2004. For ease of review, please find attached a copy of this correspondence in **Attachment 1**. We have addressed your comments in the order in which they were presented in your letter.

A. Bioequivalence Deficiencies

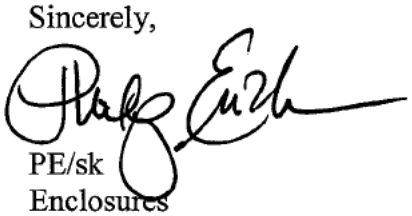
1. Please find the pharmacokinetic data and statistical analysis for O-Desmethylvenlafaxine, the venlafaxine metabolite, from the fasting (sprinkled) study (Study No. 30024) in **Attachment 2** as well as the compact disk containing the SAS Transport files in **Attachment 3**. Please note that based on comment number 2 of the aforementioned bioequivalence deficiency letter, subject no. 20 was removed from the analysis due to emesis (4 hours, 15 minutes post-dose in period 1) and as a result, the analysis includes 18 subjects instead of 19 subjects.

2. As requested, provided herein is amendment III to the fasting study (study No. 02204), titled Final Report Amendment III, deleting subject no. 1 from the study due to emesis after dosing in Period 1 (test formulation) (**Attachment 4**). In addition, included in amendment III are the pharmacokinetic parameters and statistical analysis of the data, excluding subject no. 1 (**Attachment 4**). Additionally, for completeness of the file, please find in **Attachment 5** amendments I and II regarding study no. 02204 for the revision of the venlafaxine and O-desmethylvenlafaxine validation report and the addition of statistical analysis of adverse events for European submission, respectively.

3 The dissolution medium of phosphate buffer with pH 4.5 was chosen for Venlafaxine Hydrochloride Extended-Release Capsules, 37.5 mg, 75 mg and 150 mg considering the suitability of the HPLC analytical dissolution testing method. The HPLC analysis of samples utilizing the acetate buffer presents significant fronting and high tailing. As such a phosphate buffer of pH 4.5 is more appropriate for this HPLC system.

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letter. This information is submitted for your continued review and approval of this ANDA. If there are any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/sk
Enclosures

BIOEQUIVALENCY AMENDMENT

ANDA 76-565

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)

JUN 0 4 2004

APPLICANT: Teva Pharmaceuticals USA TEL: 215-591-3000

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Steven Mazzella PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on December 10, 2002, 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(s) dated: February 13, 2003 and April 10, 2003.

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:

JUN 04 2004

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-565 APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Venlafaxine Extended Release Capsules 37.5mg,75mg & 150mg.

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. For the fasting (sprinkled) study (Study No. 30024), please submit pharmacokinetic data of venlafaxine metabolite (O-Desmethylvenlafaxine) along with summary statistical analysis for evaluation.

2. For the fasting study (Study No. 02204), it is noted that Subject #1 vomited at 4 hrs 54 minutes after dosing in Period 1 (Test formulation). However this subject was allowed to continue the study. Please note that data from subjects who experience emesis any time during the labeled dosing interval should be deleted. Please re-calculate pharmacokinetic parameters and statistically re-analyze the data without subject # 1.

3. You indicated that Phosphate buffer pH 4.5 was used in dissolution testing. However, normally pH of acetate buffer ranges from 4.1 to 5.5 and pH of phosphate buffer from 5.8 to 8. Please clarify why phosphate buffer pH 4.5 was used instead of acetate buffer pH 4.5.

Sincerely yours,

for Barbara M Davit

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MODE = MEMORY TRANSMISSION START=JUN-07 10:20 END=JUN-07 10:22

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-CDER OGD DOC RM -

********** - ***** - **********

BIOEQUIVALENCY AMENDMENT

ANDA 76-565

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)

JUN 0 4 2004

APPLICANT: Teva Pharmaceuticals USA TEL: 215-591-3000

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Steven Mazzella PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on December 10, 2002, 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(s) dated: February 13, 2003 and April 10, 2003.

