Voxver™
[Vortioxetine]

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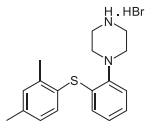
Tablets 10mg and 20mg

DESCRIPTION
Voxver (Vortioxetine) is an antidepressant that contains the beta (β) polymorph of Vortioxetine hydrobromide (HBr). Vortioxetine hydrobromide is known chemically as 1-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine, hydrobromide. Its molecular formula is $C_{18}H_{22}N_2S.HBr$ and the structural formula is:



Vortioxetine Hydrobromide

QUALITATIVE & QUANTITATIVE COMPOSITION
Voxver (Vortioxetine) Tablets are available for oral administration as:

Voxver Tablets 10mg
Each film-coated tablet contains:
Vortioxetine hydrobromide equivalent to Vortioxetine….10mg

Voxver Tablets 20mg
Each film-coated tablet contains:
Vortioxetine hydrobromide equivalent to Vortioxetine….20mg

CLINICAL PHARMACOLOGY
Mechanism of Action
The mechanism of action of Vortioxetine is thought to be related to its multimodal activity, which is a combination of two pharmacological modes of action: direct modulation of receptor activity and inhibition of the serotonin transporter. *In vitro* studies indicate that Vortioxetine is a 5-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and inhibitor of the 5-HT transporter (5-HTT).
The precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear. However, data from nonclinical serotonergic receptor and transporter occupancy studies coupled with neuronal firing and microdialysis studies suggest that the targets interact in a complex fashion, leading to modulation of neurotransmission in several systems, including serotonin, norepinephrine, dopamine, histamine, acetylcholine, gamma-aminobutyric acid (GABA) and glutamate systems within the forebrain. These multimodal pharmacological actions are thought to be responsible for the antidepressant effects of Vortioxetine.

Pharmacokinetic
Vortioxetine is slowly, but well absorbed after oral administration and the peak plasma concentration is reached within 7 to 11 hours. Following multiple dosing of 5mg, 10mg, or 20mg/day, mean C_{max} values of 9 to 33ng/mL were observed. The absolute bioavailability is 75%.

Effect of Food
No effect of food on the pharmacokinetics was observed.

Distribution
The apparent volume of distribution of Vortioxetine is approximately 2600L, 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 severe) or renal (mild, moderate, severe, ESRD) impairment is observed.

Metabolism
Vortioxetine is extensively metabolised in the liver, primarily through oxidation catalysed by CYP2D6 and to a minor extent CYP3A4/5 and CYP2C9, and subsequent glucuronic acid conjugation. *In vitro* studies indicate that the cytochrome P450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 are involved in the metabolism of Vortioxetine. No inhibitory or inducing effect of Vortioxetine was observed *in vitro* for the CYP isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5 nor was an inhibitory effect observed in vitro for CYP2D6 or CYP2EI. Vortioxetine is a poor P-gp substrate and inhibitor. The major metabolite of Vortioxetine is (Lu AA34443) pharmacologically inactive.

Excretion
The mean elimination half-life and oral clearance are 66 hours and 33L/h, respectively. Approximately 2/3 of the inactive Vortioxetine metabolites are excreted in the urine and approximately 1/3 in the feces. Only negligible amounts of Vortioxetine are excreted in the faeces. Steady-state plasma concentrations are achieved in approximately 2 weeks.

Special populations
Elderly
In elderly healthy subjects (aged ≥65 years), the exposure to Vortioxetine increased up to 27% (C_{max} and AUC) compared to young healthy control subjects (aged ≤45 years) after multiple doses of 10mg/day. The lowest effective dose of 5mg Vortioxetine once daily should always be used as the starting dose in patients ≥ 65 years. However, caution should be exercised when prescribing to elderly patients at doses higher than 10mg Vortioxetine once daily.

Renal impairment
Following a single dose of 10mg Vortioxetine, renal impairment estimated using the Cockcroft-Gault formula (mild, moderate, or severe) caused modest exposure increases (up to 30%), compared to healthy matched controls. In patients with end-stage renal disease, only a small fraction of Vortioxetine was lost during dialysis (AUC and C_{max} were 13% and 27% lower, respectively) following a single 10mg dose of Vortioxetine. No dose adjustment is needed based on renal function however, caution should be exercised.

