SNRI SR

75 mg

(Venlafaxine HCl)

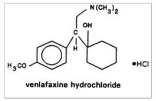
ایس این آر آئی ایس آر

۷۵ ملی گرام

(وینلافیکسین ایچ سی ایل)

DESCRIPTION

SNRI SR is a sustained release capsule for oral administration that contains 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 and has the empirical formula of C17H27NO2 HCl. Its molecular weight is 313.87. The structural formula is shown below.



venlafaxine hydrochloride

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. SNRI SR is formulated as a sustained 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,150 mg venlafaxine. Inactive ingredients consist of cellulose, ethylcellulose, gelatin, hypromellose, iron oxide, and titanium dioxide.

COMPOSITION:

Each capsule contains:
Venlafaxine HCl Sustained Release
Pellets eq.to Venlafaxine..... 75mg

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. Pharmacological 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 monoamineoxidase (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 is1.3 ± 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 SNRI SR (150 mg q 24 hours) generally resulted in lower C max (150 ng/mL for venlafaxine and 260 ng/mL for ODV) and later T max (5.5 hours for venlafaxine and 9 hours for ODV) than for immediate release venlafaxine tablets (C max 's for immediate release 75 mg q12 hours were 225 ng/mL for venlafaxine and 290 ng/mL for ODV; T max 's were 2 hours for venlafaxine and 3 hours for ODV). When equal daily doses of venlafaxine were administered as either an immediate release tablet or the sustained-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 SNRI SR capsule. SNRI SR, therefore, provides a slower rate of absorption, but the same extent of absorption compared with the immediate release tablet. Food did not affect the bioavailability of venlafaxine or its active metabolite, ODV. Time of administration (AM vs PM) did not affect the pharmacokinetics of venlafaxine and ODV from the 75 mg SNRI SR 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.

INDICATIONS AND USAGE:

Major Depressive Disorder:

SNRI SR (venlafaxine hydrochloride) sustained release capsules is indicated for the treatment of major depressive disorder. The efficacy of SNRI SR 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. 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 SNRI SR (the immediate release form of venlafaxine) in the treatment of major depressive disorder in adult inpatients meeting diagnostic criteria for major depressive disorder with melancholia was established in a 4-week controlled trial. The safety and efficacy of SNRI SR in hospitalized depressed patients have not been adequately studied.

DOSAGE AND ADMINISTRATION:

Initially, 75 mg daily administered in 2 or 3 divided doses as conventional tablets or as a single daily dose when using the sustained release capsules. Alternatively, an initial dosage of 37.5 mg daily as sustained release capsules for the first 4–7 days (followed by an increase to 75 mg daily) may be considered for some patients. If no improvement, dosage may be increased by increments of up to 75 mg daily at intervals of not less than 4 days up to a maximum dosage of 375 mg daily (usually administered in 3 divided doses) as conventional tablets or 225 mg daily as sustained release capsules.Patients with more severe depression responded to higher dosages (mean dosage of 350 mg daily).

SPECIAL POPULATIONS:

Treatment of Pregnant Women During the Third Trimester :

Neonates exposed to SNRI SR, other SNRIs,or SSRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. When treating pregnant women with SNRI SR during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tape ring SNRI SR in the third trimester

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 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% and that the dose be with held 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.

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.

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, Generalized Anxiety Disorder, Social Anxiety Disorder, or panic disorder, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

CONTRAINDICATIONS

Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation. Concomitant use in patients taking monoamine oxidase inhibitors(MAOIs) is contraindicated.

ADVERSE EFFECTS :

Adverse effects that have been reported most frequently with venlafaxine include nausea, headache, insomnia, somnolence, drymouth, dizziness, constipation, sexual dysfunction,asthenia.sweating and nervousness. Other common adverse effects have included anorexia, diarrhoea, dyspepsia, abdominal pain,anxiety,urinary frequency,visual disturbances mydriasis,vasodilation vomiting, tremor, paresthesia, hypertonia, fever, palpitations, weight gain or loss, increased serum cholesterol,agitation,abnormal dreams,confusion,arthralgia myalgia, tinnitus, pruritis, dysponea, yawning skin rashes.

Dose related increase in blood pressure have also been observed in some patients. Aggressive behaviour has developed with venlafaxine treatment particularly at the start and when stopping therapy. Suicidal ideation has been reported particularly in children

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 re-emission occurs. There has been along-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pediatric Use:

Safety and effectiveness in the pediatric population have not been established. Two placebo-controlled trials in 766 pediatric patients with MDD and two placebo- controlled trials in 793 pediatric patients with GAD have been conducted with SNRI SR, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of SNRI SR in a child or adolescent must balance the potential risks with the clinical need. Although no studies have been designed to primarily assess SNRI SR impact on the growth, development, and maturation of children and adolescents, the studies that have been done suggest that SNRI SR may adversely affect weight and height. (Changes in Height and Changes in Weight). Should the decision be made to treat a pediatric patient with SNRI SR, regular monitoring of weight and height is recommended during treatment, particularly if it is to be continued long term. The safety of SNRI SR 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 6-17), 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.

Geriatric Use:

Approximately 4% (14/357), 6% (77/1381), 2% (6/277), and 2% (16/1001) of SNRI SR-treated patients in placebo-controlled premarketing major depressive disorder, GAD, Social Anxiety Disorder, and panic disorder trials, respectively, were 65 years of age or over. Of 2,897 SNRI SR-treated patients in premarketing phase major depressive disorder studies, 12% (357) were 65 years of age or over. No overall differences in effectiveness or safety were observed between geriatric patients and younger patients, and other reported clinical experience generally has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out. As with other antidepressants, several cases of hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported, usually in the elderly.

OVERDOSAGE:

In overdosage symptoms such as sweating,dizziness,somnolence,ECG changes,cardiac arrhythmias and seizures may be noted.

INSTRUCTIONS:

Store in a cool & dry place. Protect from Heat & Sunlight. Keep all medicines out of the reach of children. To be sold on the prescription of registered medical practitioner only.

How Supplied

SNRI SR (Venlafaxine) HCl Sustained Release Tablet are available as follows:
7 Capsules in Alu Alu blister, 2 blisters in a box.

خوراک و ہدایات:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔ خشک اور ٹھنڈی جگہ پر رکھیں
گرمی اور دھوپ سے بچائیں۔ تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

Manufactured by:
Semos Pharmaceuticals (Pvt.) Ltd.
Plot # 11, Sector 12-A, North Karachi,
Industrial Area, Karachi-75850, Pakistan.

Marketed by:
ORGANIC Pharmaceuticals