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:

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591 3141
Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

April 1, 2004

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

ORIG AMENDMENT
N/am

ANDA # 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES,
37.5 mg, 75 mg, and 150 mg
MINOR AMENDMENT – RESPONSE TO MAY 27, 2003, NOVEMBER 28, 2003 AND DECEMBER 11, 2003 REVIEW LETTERS

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced, pending Abbreviated New Drug Application in response to review letters dated May 27, 2003, November 28, 2003, and December 11, 2003. For ease of review, please find attached copies of these letters **(Attachment 1)**. Please note that the review letter dated December 11, 2003 was sent to replace the first page of the November 28, 2003 review letter to revise labeling review comments. We have addressed your comments in the order in which they were presented in you letters.

A. Deficiencies

1. Drug substance:

   a. Please find a copy of the cover letter sent to the agency on August 8, 2003, by the drug substance manufacturer responding to the deficiencies cited within DMF # 16281, in **Attachment 2.**

C. Labeling Deficiencies

Please find in **Attachment 16** a revised patent certification and exclusivity statement updated to include a new exclusivity, I-261, which covers treatment of social anxiety disorder. The patent certification provides for a paragraph IV certification with respect to the 6,403,120 and 6,419,958 patents regarding the treatment of depression. Also TEVA Pharmaceuticals USA is certifying with a method of use statement to these patents with respect to the use codes for both Generalized Anxiety Disorder (U-451 and U-459) and Social Anxiety Disorder (U-535). As such, the indications protected by these exclusivities have been removed from the proposed labeling. Additionally, we acknowledge that this product would not be eligible for marketing with either the General Anxiety Disorder or Social Anxiety Disorder indications until September 20, 2017 when U.S. patent # 6,419,958 and # 6,403,120 expire. Accordingly, the wording related to these indications will not be included in our product labeling until expiration of these patents.

As requested, we have revised the package insert and container labeling in accord with the November 28, 2003 and December 11, 2003 labeling review letters. Please find in **Attachment 17** the revised draft container labels as well as a comparison to the previous revision and the revised package insert with the side by side comparison to the previous edition. In addition, provided in **Attachment 18** is the patient package insert with a side by side comparison to the innovator's label, modeled after the Patient Information sheet for Effexor® XR.

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letters. This information is submitted for your continued review and approval of this ANDA. If there are any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/sk
Enclosures

MINOR AMENDMENT

ANDA 76-565

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)

MAY 27 2003

APPLICANT: Teva Pharmaceuticals USA TEL: 215-591-3000

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Thomas Hinchliffe PROJECT MANAGER: 301-827-5771

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 10, 2002, 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.

Reference is also made to your amendment(s) dated: February 13, 2003 and March 19, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 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. Labeling comments will follow when their review is completed.

MAY 27 2003

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-565
APPLICANT: Teva Pharmaceuticals USA
DRUG PRODUCT: Venlafaxine Hydrochloride Extended Release Capsules, 37.5mg, 75mg, and 150 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Regarding the drug substance we have the following comments:

(b) (4)

[redacted]

2. Regarding manufacturing and processing we have the following comments:

(b) (4)

3. Regarding the container/closure systems we have the following comments:

(b) (4)

4. Regarding the finished drug product controls and stability studies we have the following comments:

(b) (4)

5. For the approval of using drug substance manufactured at the alternate facility, you need to provide the following information:

   a. Executed batch record for one batch of one strength of drug product (strength used in the bioequivalency study in support of

this application) manufactured using drug substance from the alternate facility;

b. CoA of the executed batch with justification for equivalence for Venlafaxine Hydrochloride manufactured from the alternative facility;

c. Commitment to place the first commercial batch using drug substance from the alternate facility on long term stability and submit data in the annual report.

You may also choose to commit to submit the above information in a post approval CBE(0) supplemental application.