Hepatic impairment
The pharmacokinetics in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Criteria A, B, or C, respectively) were compared to healthy volunteers. The changes in AUC were less than 10% lower in subjects with mild or moderate hepatic impairment, and 10% higher in those with severe hepatic impairment. The changes in C_{max} were less than 25% lower in all groups. No dose adjustment is needed based on hepatic function however, caution should be exercised.

CYP2D6 gene types
The plasma concentration of Vortioxetine was approximately two times higher in CYP2D6 poor metabolisers than in extensive metabolisers. Co-administration of strong CYP3A4/2C9 inhibitors to CYP2D6 poor metabolisers could potentially result in higher exposure.
In CYP2D6 ultra-rapid metabolisers, the plasma concentration of Vortioxetine 10mg/day were between those obtained in extensive metabolisers at 5mg/day and 10mg/day. Depending on individual patient response, a dose adjustment may be considered

Paediatric population
Pharmacokinetics of Vortioxetine in paediatric patients with major depressive disorder following oral administration of 5mg to 20mg once daily was characterized using population modeling analyses based on data from a pharmacokinetic study (7-17 years) and an efficacy and safety study (12-17 years). The pharmacokinetics of Vortioxetine in pediatric patients was similar to that observed in adult patients.

THERAPEUTIC INDICATIONS
Voxver (Vortioxetine) is indicated for the treatment of major depressive disorder in adults including prevention of relapse.

DOSAGE & ADMINISTRATION
The starting and recommended dose of Voxver (Vortioxetine) Tablets in adults less than 65 years of age is 10mg once daily, taken with or without food. Depending on individual patient response, the dose may be increased to a maximum of 20mg daily or reduced to a minimum of 5mg daily. An antidepressant effect of Vortioxetine based on the primary efficacy measure was generally observed starting at week 2. If the depressive symptoms resolve, treatment for at least 6 months is recommended for consolidation of the antidepressive response. Physicians should periodically re-evaluate the usefulness of the drug for individual patients.

Treatment discontinuation
Patients treated with Voxver (Vortioxetine) can abruptly stop taking the medicinal product without the need for a gradual reduction in dose. However, it is recommended that the dose be decreased to 10mg/day for one week before full discontinuation of Voxver (Vortioxetine) 15mg/day or 20mg/day.

Missed dose
If a dose is missed, the next dose should be taken at the usual time. Patients should not take a double dose to make up for a missed dose.

Special populations
Elderly patients
The recommended starting dose is 5mg Vortioxetine once daily and should always be used as the starting dose in patients ≥ 65 years of age. Caution is advised when treating patients ≥ 65 years of age with doses higher than 10mg Vortioxetine once daily.

Patients with renal impairment
No dose adjustment is recommended for patients with renal impairment or for patients with end-stage renal disease. However, as with any medicine, caution should be exercised when treating patients with severe renal insufficiency.

Patients with hepatic impairment
No dose adjustment is recommended for patients with mild or moderate hepatic impairment. Vortioxetine has not been studied in patients with severe hepatic impairment and caution should be exercised when prescribing to these patients.

Cytochrome P450 inhibitors
Depending on individual patient response, a lower dose of Vortioxetine may be considered if a strong CYP2D6 inhibitor (e.g. bupropion, quinidine, fluoxetine, paroxetine) is added to Vortioxetine treatment.

Cytochrome P450 inducers
Depending on individual patient response, a dose adjustment of Vortioxetine may be considered if a broad cytochrome P450 inducer (e.g., rifampicin, carbamazepine, phenytoin) is added to Vortioxetine treatment.

Pediatric population
The safety and efficacy of Vortioxetine in children aged 7 to 11 years have not been established. No data are available .Vortioxetine should not be used in adolescents aged 12 to 17 years with major depressive disorder (MDD) because efficacy has not been demonstrated.

ADVERSE REACTIONS
The following adverse reactions have been reported with the use of Vortioxetine therapy:

Very common
Nausea.

Common
Abnormal dreams, dizziness, diarrhoea, constipation, vomiting, pruritus including pruritus generalised, hyperhidrosis.

Uncommon
Flushing, night sweats, vertigo, dry eye, abdominal distension, gastritis, epigastric discomfort, salivary hypersecretion, chest discomfort, malaise, weight increased, electrocardiogram QT prolonged, heart rate increased, low density lipoprotein increased, blood cholesterol increased, blood triglycerides increased, dysgeusia, lethargy, tremor, myoclonus, formication, tension, bruxism, abnormal dreams, restlessness, derealisation, micturition urgency, nocturia, rash, hypotension.

