VORSCOT Tablets

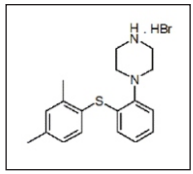
ورسکاٹ ٹیبلٹس

WARNING: SUICIDAL THOUGHTS AND BEHAVIOURS

- Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants.
- Monitor for worsening and emergence of suicidal thoughts and behaviors.
- Vortioxetine has not been evaluated for use in pediatric patients.

COMPOSITION:
Each Film Coated Tablet Contains:
Vortioxetine (as hydrobromide) .....5, 10, 15 & 20 mg, respectively.

DESCRIPTION:
VORSCOT is an immediate-release tablet for oral administration that contains the beta (β) polymorph of vortioxetine hydrobromide (HBr), an antidepressant. Vortioxetine HBr is known chemically as 1-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine, hydrobromide. The empirical formula is $C_{18}H_{22}N_2S$, HBr with a molecular weight of 379.36 g/mol. The structural formula is:



Formula of Vortioxetine

CLINICAL PHARMACOLOGY:
Mechanism of Action*:* The mechanism of the antidepressant effect of vortioxetine is not fully understood, but is thought to be related to its enhancement of serotonergic activity in the CNS through inhibition of the reuptake of serotonin (5-HT). It also has several other activities including 5-HT3 receptor antagonism and 5-HT1A receptor agonism. The contribution of these activities to vortioxetine's antidepressant effect has not been established.

Pharmacodynamics:
Vortioxetine binds with high affinity to the human serotonin transporter (Ki=1.6 nM), but not to the norepinephrine (Ki=113 nM) or dopamine (Ki>1000 nM) transporters. Vortioxetine potently and selectively inhibits reuptake of serotonin (IC50=5.4 nM). Vortioxetine binds to 5-HT3 (Ki=3.7 nM), 5-HT1A (Ki=15 nM), 5-HT7 (Ki=19 nM), 5-HT1D (Ki=54 nM), and 5-HT1B (Ki=33 nM), receptors and is a 5-HT3, 5-HT1D, and 5-HT7 receptor antagonist, 5-HT1B receptor partial agonist, and 5-HT1A receptor agonist.

Pharmacokinetics: Vortioxetine pharmacological activity is due to the parent drug. The pharmacokinetics of vortioxetine (2.5 mg to 60 mg) are linear and dose-proportional when vortioxetine is administered once daily. The mean terminal half-life is approximately 66 hours, and steady state plasma concentrations are typically achieved within two weeks of dosing.

Absorption*:* The maximal plasma vortioxetine concentration (Cmax) after dosing is reached within 7 to 11 hours postdose (Tmax). Steady state mean Cmax values were 9, 18, and 33 ng/mL following doses of 5, 10, and 20 mg/day. Absolute bioavailability is 75%. No effect of food on the pharmacokinetics was observed.

Distribution: The apparent volume of distribution of vortioxetine is approximately 2600 L, indicating extensive extravascular distribution. The plasma protein binding of vortioxetine in humans is 98%, independent of plasma concentrations. No apparent difference in the plasma protein binding between healthy subjects and subjects with hepatic (mild, moderate) or renal (mild, moderate, severe, ESRD) impairment is observed.

Metabolism and Elimination*:* Vortioxetine is extensively metabolized primarily through oxidation via cytochrome P450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 and subsequent glucuronic acid conjugation. CYP2D6 is the primary enzyme catalyzing the metabolism of vortioxetine to its major, pharmacologically inactive, carboxylic acid metabolite, and poor metabolizers of CYP2D6 have approximately twice the vortioxetine plasma concentration of extensive metabolizers. Following a single oral dose of [14C]-labeled vortioxetine, approximately 59% and 26% of the administered radioactivity was recovered in the urine and feces, respectively as metabolites. Negligible amounts of unchanged vortioxetine were excreted in the urine up to 48 hours. The presence of hepatic (mild or moderate) or renal impairment (mild, moderate, severe and ESRD) did not affect the apparent clearance of vortioxetine.