6. On the How Supplied section of the labeling insert , the imprinting for the 150 mg capsules is listed as " (b) (4) and "(b) (4)" on the body. However, these are not the imprint "93" and " 7368" intended for commercial production. Please comment and revise, if necessary.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

The bioequivalence review comments will be provided to you under separate cover. If the Office of Bioequivalence recommends a different Dissolution test and specification from the one proposed in this application, please revise the Dissolution testing method and specification for the finished drug products release and stability protocols accordingly and resubmit the comparative dissolution profile data.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

ANDA Number: 76-565

Date of Submissions: December 10, 2002, February 13, 2003, and, & April 1, 2003.

Applicant's Name: Teva Pharmaceutical USA.

Established Name: Venlafaxine Hydrochloride Extended-Release Capsules,
37.5 mg, 75 mg, & 150 mg.

Proposed Proprietary Name: None

Labeling Deficiencies:

1. GENERAL

   a. Please note that there is a "Patient Information Sheet" available for the reference listed drug, Effexor XR, and it should be a part of the generic labeling as well. You may use the attached text as a model. Please include a statement "Pharmacist: Patient Information Sheet enclosed" or something similar on the container label.

   b. Effexor XR now has a new exclusivity for the treatment of social anxiety disorder (I-261) which expires on February 11, 2006. Please submit an updated exclusivity statement to reflect the change and revise your labeling to include wording regarding social anxiety disorder as provided below.

   c. Revise the storage temperature recommendation as follows:

      "Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature] Dispense in a tight , light-resistant container as defined in the USP, with a child-resistant closure as required"

   d. Please note that this product would not be eligible for marketing with the Major Depressive Disorder indication until June 13, 2008 when the patent #4535186 expires and the General Anxiety Disorder indication until September 20, 2017 when the patent #6419958 expires.

2. CONTAINER – 100 & 500 bottles for 37.5 mg, 75 mg, and 150 mg.

a. See comments (a) and (d) under GENERAL.

b. Please ensure that the established name and strength appear prominently on the labels.

c. Since your drug product is available in multiple strength, we strongly encourage you to differentiate the strengths by using boxing, contrasting colors, and/or some other means.

3. PHYSICIAN INSERT:

*Deletions are marked with cross outs and additions with underlines.

(b) (4)

[redacted]

9 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

4. PATIENT PACKAGE INSERT

Please follow the attached Patient Information sheet for Effexor XR as a model.

Please revise your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labels with your last submission with all differences annotated and explained.

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Patient Information sheet for Effexor XR

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591 3141
Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

April 10, 2003

ORIG AMENDMENT
NAB

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UNSOLICITED AMENDMENT
BIOEQUIVALENCE

ANDA # 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES,
37.5 mg, 75 mg, and 150 mg
UNSOLICITED AMENDMENT – BIOEQUIVALENCE

Dear Mr. Buehler,

We submit herewith an Unsolicited Amendment to the above-referenced pending ANDA. The purpose of this amendment is to provide information pertaining to the administration of the contents of the extended-release capsule when mixed with applesauce under fasting conditions.

Several key pieces of information regarding the RLD product Effexor® XR appear to be missing, or at best, unclear. These items include the following:

There exist multiple revisions of Effexor® XR inserts within FDA and Wyeth websites.

It appeared that FDA approved Wyeth's proposal for the inclusion of a *sprinkle* dosing within the text of their product insert on October 22, 2002. No electronic link to the "approved" RLD text was provided.

Subsequently "approved" Effexor® XR insert text does not include provisions for a *sprinkle* dosing. (Text approved February 11, 2003.) As such, it remains unclear as to whether or not Wyeth actually has approval for a *sprinkle* dosing or plans to market product with such labeling.

In the event that Wyeth did obtain approval for such a *sprinkle* dosing, and product is so marketed, TEVA anticipates that the Agency will want to receive and review a sprinkle dose bioequivalence study. Hence TEVA has conducted a bioequivalence study that involved the administration of the extended-release capsule contents when mixed with applesauce under fasting conditions.