Rare
Mydriasis.

Not known
Anaphylactic reaction, hyperprolactinemia, hyponatremia, insomnia, agitation, aggression, serotonin syndrome, headache, haemorrhage (including contusion, ecchymosis, epistaxis, gastrointestinal or vaginal bleeding), angioedema, urticaria, rash, activation of mania/hypomania.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
Vortioxetine is contraindicated in:
- Patients with hypersensitivity to Vortioxetine or any of the excipient of the product.
- Combination with a MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Vortioxetine should be discontinued for at least 14 days before starting treatment with a MAOI.

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults.
In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors.
Vortioxetine has not been evaluated for use in pediatric patients.

PRECAUTIONS
Clinical worsening and Suicide Risk
Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.
Patients with comorbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Serotonin syndrome/Neuroleptic Malignant Syndrome (NMS)
Development of serotonin syndrome / NMS may occur in association with treatment with serotonergic antidepressants, particularly when given in combination with MAOIs or other serotonergic agents. Symptoms and signs of serotonin syndrome/NMS include rapid onset of neuromuscular excitation (hyperreflexia, incoordination, myoclonus, tremor), altered mental status (confusion, agitation, hypomania) and autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering and rapidly fluctuating vital signs). Treatment with Vortioxetine should be discontinued if such events occur and supportive symptomatic treatment initiated.

Activation of Mania/Hypomania
As with all drugs effective in the treatment of depression, Vortioxetine should be used with caution in patients with a history of mania/hypomania and should be discontinued in any patient entering a manic phase. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder.

Aggression/agitation
Patients treated with antidepressants, including Vortioxetine, may also experience feelings of aggression, anger, agitation and irritability. Patient's condition and disease status should be closely monitored. Patients (and caregivers of patients) should be alerted to seek medical advice, if aggressive/agitated behaviour emerges or aggravates.

Seizures
Seizures are a potential risk with antidepressant drugs. Therefore, as with other antidepressants, Vortioxetine should be introduced cautiously in patients who have a history of seizures or in patients with unstable epilepsy. Treatment should be discontinued in any patient who develops seizures or where there is an increase in seizure frequency.

Hemorrhage
As with any antidepressant with serotonergic effect, including Vortioxetine bleeding abnormalities, such as ecchymoses, purpura and gastrointestinal or gynecological hemorrhage may occur. Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function (e.g. NSAIDs or aspirin), and in patients with known bleeding tendencies.

Hyponatremia
Hyponatremia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported rarely with the use of antidepressants with serotonergic effect. Caution should be exercised in patients at risk, such as elderly, cirrhotic patients or patients concomitantly treated with medications known to cause hyponatraemia.

Angle-closure Glaucoma
Antidepressants including Vortioxetine may have an effect on pupil size resulting in mydriasis. This mydriatic effect has the potential to narrow the eye angle resulting in increased intraocular pressure and angle-closure glaucoma, especially in pre-disposed patients. Vortioxetine should therefore be used with caution in patients with raised intraocular pressure and in those at risk of angle-closure glaucoma.

Effects on laboratory tests
There have been reports of false positive results in urine enzyme immunoassays for methadone in patients who have taken Vortioxetine. Caution should be exercised in the interpretation of positive urine drug screen results, and confirmation by an alternative analytical technique (e.g., chromatographic methods) should be considered.

Sexual Dysfunction
Use of serotonergic antidepressants, including Vortioxetine, may cause symptoms of sexual dysfunction. In male patients, serotonergic antidepressant use may result in ejaculatory delay or failure, decreased libido, and erectile dysfunction. In female patients, use may result in decreased libido and delayed or absent orgasm.

Switching a Patient to or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders
At least 14 days must elapse between discontinuation of a MAOI intended to treat psychiatric disorders and initiation of therapy with Vortioxetine to avoid the risk of Serotonin Syndrome. Conversely, at least 21 days must elapse after stopping Vortioxetine therefore starting an MAOI intended to treat psychiatric disorders.

Use of Vortioxetine in Known CYP2D6 Poor Metabolizers or in Patients Taking Strong CYP2D6 Inhibitors
The maximum recommended dose of Vortioxetine is 10mg/day in known CYP2D6 poor metabolizers. Reduce the dose of Vortioxetine 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 Vortioxetine in Patients Taking Strong CYP Inducers
Consider increasing the dose of Vortioxetine 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 Vortioxetine should be reduced to the original level within 14 days, when the inducer is discontinued.

