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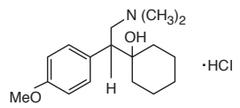
VENLIFT OD

(Venlafaxine hydrochloride 37.5, 75 & 150 mg once a day capsules)

DESCRIPTION

VENLIFT OD is an extended-release capsule for oral administration that contains venlafaxine hydrochloride, a structurally novel antidepressant. Venlafaxine hydrochloride is chemically unrelated to tricyclic, tetracyclic, and other available antidepressants and to other agents used to treat Generalized Anxiety Disorder. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[a- [(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride and has the empirical formula of $C_{17}H_{27}NO_2$ hydrochloride. Its molecular weight is 313.87. The structural formula is shown below.



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. 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 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 immediate release venlafaxine tablets ($C_{max's}$ for immediate release 75 mg q12 hours were 225 ng/ml for venlafaxine and 290 ng/ml for ODV; $T_{max's}$ were 2 hours for venlafaxine and 3 hours for ODV). 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 extended release capsules

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.

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 patients 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 patients compared to normal subjects. ODV elimination half-life was prolonged by about 60%, and clearance decreased by about 30% in cirrhotic patients 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. Dosage adjustment is necessary in these patients.

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=10-70 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=10-70 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.

Clinical Efficacy

Depression

The efficacy of Venlafaxine extended release capsules as a treatment for depression was established in two placebo-controlled, short-term, flexible-dose studies in adult outpatients meeting DSM-III-R or DSM-IV criteria for major depression.

A 12-week study utilizing Venlafaxine extended release capsules doses in a range 75-150 mg/day (mean dose for completers was 136 mg/day) and an 8-week study utilizing Venlafaxine extended release capsules doses in a range 75-225 mg/day (mean dose for completers was 177 mg/day) both demonstrated superiority of Venlafaxine 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 extended release capsules was also significantly better than placebo for certain factors of the HAM-D, including the anxiety/Somatisation 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 depression with melancholia utilizing Venlafaxine (the immediate release form of venlafaxine) in a range of 150 to 375 mg/day (t.i.d. schedule) demonstrated superiority of Venlafaxine 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.

INDICATIONS AND USAGE

Major Depression: VENLIFT OD (venlafaxine hydrochloride) extended-release capsules are indicated for the treatment of major depression.

The psychiatrists who elect to use **VENLIFT OD** for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

VENLIFT OD capsules are contraindicated in patients known to be hypersensitive to venlafaxine hydrochloride. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated.

WARNINGS

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, because venlafaxine is an inhibitor of both norepinephrine and serotonin reuptake, it is recommended that VENLIFT OD 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.

Sustained Hypertension

Venlafaxine is associated with sustained increase in blood pressure in some patients. Among patients treated with 75-375 mg per day of Venlafaxine extended release capsules in premarketing depression studies, 3% (19/705) experienced sustained hypertension [defined as treatment-emergent supine diastolic blood pressure (SDBP) > 90 mmHg and > 10 mmHg above baseline for 3 consecutive on-therapy visits]. Among patients treated with 75-225 mg per day of Venlafaxine extended release capsules in premarketing GAD studies, 0.4% (2/476) experienced sustained hypertension.

In placebo-controlled premarketing depression studies with Venlafaxine extended release capsules 75-225 mg/day, a final on-drug mean increase in supine diastolic blood pressure (SDBP) of 1.2 mmHg was observed for Venlafaxine extended release capsules treated patients compared with a mean decrease of 0.2 mmHg for placebo-treated patients. In placebo-controlled premarketing GAD studies with Venlafaxine extended release capsules 75-225 mg/day, a final on-drug mean increase in SDBP of 1.1 mmHg was observed for Venlafaxine extended release capsules treated patients compared with a mean decrease of 0.9 mmHg for placebo-treated patients.

Sustained increases of SDBP could have adverse consequences. Therefore, it is recommended that patients receiving **VENLIFT OD** 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.

PRECAUTIONS

General

Insomnia and Nervousness

Treatment-emergent insomnia and nervousness were more commonly reported for patients treated with Venlafaxine extended release capsules than with placebo in pooled analyses of short-term depression and GAD studies.

Changes in Appetite and Weight

Treatment-emergent anorexia was more commonly reported for Venlafaxine extended release capsules-treated (8%) than placebo-treated patients (4%) in the pool of short-term depression studies. Significant weight loss, especially in underweight depressed patients, may be an undesirable result of Venlafaxine extended release capsules treatment.

Activation of Mania/Hypomania

During premarketing depression studies, mania or hypomania occurred in 0.3% of Venlafaxine extended release capsules-treated patients and 0.0% placebo patients. In premarketing GAD studies, 0.0% of Venlafaxine extended release capsules-treated patients and 0.5% of placebo-treated patients experienced mania or hypomania. In all premarketing depression trials with Venlafaxine, mania or hypomania occurred in 0.5% of venlafaxine-treated patients compared with 0% of placebo patients. Mania/hypomania has also been reported in a small proportion of patients with mood disorders who were treated with other marketed antidepressants. As with all antidepressants, VENLIFT OD should be used cautiously in patients with a history of mania.