Attachment 1 contains a full report of an *in vivo* bioequivalence study, including Financial Disclosure Form FDA 3454. The study compared Venlafaxine Hydrochloride Extended Release Capsules, 150 mg manufactured by Teva Pharmaceutical Industries, Ltd. to the referenced listed drug, Effexor® XR, 150 mg. The same lots of test and reference products were utilized in the *sprinkle* study as that of the study submitted in our original application. The results of this study demonstrate the bioequivalence of our proposed product to that of the RLD under sprinkle dosing, fasted conditions. Please note that our original application included the appropriate in vivo studies utilizing the intact capsules.

We ask that this study be incorporated into our ANDA for your review. Should there be any questions regarding the information contained herein, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/sah
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591 3141
Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

April 1, 2003

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT INFORMATION

NEW CORRESP
NC

ANDA # 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES, 37.5 mg, 75 mg, and 150 mg
RECEIPT OF NOTICE/ END OF 45-DAY CLOCK/ LEGAL STATUS OF U.S. PATENT Nos. 6,274,171, 6,403,120, 6,419,958 and 6,444,708

Dear Mr. Buehler:

150 mg:

Teva Pharmaceuticals USA hereby certifies that in accord with 21 CFR 314.95(b), Notice of Certification of Non-Infringement of U.S. Patent Nos. 6,444,708, 6,274,171, 6,419,958, and 6,403,120 was provided to Wyeth-Ayerst as the holder of NDA 20-699 for Effexor® XR Capsules and owner of the patents. Please note that the Notice dated February 6, 2003 contains the information required under 21 CFR 314.95(c).

Notice was received by Wyeth-Ayerst on February 10, 2003. Therefore, in accord with 21 CFR 314.95(f), the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act began on February 11, 2003 and ended on March 27, 2003. In accord with 21 CFR 314.95(e), a copy of the U.S. Postal Service return receipt card showing delivery to Wyeth-Ayerst in Madison, New Jersey is provided herein as documentation of the receipt of Notice (**Attachment 1**).

37.5 mg and 75 mg:

Teva Pharmaceuticals USA hereby certifies that in accord with 21 CFR 314.95(b), Notice of Certification of Non-Infringement of U.S. Patent Nos. 6,444,708, 6,274,171, 6,419,958, and 6,403,120 was provided to Wyeth-Ayerst as the holder of NDA 20-699 for Effexor® XR Capsules and owner of the patents. Please note that the Notice dated February 12, 2003 contains the information required under 21 CFR 314.95(c).

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Please note that a request to provide Federal Express Tracking Documentation as evidence of receipt of the Notice of Certification by Wyeth-Ayerst in Madison, New Jersey was approved by CDR Gregg Davis of the Agency. This documentation is provided along with a copy of the United States Postal Service return receipt card in accord with 21 CFR 314.95(e). **(Attachment 2)**

Notice was received by Wyeth-Ayerst on February 13, 2003. Therefore, in accord with 21 CFR 314.95(f), the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act began on February 14, 2003 and ended on March 30, 2003.

We hereby inform the Agency of a suit filed by Wyeth-Ayerst against Teva Pharmaceuticals USA concerning U.S. Patent Nos. 6,274,171, 6,403,120, and 6,419,958. The suit, Civil Action No. 03cv1293 was filed on March 24, 2003 in the United States District Court for the District of New Jersey. The aforementioned suit was filed within the 45-day period. Teva hereby commits to provide notification of the outcome of this suit in an appropriate submission to this application. A copy of the complaint is provided in **Attachment 3**.

Please note that, for all three strengths, suit was not filed concerning U.S. Patent No. 6,444,708 within the 45 day period, therefore Wyeth has waived its right to pursue future legal action under the scope of the Waxman-Hatch Act.