Effects on ability to drive and use machines
Patients should exercise caution when driving or operating hazardous machinery especially when starting treatment with Vortioxetine or when changing the dose relative to placebo.

Pregnancy
There are limited human data on Vortioxetine use during pregnancy to inform any drug-associated risks. However, there are clinical considerations regarding neonates exposed to SSRIs and SNRIs, including Vortioxetine, during the third trimester of pregnancy. Neonates exposed to SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support and tube feeding. Exposure during late pregnancy to SSRIs may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). Vortioxetine should only be administered to pregnant women if the expected benefits outweigh the potential risk to the fetus.

Nursing Mothers
It is expected that Vortioxetine will be excreted into human milk. Consequently, breast-feeding is not recommended during treatment.

DRUG INTERACTIONS
Monoamine Oxidase Inhibitors (MAOIs)
The concomitant use of SSRIs and SNRIs including Vortioxetine with MAOIs increases the risk of serotonin syndrome. However, concomitant use of Vortioxetine is contraindicated:
- With an MAOI intended to treat psychiatric disorders or within 21 days of stopping treatment with Vortioxetine.
- Within 14 days of stopping an MAOI intended to treat psychiatric disorders.
- In a patient who is being treated with linezolid or intravenous methylene blue.

Examples include: selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue.

Other Serotonergic Drugs
Concomitant use of Vortioxetine with other serotonergic drugs increases the risk of serotonin syndrome. Therefore, monitor for symptoms of serotonin syndrome when Vortioxetine is used concomitantly with other drugs that may affect the serotonergic neurotransmitter systems. If serotonin syndrome occurs, consider discontinuation of Vortioxetine and/or concomitant serotonergic drugs
Examples include SNRIs, SSRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, amphetamines, tryptophan, and St. John's Wort.

Strong Inhibitors of CYP2D6
Concomitant use of Vortioxetine with strong CYP2D6 inhibitors increases plasma concentrations of Vortioxetine. Therefore, reduce Vortioxetine dose by half when a strong CYP2D6 inhibitor is coadministered. Examples include bupropion, fluoxetine, paroxetine, quinidine.

Strong CYP Inducers
Concomitant use of Vortioxetine with a strong CYP inducer decreases plasma concentrations of Vortioxetine. Therefore, consider increasing the Vortioxetine dose when a strong CYP inducer is coadministered. The maximum dose is not recommended to exceed three times the original dose. Examples include rifampin, carbamazepine, phenytoin.

Drugs that Interfere with Hemostasis (antiplatelets agents and anticoagulants)
Concomitant use of Vortioxetine with an antiplatelet or anticoagulant drug may potentiate the risk of bleeding. Therefore, inform patients of the increased risk of bleeding associated with the concomitant use of Vortioxetine and antiplatelet agents and anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio.
Examples include aspirin, clopidogrel, heparin, warfarin.

Drugs Highly Bound to Plasma Protein
Vortioxetine is highly bound to plasma protein. The concomitant use of Vortioxetine with another drug that is highly bound to plasma protein may increase free concentrations of Vortioxetine or other tightly-bound drugs in plasma. Therefore, monitor for adverse reactions and reduce dosage of Vortioxetine or other protein bound drugs as warranted. Example include warfarin.

St. John's Wort
Concomitant use of antidepressants with serotonergic effect and herbal remedies containing St. John´s Wort (Hypericum perforatum) may result in an increased incidence of adverse reactions including serotonin syndrome.

OVERDOSAGE
Ingestion of Vortioxetine in the dose range of 40mg to 75mg was associated with increased rates of nausea, dizziness, diarrhea, abdominal discomfort, generalized pruritus, somnolence, and flushing.
The most frequently reported symptoms with overdoses up to 80mg (four times the maximum recommended daily dose) were nausea and vomiting. With overdoses greater than 80mg, a case of serotonin syndrome in combination with another serotonergic drug, and a case of seizure, have been reported. Management of overdose should consist of treating clinical symptoms and relevant monitoring. Medical follow-up in a specialised environment is recommended.

STORAGE
Do not store above 30°C.
Protect from sunlight & moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Voxver (Vortioxetine) Tablets 10mg are available in blister pack of 14's.
Voxver (Vortioxetine) Tablets 20mg are available in blister pack of 14's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

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