Seizures

VENLIFT OD like many antidepressants, should be used cautiously in patients with a history of seizures and should be discontinued in any patient who develops seizures.

Suicide : The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy.

Use in Patients With Concomitant Illness : Caution is advised in administering **VENLIFT OD** 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.

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, co-administration of cimetidine had no apparent effect on the pharmacokinetics of ODV, which is present in much greater quantity in the circulation than venlafaxine.

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 Cmax increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life (t1/2) 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.

Drugs Highly Bound to Plasma Protein : Venlafaxine is not highly bound to plasma proteins; therefore, administration of VENLIFT OD to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

CYP2D6 Inhibitors : No dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor. The concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Therefore, caution is advised should a patient's therapy include venlafaxine and any agent(s) that produce simultaneous inhibition of these two enzymes systems. 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 are unknown.

Risperidone: Venlafaxine administered under steady-state conditions at 150 mg/day slightly inhibited the CYP2D6-mediated metabolism of risperidone (administered as a single 1mg 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.

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.

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

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-desmethyl venlafaxine (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 & Nursing Mothers : There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, venlafaxine should be used during pregnancy only if clearly needed. Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from VENLIFT OD 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. The effect of venlafaxine on labor and delivery in humans is unknown.

Pediatric Use : Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS :

The most common adverse events associated with the use of venlafaxine (incidence 5% or greater) and not seen in an equivalent incidence among placebo treated patients were asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, blurred vision as well as abnormal ejaculation/orgasm and impotence in men. A comparison of adverse event rates in a fixed dose study comparing Venlafaxine 75,225 and 375 mg/day with placebo revealed a dose dependency for some of the most common adverse events associated with venlafaxine use.

Treatment emergent adverse experience incidence in a dose comparison trial

Adverse events	Placebo	Venlafaxine 75mg/day	Venlafaxine 225 mg/day	Venlafaxine 375 mg/day
Hypertension	1.1%	1.1%	2.2%	4.6%
Nausea	14.1%	32.6%	38.2%	58.0%
Vomiting	1.1%	7.9%	3.4%	6.8%
Anorexia	0.0%	1.1%	2.2%	4.5%
Decreased libido	1.1%	2.2%	1.1%	5.7%
Insomnia	9.8%	22.5%	20.2%	13.6%
Sweating	5.4%	6.7%	12.4%	19.3%

DOSAGE AND ADMINISTRATION : VENLIFT OD 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.

Initial Treatment

Major Depression : For most patients, the recommended starting dose for **VENLIFT OD** is 75 mg/day, administered in a single dose. In the clinical trials establishing the efficacy of **VENLIFT OD** 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. 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 140-180 mg/day.

Switching Patients from **VENLIFT Tablets**

Depressed patients who are currently being treated at a therapeutic dose with **VENLIFT** may be switched to **VENLIFT OD** at the nearest equivalent dose (mg/day), e.g., 37.5 mg venlafaxine two-times-a-day to 75 mg **VENLIFT OD** once daily. However, individual dosage adjustments may be necessary.

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 compared with normal subjects. It is recommended that the starting dose be reduced by 50% in patients with moderate hepatic impairment. Because there was much individual variability in clearance between patients with cirrhosis, individualization of dosage 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 = 10-70 mL/min) compared with normal subjects. It is recommended that the total daily dose be reduced by 25%-50%. In patients undergoing hemodialysis, it is recommended that the total daily dose be reduced by 50% and that the dose be withheld until the dialysis treatment is completed (4 hrs). 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 depression or generalized anxiety disorder, however, caution should be exercised in treating the elderly.

Discontinuing VENLIFT OD : When discontinuing **VENLIFT OD** after more than 1 week of therapy, it is generally recommended that the dose be tapered to minimize the risk of discontinuation symptoms.

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 **VENLIFT OD.** In addition, at least 7 days should be allowed after stopping **VENLIFT OD** before starting an MAOI.

OVERDOSAGE :

In case of overdose treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

STORAGE

Store below 30°C

KEEP MEDICINE OUT OF REACH OF CHILDREN.

TAKE MEDICINE ON THE PRESCRIPTION OF A PSYCHIATRIST ONLY.

PRESENTATION & AVAILABILITY

VENLIFT OD 37.5 mg : It is available in blister pack of 10s and 15s.

VENLIFT OD 75 mg : It is available in blister pack of 10s and 7s.

VENLIFT OD 150 mg : It is available in blister pack of 10s and 7s.

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Manufactured by :
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