If there are any questions regarding the information presented herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/PE

PE/sah
Enclosures

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW ▪ Washington, DC 20005-3315 ▪ 202.408.4000 ▪ Fax 202.408.4400
www.finnegan.com

NEW CORRESP

NC

March 26, 2003

Food & Drug Administration
Office of Generic Drugs
(HFD-600)
7500 Standish Place
Rockville, Maryland 20855

HAND DELIVERY VIA
WASHINGTON EXPRESS SERVICES, INC.

4/11/03
P.M.P
-Letter from patent holder ('171, '120, '958)

Attn: Mr. Gregory Davis

Venlafaxine HCl Extended-Release Capsules, 37.5, 75 and 150 mg
Abbreviated New Drug Application No. 76-565
Notification of Filing of Legal Action for Patent Infringement

Dear Mr. Davis:

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) Kurt Nielsen, Ph.D., Executive Director, Generic Research & Development at Teva Pharmaceuticals USA, Inc. (Teva), sent letters to Wyeth-Ayerst dated February 6, 2003 and February 12, 2003, stating in both letters that Teva was providing information pursuant to "21 U.S.C. § 355(j)(2)(B)(I) and (ii)." Based on those letters, we provide the following information:

(i) Teva 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.

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(ii) Teva's ANDA number is ANDA 76-565.

(iii) The established name of the proposed drug product is "Venlafaxine HCl Extended-Release Capsules, 37.5 mg, 75 mg, and 150 mg."

(iv) The active ingredient, strength, and dosage form of the proposed drug product is 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 Teva alleges to be invalid, unenforceable and/or 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, each of which expire on March 20, 2017. In addition, the pediatric exclusivity for these patents expires on September 20, 2017.

(2) Wyeth received Teva's February 6, 2003 letter on or about February 10, 2003. Wyeth received Teva's February 12, 2003 amended letter on or about February 13, 2003.

CERTIFICATION

We hereby certify that on March 24, 2003, Wyeth filed an action for patent infringement against Teva in the United States District Court for the District of New Jersey (Civil Action No. 03-CV-1293 (KSH)). Wyeth filed that action within 45 days of receipt of both Teva's original and amended notice of the Paragraph IV Certification. In its complaint, Wyeth states, among other things, that Teva's submission to the FDA of an ANDA to obtain approval for the commercial manufacture, use, or sale of 37.5 mg, 75 mg, and 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 Teva's ANDA 76-565 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 February 13, 2003, and ending on August 13, 2005, or until such time as ordered by the Court.

Moreover, Teva's ANDA cannot even be finally approved on the above-identified date because Teva has not notified Wyeth that it has made a certification under paragraph IV as to U.S. Patent No. 4,535,186, which is also listed in the Orange Book

for EFFEXOR® XR. Accordingly, approval of Teva's ANDA may not be made effective until the expiration of both that patent and the pediatric exclusivity period on June 13, 2008.

Sincerely,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

LAW/dmb

By: Linda A. Wadler
Linda A. Wadler

cc: Kurt Nielsen, Ph.D. (via first class mail)
Executive Director, Generic R & D
Teva Pharmaceuticals USA, Inc.
1090 Horsham Road
North Wales, PA 19454-1090

2-1

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591 3141
Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

March 19, 2003

TELEPHONE AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AC

ANDA # 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES, 37.5 mg, 75 mg, and 150 mg
TELEPHONE AMENDMENT – RESPONSE TO MARCH 13, 2003 COMMENT

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced, pending Abbreviated New Drug Application in response to a March 13, 2003 telephone request made by Arianne Camphire of your office. The topic of this telephone discussion concerned the manufacturing sites contained in DMF 16281.

