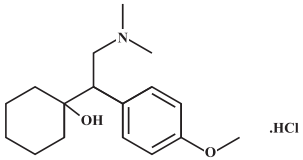
VENALAX
(Venlafaxine) USP

TABLETS
CAPSULES

DESCRIPTION

VENALAX contains venlafaxine hydrochloride, a structurally novel antidepressant. It is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant and to other agents used to treat generalized anxiety disorders. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxy-phenyl) ethyl] cyclohexanol hydrochloride or (±)-1-[a-[(dimethylamino) methyl]-p-methoxybenzyl] cyclohexanol hydrochloride and has the empirical formula of $C_{17}H_{27}NO_2HCl$. Its molecular weight is 313.87. The structural formula is shown below.



Venlafaxine Hydrochloride is a white to off white crystalline solid with a solubility of 572mg/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.

COMPOSITION

VENALAX tablets: Each tablet contains:
Venlafaxine (as hydrochloride) (USP).....37.5mg

VENALAX SR capsules: Each sustained-released capsule contains:
Venlafaxine (as hydrochloride) (USP).....75mg
(as sustain release pellets)
Product complies with USP Dissolution Test 2.

CLINICAL PHARMACOLOGY

MODE OF ACTION

Venlafaxine and its active metabolite, O-desmethylvenlafaxine, are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitor of dopamine reuptake. The antidepressant activity of venlafaxine is thought to be associated with potentiation of neurotransmitter activity in the central nervous system (CNS). Venlafaxine and O-desmethylvenlafaxine have no significant affinity for muscarinic, histaminergic, or α_1 adrenergic receptors in vitro. Activity at these receptors is potentially associated with various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. In preclinical rodent models, venlafaxine demonstrated activity predictive of antidepressant and anxiolytic actions, and cognitive enhancing properties.

PHARMACOKINETICS

ABSORPTION

At least 92% of venlafaxine is absorbed following single oral doses of immediate-release venlafaxine. Absolute bioavailability is 40% to 45% due to presystemic metabolism. In single-dose studies with 25 to 150mg of immediate release venlafaxine (37.5 or 75mg), mean peak plasma concentrations (Cmax) range from 37 to 163ng/ml and are attained within 2.1 to 2.4 hours (tmax). After immediate release venlafaxine administration, the peak plasma concentrations of venlafaxine and O-desmethylvenlafaxine occur in 2 and 3 hours, respectively.

Following the administration of venlafaxine extended release capsules (VENALAX SR), peak plasma concentrations of venlafaxine and o-desmethylvenlafaxine are attained within 5.5 hours and 9 hours, respectively. Venlafaxine extended release capsules and venlafaxine immediate release tablets are associated with a similar extent of absorption.

Note: The rest of the pharmacokinetic parameters are same for both the strengths i.e. plain as well as SR.

DISTRIBUTION

Steady state concentrations of both Venlafaxine and O-desmethylvenlafaxine are attained within three days of multiple dose therapy of immediate release venlafaxine. Both show linear kinetics over a dose range of 75 to 450mg/day when administered every 8 hours. Venlafaxine and O-desmethylvenlafaxine are approximately 27±2% and 30±12% bound to human plasma proteins, at concentrations ranging from 100-500ng/ml, both venlafaxine and O-desmethylvenlafaxine have low potential for involvement in significant drug-drug interactions Involving drug displacement from serum proteins. The volume of distribution for venlafaxine & ODV at steady state is 7.5±3.7 & 5.7±1.8 L/kg following intravenous administration respectively.

METABOLISM

Venlafaxine undergoes extensive hepatic metabolism. In vitro and in vivo studies indicate venlafaxine is bio-transformed to its active metabolite. O-desmethylvenlafaxine, by the P450 isoenzyme CYP2D6. Although the relative activity of CYP2D6 may differ among patients, related modification of venlafaxine dosage regimen is not required. Drug exposure (AUC) and fluctuation in the plasma levels of venlafaxine and O-desmethylvenlafaxine were comparable following administration of equal doses of venlafaxine as b.i.d or t.i.d regimens of immediate release venlafaxine.

ELIMINATION

Venlafaxine and its metabolites are excreted mainly through kidneys. Approximately 87% of the venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated O-desmethylvenlafaxine (29%), conjugated O-desmethylvenlafaxine (26%), or other minor inactive metabolites(27%).

EFFECT OF FOOD

Food has no significant effect on the absorption of venlafaxine or the formation of O-desmethylvenlafaxine.