INDICATIONS AND USAGE:
Major Depressive Disorder
Vorscot is indicated for the treatment of major depressive disorder (MDD). The efficacy of Vorscot was established in six 6 to 8 week studies (including one study in the elderly) and one maintenance study in adults.

CONTRAINDICATIONS:
Hypersensitivity to vortioxetine or any components of the formulation. Angioedema has been reported in patients treated with vortioxetine.
The use of MAOIs intended to treat psychiatric disorders with vortioxetine or within 21 days of stopping treatment with vortioxetine is contraindicated because of an increased risk of serotonin syndrome. The use of vortioxetine within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated. Starting vortioxetine in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome.

ADVERSE REACTIONS:
- Hypersensitivity
- Clinical Worsening and Suicide Risk
- Serotonin Syndrome
- Abnormal Bleeding
- Activation of Mania/Hypomania
- Hyponatremia

DRUG INTERACTIONS:
CNS Active Agents
Monoamine Oxidase Inhibitors
Adverse reactions, some of which are serious or fatal, can develop in patients who use MAOIs or who have recently been discontinued from an MAOI and started on a serotonergic antidepressant(s) or who have recently had SSRI or SNRI therapy discontinued prior to initiation of an MAOI.

Serotonergic Drugs
Based on the mechanism of action of vortioxetine and the potential for serotonin toxicity, serotonin syndrome may occur when vortioxetine is co-administered with other drugs that may affect the serotonergic neurotransmitter systems (e.g., SSRIs, SNRIs, triptans, buspirone, tramadol, and tryptophan products etc.). Closely monitor symptoms of serotonin syndrome if Vortioxetine is co-administered with other serotonergic drugs. Treatment with vortioxetine and any concomitant serotonergic agents should be discontinued immediately if serotonin syndrome occurs.

Other CNS Active Agents
No clinically relevant effect was observed on steady state lithium exposure following coadministration with multiple daily doses of vortioxetine. Multiple doses of vortioxetine did not affect the pharmacokinetics or pharmacodynamics (composite cognitive score) of diazepam.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no adequate and well-controlled studies of vortioxetine in pregnant women. The incidence of malformations in human pregnancies has not been established for Vortioxetine. All human pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. Vortioxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether vortioxetine is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from Vortioxetine, 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
Clinical studies on the use of vortioxetine in pediatric patients have not been conducted; therefore, the safety and effectiveness of vortioxetine in the pediatric population have not been established.

Geriatric Use
No dose adjustment is recommended on the basis of age.

Use in Other Patient Populations
No dose adjustment of vortioxetine on the basis of race, gender, ethnicity, or renal function (from mild renal impairment to end-stage renal disease) is

necessary. In addition, the same dose can be administered in patients with mild to moderate hepatic impairment.

WARNINGS AND PRECAUTIONS

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.

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with serotonergic antidepressants including Vorscot, when used alone but more often when used concomitantly with other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort), and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of Vorscot with MAOIs intended to treat psychiatric disorders is contraindicated. Vorscot should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue.

If concomitant use of Vorscot with other serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with Vorscot and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Abnormal Bleeding

The use of drugs that interfere with serotonin reuptake inhibition, including Vorscot, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants 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 drugs that inhibit serotonin reuptake have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the increased risk of bleeding when Vorscot is co-administered with NSAIDs, aspirin, or other drugs that affect coagulation or bleeding.