The DMF authorization letter provided in our amendment dated February 13, 2003 referenced the Teva Tech (Be'er Sheva) production site while the [redacted] (b) (4) site was the actual manufacturing site of the raw material used in the pivotal lots. Provided in **Attachment 1** is a revised DMF authorization letter referencing both manufacturing sites. Please note that both manufacturing sites were referenced in the DMF itself and provided as page 4013 of the original application is a declaration stating that DMF 16281 covers both sites. Provided in **Attachment 2** is a copy of the declaration (page 4013) from the original application as well as an excerpt from the DMF listing both manufacturing sites.

It is Teva Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned telephone contact. This information is submitted for your continued review. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/sah
Enclosures

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Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591 3141
Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

505(j)(2)(A) OK
24-MAR-2003

ORIG AMENDMENT
NDAC

February 13, 2003

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 76-565
VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, 150 mg
UNSOLICITED AMENDMENT – ADDITION OF 37.5 mg AND 75 mg STRENGTHS

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending abbreviated new drug application for the addition of 37.5 mg and 75 mg strengths of the drug product Venlafaxine HCl Extended-Release Capsules. Please note that this submission is presented in the same basic format of an ANDA for ease of your review.

In support of this amendment, we have provided Chemistry, Manufacturing, and Controls (CMC) documentation relevant to the 37.5 mg and 75 mg strengths and updated CMC documentation applicable to the 150 mg capsule. Please note that a waiver of *in-vivo* bioequivalence / bioavailability studies is requested pursuant to the Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations Section V(C)(2)(a).

Two separately bound copies of the finished product and bulk drug analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141, or by facsimile at (215) 591-8812.

Sincerely,

PE/sah
Enclosures

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FEB 13 2003
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ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA# 76-565 **FIRM NAME** TEVA PHARMACEUTICALS USA

RELATED APPLICATION(S) NA **FIRST GENERIC? YES**

DRUG NAME: VENLAFAXINE HYDROCHLORIDE
DOSAGE FORM: EXTENDED-RELEASE CAPSULES, 150 MG

Electronic Submission: NA E-mail notification sent: NA Comments: NA

Random Assignment Queue: Random 10 Chem Team Leader: Rosencrance, Susan PM: Hinchcliffe, Thomas

Labeling Reviewer: Dillahunt, Michelle Micro Review: NA PD study (Med Ofcr): NA

Letter Date DECEMBER 10, 2002	**Received Date** DECEMBER 11, 2002
Comments EC 1 YES **On Cards YES** **ANTIDEPRESSANTS**	**Therapeutic Code 2020100**
Methods Validation Package (3 copies) (Required for Non-USP drugs) YES	
Archival, and Review copies Field Copy Certification (Original Signature) YES ✓ (pg 4876)	
Cover Letter YES ✓	
Table of Contents YES ✓	

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** ✓ (Statement regarding Rx/OTC Status) RX YES	✓ ☒
Sec. II	**Basis for Submission** **NDA: 20-699** ✓ RLD: EFFEXOR XR ✓ Firm: WYETH AYERST ✓ ANDA suitability petition required? NO If yes, consult needed for pediatric study requirement.	✓ ☒

Sec. III	**Patent Certification** 1. Paragraph: IV 2. Expiration of Patent: MARCH 20 2017 , MARCH 17, 2017 U-451, MARCH 20, 2017 U-459 DECEMBER 13, 2007 JUNE 28, 2013 U-398 JUNE 28, 2013 Is section viii statement Allowable for the '923 patent & it's corresponding U-398 designation. A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement YES MARCH 11, 2002 AND MAY 2, 2004** ✓	☒
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use ✓ 2. Active ingredients ✓ 3. Route of administration ✓ 4. Dosage Form ✓ 5. Strength ✓	☑ ✓
Sec. V	**Labeling** 1. 4 copies of draft (each strength and container) or 12 copies of FPL ✓ 2. 1 RLD label and 1 RLD container label ✓ 3. 1 side by side labeling comparison with all differences annotated and explained ✓ AVAILABLE IN 100's & 500's	☑ ✓
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) YES **2. Request for Waiver of In-Vivo Study(ies):** N/A **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) ONE Strength **4. Lot Numbers of Products used in BE Study(ies):** Test K-30455 **5. Study Type:** (Continue with the appropriate study type box below)	☐
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING AND FED a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) b. Data Files (Computer Media) Submitted YES c. In-Vitro Dissolution YES ✓ (pg 108A)	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. Data Files (Computer Media) Submitted	☐