PATIENTS WITH HEPATIC IMPAIRMENT

The pharmacokinetic disposition of venlafaxine and O desmethylvenlafaxine are significantly altered in some patients with compensated hepatic cirrhosis following oral administration of single-dose venlafaxine. In hepatically impaired patients, mean plasma clearance of venlafaxine and O-desmethylvenlafaxine are reduced approximately to 30 to 33% and mean elimination half-lives are prolonged 2-fold or more compared to normal subjects.

PATIENTS WITH RENAL IMPAIRMENT

Venlafaxine and O-desmethylvenlafaxine elimination half-life increase with the degree of impairment in renal function. Elimination half-life increased approximately 1.5 fold in patients with moderate renal impairment and 3-fold in patients with end stage renal disease.

AGE AND GENDER STUDIES

A population pharmacokinetic analysis of 404 immediate release venlafaxine treated patients from two studies involving both b.i.d and t.i.d regimens showed that dose normalized through plasma levels of either venlafaxine or O-desmethylvenlafaxine were unaltered by age or gender differences.

INDICATIONS

Treatment of depression, including depression with associated anxiety. For prevention of relapse and recurrence of depression. Treatment of anxiety or Generalized Anxiety Disorder, including long-term treatment.
Social Anxiety Disorder (SAD).

DOSAGE AND ADMINISTRATION

The recommended starting dose of sustained release venlafaxine is 75mg given once daily. Patients not responding to the initial 75mg/day may benefit from dose increases to a maximum of 225mg/day. While the recommended dose for moderately depressed patients is 225mg/day for immediate release venlafaxine, more severely depressed patients in one study responded to a mean dose of 350mg/day (range of 150 to 375mg/day). Sustained release venlafaxine dosage increase can be made at intervals of approximately 2 weeks or more, but not less than 4 days. Patients treated with venlafaxine immediate release tablets may be switched to venlafaxine sustained release capsule at the nearest equivalent daily dosage. For example, venlafaxine immediate release tablets 37.5mg twice daily may be switched to venlafaxine sustained release capsule 75mg once daily. Individual dosage adjustment may be necessary. Dose tapering is recommended when discontinuing venlafaxine therapy. Tapering over at least two week period is recommended if venlafaxine has been used for more than 6 weeks. In venlafaxine sustained release capsules, tapering was achieved by reducing the daily dose by 75mg at 1-week intervals. The period required for tapering may depend on the dose, duration of therapy, and the individual patients. It is recommended that venlafaxine sustained release capsules be taken with the food, at approximately the same time each day. Capsules must be swallowed whole with fluid and not divided, crushed, chewed or placed in water.

USE IN PATIENTS WITH RENAL IMPAIRMENT

The total daily dose of venlafaxine must be reduced by 25% to 50% for patients with renal impairment with a glomerular filtration rate (GFR) of 10 to 70ml/min. The total daily dose of venlafaxine must be reduced by 50% in hemodialysis patients. Administration must be with held until the dialysis session is completed.

USE IN PATIENTS WITH HEPATIC IMPAIRMENT

The total daily dose of venlafaxine must be reduced by 50% in patients with moderate impaired hepatic impairment. Reductions of more than 50% may be appropriate for some patients.

USE IN CHILDREN

There is insufficient experience with the use of venlafaxine in patients less than 18 years of age.

USE IN ELDERLY PATIENTS

No specific dosage-adjustment of venlafaxine are recommended based on patients age.

CONTRAINDICATIONS

Hypersensitivity to venlafaxine or any excipients in the formulation.
Concomitant use of venlafaxine and any monoamine oxidase inhibitor (MAOI). Venlafaxine must not be initiated for at least 14 days after discontinuation of treatment with a MAOI; a shorter interval may be justified in case of reversible MAOI (see prescribing information of reversible MAOI). Venlafaxine must be discontinued for at least 7 days before starting treatment with any MAOI.

PRECAUTIONS

Venlafaxine has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Therefore it should be used with caution in these patients. Dose-related increase in blood pressure has been reported in some patients treated with venlafaxine. Measurement of blood pressure is recommenced for patients receiving venlafaxine Increase in the heart rate can occur, particularly in patients receiving higher doses. Caution should be exercised in patients whose underlying conditions might be compromised by increase in the heart rate. Convulsions may occur with venlafaxine therapy. As with all antidepressants, venlafaxine should be introduced with caution in patients with a history of convulsions. Mydriasis may occur in association with venlafaxine. It is recommended that patients with raised intraocular pressure or patients at risk for acute narrow angle glaucoma be closely monitored. Mania/hypomania may occur in a small proportion of patients with mood disorders who have received antidepressants, including venlafaxine. As with other antidepressants venlafaxine should be used cautiously in patients with a history of mania. Cases of hyponatremia and/or the syndrome of inappropriate antidiuretic hormone (SIADH) secretion may occur with venlafaxine, usually in volume depleted or dehydrated patients, including elderly patients and patients taking diuretics. The risk of suicide attempt must be considered in all depressed patients. And the smallest quantity of the drug should be provided initially to reduce the risk of overdose. The risk of skin and mucous membrane bleeding may be increased in patients taking venlafaxine. As with other serotonin-reuptake inhibitors, venlafaxine should be used cautiously in patients predisposed to bleeding at these sites. The safety and efficacy of venlafaxine in combination with weight loss agents, including phentermine, have not been established. Co-administration of venlafaxine and weight loss