Activation of Mania/Hypomania

Symptoms of mania/hypomania were reported in <0.1% of patients treated with Vortioxetine in pre marketing clinical studies. Activation of mania/hypomania has been reported in a small proportion of patients with major affective disorder who were treated with other antidepressants. As with all antidepressants, use Vorscot cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

DOSAGE AND ADMINISTRATION

General Instruction for Use

The recommended starting dose is 10 mg administered orally once daily without regard to meals. Dosage should then be increased to 20 mg/day, as tolerated, because higher doses demonstrated better treatment effects in trials conducted in the United States. The efficacy and safety of doses above 20 mg/day have not been evaluated in controlled clinical trials. A dose decrease down to 5 mg/day may be considered for patients who do not tolerate higher doses.

Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of major depression should be followed by several months or longer of sustained pharmacologic therapy. A maintenance study of Vortioxetine demonstrated that Vortioxetine decreased the risk of recurrence of depressive episodes compared to placebo.

Discontinuing Treatment

Although Vortioxetine can be abruptly discontinued, in placebo-controlled trials patients experienced transient adverse reactions such as headache and muscle tension following abrupt discontinuation of Vortioxetine 15 mg/day or 20 mg/day. To avoid these adverse reactions, it is recommended that the dose be decreased to 10 mg/day for one week before full discontinuation of Vortioxetine 15 mg/day or 20 mg/day.

Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of a MAOI intended to treat psychiatric disorders and initiation of therapy with Vorscot to avoid the risk of Serotonin Syndrome. Conversely, at least 21 days should be allowed after stopping Vorscot before starting an MAOI intended to treat psychiatric disorders.

Use of Vorscot with Other MAOIs such as Linezolid or Methylene Blue

Do not start Vorscot in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered.

In some cases, a patient already receiving Vorscot therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, Vorscot should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 21 days or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with Vorscot may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue.

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with Vorscot is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use.

Use of Vorscot in Known CYP2D6 Poor Metabolizers or in Patients Taking Strong CYP2D6 Inhibitors

The maximum recommended dose of Vorscot is 10 mg/day in known CYP2D6 poor metabolizers. Reduce the dose of Vorscot by one half when patients are receiving a CYP2D6 strong inhibitor (e.g., bupropion, fluoxetine, paroxetine, or quinidine) concomitantly. The dose should be increased to the original level when the CYP2D6 inhibitor is discontinued.

Use of Vorscot in Patients Taking Strong CYP Inducers

Consider increasing the dose of Vorscot when a strong CYP inducer (e.g., rifampin, carbamazepine, or phenytoin) is coadministered for greater than 14 days. The maximum recommended dose should not exceed three times the original dose. The dose of Vorscot should be reduced to the original level within 14 days, when the inducer is discontinued.

OVERDOSAGE:

Human Experience

There is limited clinical trial experience regarding human overdosage with Vortioxetine. In pre-marketing clinical studies, cases of overdose were limited to patients who accidentally or intentionally consumed up to a maximum dose of 40 mg of Vortioxetine The maximum single dose tested was 75 mg in men. Ingestion of Vortioxetine in the dose range of 40 to 75 mg was associated with increased rates of nausea, dizziness, diarrhea, abdominal discomfort, generalized pruritus, somnolence, and flushing.

Management of Overdose

No specific antidotes for Vortioxetine are known. In managing over dosage, consider the possibility of multiple drug involvement.

STORAGE/PRECAUTIONS:

Store in a cool, dry and dark place below 25 °C. Keep all medicines out of reach of children. To be sold and used on the prescription of Registered Medical Practitioners only.

PRESENTATION:

Vorscot 5 mg, 10 mg, 15 mg, & 20 mg tablets are available in packing containing 14 film coated tablets, respectively.

خوراک: ڈاکٹر کی ہدایت کے مطابق۔ احتیاط: روشنی، نمی اور گرمی سے بچائیں۔ 25 ڈگری سینٹی گریڈ سے کم درجہ حرارت پر محفوظ کریں۔ تمام ادویات بچوں کی پہنچ سے دور رکھیں۔ مستند ڈاکٹر کے نسخہ پر فروخت اور استعمال کریں۔

Complete Medical Information available only for doctors on request.

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