Patents '186 exp. 6/13/08 PII
'923 exp. 12/28/13 U-348: Tx of generalized anxiety disorder Section viii statement
'171 exp. 9/20/17 PIV
'120 exp. 9/20/17 U-451: Tx of depression & generalized anxiety disorder PIV
'958 exp. 9/20/17 U-459: Tx of depression & generalized anxiety disorder PIV
'708 exp. 12/28/13 PIV

Study Type	**TRANSDERMAL DELIVERY SYSTEMS** a. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. Data Files (Computer Media) Submitted b. Adhesion Study c. Skin Irritation/Sensitization Study	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** a. Solutions (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. Suspensions (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. Data Files (Computer Media) Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. Data Files (Computer Media) Submitted 3. 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)** a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation ✓ 2. Inactive ingredients as appropriate ✓	☑

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers ✓ b. Type II DMF authorization letters or synthesis ✓ c. COA(s) specifications and test results from drug substance mfgr(s) ✓ d. Applicant certificate of analysis ✓ e. Testing specifications and data from drug product manufacturer(s) ✓ f. Spectra and chromatograms for reference standards and test samples ✓ g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified ✓ b. Testing specifications (including identification and characterization) ✓ c. Suppliers' COA (specifications and test results) ✓ d. Applicant certificate of analysis ✓	☐ ✓
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) ✓ 2. CGMP Certification YES pg 4203 3. CFN numbers	☑
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address 2. Functions 3. CGMP Certification/GLP 4. CFN numbers None utilized	☑
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) ✓ 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified ✓ 3.If sterile product: Aseptic fill / Terminal sterilization N/A 4.Filter validation (if aseptic fill) N/A 5. Reprocessing Statement ✓	☑
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record (Antibiotics/3 Batches if bulk product produced by fermentation) with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation ✓ 2. In-process Controls - Specifications and data ✓	☑
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) ✓ 2. Components Specification and Test Data (Type III DMF References) ✓ 3. Packaging Configuration and Sizes ✓ 4. Container/Closure Testing ✓ 5. Source of supply and suppliers address ✓	☑

SCALE UP [redacted] (b) (4) Area cap. wt : [redacted] (b) (4) mg

[redacted] (b) (4)

Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data 2. Certificate of Analysis for Finished Dosage Form	☐
Sec. XV	**Stability of Finished Dosage Form** (strpg 4562, bottles of 100's of CRC & non CRC) 1. Protocol submitted ✓ 2. Post Approval Commitments ✓ 3. Expiration Dating Period ✓ 4. Stability Data Submitted a. 3 month accelerated stability data ✓ b. Batch numbers on stability records the same as the test batch ✓	☑
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance ✓ 2. Finished Dosage Form ✓ 3. Same lot numbers	☑
Sec. XVII	**Environmental Impact Analysis Statement**	☑
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other**: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A 2. Debarment Certification (original signature) YES ✓ 3. List of Convictions statement (original signature) ✓	☑

Reviewing CSO/CST Martin H. Shimer **Date**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: [signature]	**Date:** 22-JAN-2003
Duplicate copy sent to bio: (Hold if RF and send when acceptable)	
Duplicate copy to **HFD-** for consult: Type:	

ADDITIONAL COMMENTS REGARDING THE ANDA:
- can firm submit a MOU statement to the '923 patent (U-398)

Philip Erickson (215) 591-3141

OGD Form Revised 11/30/2001

ANDA 76-565

JAN 22

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

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 made to the telephone conversations dated January 10, 2003 and January 17, 2003 and your correspondence dated January 17, 2003.