agents is not recommended. Venlafaxine hydrochloride is not recommended for weight loss alone or in combination with other products.

PREGNANCY
The safety of venlafaxine in human pregnancy has not been established Venlafaxine should be administered to pregnant women only if the expected benefits outweigh any possible risk. If venlafaxine is used until or shortly after birth, discontinuation effects should be considered.

LACTATION
Venlafaxine and O-desmethylvenlafaxine are excreted in human milk; therefore, a decision should be made whether not to breast-feed or to discontinue venlafaxine.

PEDIATRIC USE
Safety and efficacy in patients less than 18 years of age has not been established.

GERIATRIC USE
No specific dosage adjustments of venlafaxine are recommended based on patient age.

INTERACTIONS
MONOAMINE OXIDASE INHIBITORS (MAOI).
Severe adverse reactions have been reported in patients who have recently been discontinued from MAOI and started on venlafaxine. Or have recently had venlafaxine therapy discontinued prior to initiation of a MAOI. These reactions include tremors, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyponatremia with features resembling neuroleptic malignant syndrome, seizures, and death.

INDINAVIR
A pharmacokinetic study with indinavir has shown a 28% decrease in AUC and a 36% decrease in Cmax for indinavir. Indinavir did not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. The clinical significance of this interaction is unknown.

WARFARIN
Potentiation of anticoagulant effects may occur in patients taking warfarin following the addition of venlafaxine.

ETHANOL
Venlafaxine has been shown not to increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS active drugs, patients should be advised to avoid alcohol consumption while taking venlafaxine.

HALOPERIDOL
A pharmacokinetic study with haloperidol has shown for haloperidol a 42% decrease in total oral clearance, a 70% increase in AUC and 88% increases in Cmax, but no change in half-life. This should be taken into account in patients treated with haloperidol and venlafaxine concomitantly.

CIMETIDINE
At steady-state, cimetidine has been shown to inhibit first-pass metabolism of venlafaxine however cimetidine had no effect on the pharmacokinetics of O-desmethylvenlafaxine. The overall pharmacological activity of venlafaxine plus O-desmethylvenlafaxine is expected to increase only slightly in most patients. In the elderly and patients with hepatic dysfunction this interaction may be more pronounced.

IMIPRAMINE
Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However desipramine AUC, Cmax and Cmin increased by about 35% in the presence of venlafaxine. There was an increase of 2-OH-desipramine AUC by 2.5 to 4.5 fold Imipramine did not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. This should be taken into account in patients treated with imipramine and venlafaxine concomitantly.

RESPERIDONE
Venlafaxine increased the resperidone AUC by 32% but did not significantly alter the pharmacokinetic profile of the total active moiety (resperidone plus 9-hydroxyresperidone). The clinical significance of this interaction is unknown.

DIAZEPAM
Diazepam does not appear to affect the pharmacokinetics of either venlafaxine or O-desmethylvenlafaxine. Venlafaxine has no effect on the pharmacokinetics and pharmacodynamics of diazepam and its active metabolite, desmethyldiazepam.

CNS ACTIVE DRUGS
Based on the known mechanism of action of venlafaxine and the potential for serotonin syndrome, caution is exercised when venlafaxine is co-administered with other drugs that may affect the serotonergic neurotransmitter systems (such as triptans, selective serotonin reuptake inhibitors, lithium).

LITHIUM
The steady state pharmacokinetics of either venlafaxine or O-desmethylvenlafaxine are not affected when lithium is co-administered. Venlafaxine also has no effect on the pharmacokinetics of lithium.

DRUGS HIGHLY BOUND TO PLASMA PROTEINS
Venlafaxine is not highly bound to plasma proteins (27% bound): therefore, administration of venlafaxine to a patient taking another drug that is highly protein bound is not excreted to cause increased free concentrations of the other drug.