NAME OF DRUG: Venlafaxine Hydrochloride Extended-release Capsules, 150 mg

DATE OF APPLICATION: December 10, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 11, 2002

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 court order or judgement 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 Gregg Davis, 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) 827-5849

Sincerely yours,

Gregory K. Davis for

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-565
DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/GDavis, Chief, RSB _____ date 22-JAN-2003
HFD-615/MShimer, CSO _____ date 22 January 2003
Word File V:\Firmsnz\Teva\Ltrs&rev\76565.ack
FT/EEH 01/22/03
ANDA Acknowledgment Letter!

JAN 2 2003

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS
First Generic ANDA

ANDA# 76565 FIRM NAME Teva Pharm.

DRUG NAME Venlafaxine HCl

DOSAGE FORM ER Capsules 150mg

Requested by: _____
Chief, Regulatory Support Team, (HFD-615)

Summary of Findings by Division of Bioequivalence

☑ **Study meets statutory requirements** Fasting Study & Non Fasting Study

☐ **Study does NOT meet statutory requirements**
Reason:

☐ **Waiver meets statutory requirements** N/A

☐ **Waiver does NOT meet statutory requirements**
Reason:

RECOMMENDATION: ✓ COMPLETE ___ INCOMPLETE

Reviewed by:

Hoainhon Nguyen Date: 12/27/02
Reviewer

Team Leader Date: 12/31/2002

Director, Division of Bioequivalence Date: 1-2-2003

76-565 Fasting Study & Non Fasting Study

BIO Batch Size	✓				
Assay of Active Content Drug	✓				
Content Uniformity	✓				
Date of Manufacture	✓				
Exp. Date of RLD	✓				
BioStudy Lot Numbers	✓				
Statistics	✓✓				
Summary results provided by the firm indicate studies pass BE criteria	✓✓				
Waiver requests for other strengths / supporting data	N/A				

Additional Comments regarding the ANDA:

76-565 Fasting Study & Non Fasting Study

Item Verified:	Yes	No	Required Amount	Amount Sent	Comments
Protocol	✓				
Assay Methodology	✓				
Procedure SOP	✓				
Methods Validation	✓				
Study Results Ln/Lin	✓				
Adverse Events	✓				
IRB Approval	✓				
Dissolution Data	✓				
Pre-screening of Patients	✓				
Chromatograms	✓				
Consent Forms	✓				
Composition	✓				
Summary of Study	✓				
Individual Data & Graphs, Linear & Ln	✓				
PK/PD Data Disk (or Elec Subm)	✓				
Randomization Schedule	✓				
Protocol Deviations	✓				
Clinical Site	✓				
Analytical Site	✓				
Study Investigators	✓				
Medical Records	✓				
Clinical Raw Data	✓				
Test Article Inventory	✓				

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3141
FAX: (215) 591 8812

December 10, 2002

505(j)(2)(A) OK
22-JAN-2003
Gregory D. Davis

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
VENLAFAXINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, 150 mg

Dear Mr. Buehler:

We submit herewith an abbreviated new drug application for the drug product Venlafaxine Hydrochloride Extended-Release Capsules, 150 mg.

Enclosed are archival and review copies assembled in accord with Office of Generic Drugs February 1999 Guidance for Industry: Organization of an ANDA (OGD #1, Rev. 1). These copies are presented in a total of **23** volumes; **11** for the archival copy and **12** for the review copy.

The application contains a full report of two *in vivo* bioequivalence studies. These studies compared Venlafaxine Hydrochloride Extended-Release Capsules, 150 mg manufactured by TEVA Pharmaceutical Industries, Ltd. to the reference listed drug, Effexor® XR Extended-Release Capsules, 150 mg under both fasting and post-prandial conditions.

Two separately bound copies of the finished product and bulk drug analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

Philip Erickson

PE/sah
Enclosures

RECEIVED
DEC 11 2002
OGD / CDER