DRUGS METABOLIZED BY CYTOCHROME P450 ISOENZYMES
Studies indicate that venlafaxine is a weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP3A4, CYP1A2, and CYP2C9 in vitro. This was confirmed by in vivo studies with the following drugs: alprazolam (CYP3A4), caffeine (CYP1A2). Carbamazepine (CYP3A4), and diazepam (CYP3A4 and CYP2C19).

EFFECTS ON ACTIVITIES REQUIRING CONCENTRATION AND PERFORMANCE
Venlafaxine did not affect psychomotor, cognitive or complex behavior performance in healthy volunteers. However, any psychoactive drug may impair judgment, thinking and motor skills. Therefore patients should be cautioned about their ability to drive or operate hazardous machinery.

ABUSE AND DEPENDENCE
Clinical studies did not show evidence of drug seeking behavior, development of tolerance, or dose escalation over time. 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 ability.

ADVERSE EFFECTS
COMMON: ≥1%
UNCOMMON: ≥ 0.1 % and < 1 %

RARE: ≥ 0.01 % and < 0.1 %
VERY RARE: <0.01%

BODY AS A WHOLE	
• Common:	asthenia/fatigue
• Uncommon:	photosensitivity reaction
• Very rare:	Anaphylaxis
CARDIOVASCULAR	
• Common:	hypertension, vasodilation (mostly hot flushes / flushes)
• Uncommon:	hypotension, postural hypotension, tachycardia QT prolongation, ventricular fibrillation, ventricular
• Very rare:	tachycardia
DIGESTIVE	
• Common:	decreased appetite, constipation, nausea vomiting
METABOLIC / NUTRITIONAL	
• Common:	serum cholesterol increased (particularly with prolonged administration and possibly with higher doses), weight loss
• Uncommon:	abnormal liver function tests, hyponatremia, hepatitis syndrome of inappropriate antidiuretic hormone
• Rare	secretion (SIADH)
NERVOUS SYSTEM	
• Common:	Abnormal dreams, decreased libido, dizziness, dry mouth increased muscle tone, insomnia, nervousness paresthesia, sedation, tremor,
• Uncommon:	Apathy, hallucinations, myoclonus
• Rare:	convulsion, manic reaction, neuroleptic malignant syndrome (NMS), serotonergic Syndrome
RESPIRATORY SYSTEM	
• Common:	yawning
• Undetermined	eosinophilia
SKIN	
• Common:	sweating (including night sweats)
• Uncommon:	rash, alopecia
SPECIAL SENSES	
• Common:	abnormality of accommodation, mydriasis, visual disturbances
• Uncommon:	altered taste sensation
UROGENITAL	
• Common:	abnormal ejaculation/orgasm / males erectile dysfunction impaired urination
• Uncommon:	abnormal orgasm (females), menorrhagia, urinary retention

Discontinuation effects are well known to occur with antidepressants, and it is therefore recommended that the dosage of either formulation of venlafaxine be tapered gradually and the patient monitored. The following symptoms have been reported in association with abrupt discontinuation or dose-reduction, or tapering of treatment: hypomania, anxiety, agitation, nervousness, confusion, or other sleep disturbances, fatigue, somnolence, paresthesia, dizziness, vertigo, headache, sweating, dry mouth, anorexia, diarrhea, nausea, and vomiting. The majority of discontinuation reactions are mild and resolve without treatment.

OVER-DOSAGE
In post-marketing experience, overdose with venlafaxine was reported predominantly in combination with alcohol and/or other drugs. Electrocardiographic changes (e g., prolongation of QT interval, bundle branch blocks, QRS prolongation, sinus and ventricular tachycardia, bradycardia, hypotension, vertigo, disturbances of consciousness (ranging from somnolence to coma), seizures, and death have been reported.

RECOMMENDED TREATMENT
General supportive or symptomatic measures are recommended, cardiac rhythm and vital signs must be monitored. When there is a risk of aspiration, induction of emesis is not recommended. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Administration of activated charcoal may also limit drug absorption. Forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to benefit. No specific antidotes for venlafaxine are known.

INSTRUCTIONS
Store below 30°C. Protect from heat, light & moisture. Keep all medicines out of the reach of children. To be sold on the prescription of a registered medical practitioner only.

PRESENTATION
VENALAX 37.5mg tablets available in a blister pack of 2 x 10's.
VENALAX 75mg SR capsules available in a blister pack of 2 x 7's.

وینالیکس ٹیبلیٹس / کیپسول
(وینلافیکسین) یو ایس پی

ہدایات: 30° سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ گرمی، روشنی اور نمی سے بچائیں۔
تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔ صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

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