Front

VORTI
(Vortioxetine)

Tablet

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COMPOSITION:
Vorti Tablet 5 mg:
Each film coated tablet contains:
Vortioxetine Hydrobromide equivalent to
Vortioxetine ..... 5 mg.

Product Specs.: Innovator

Vorti Tablet 10 mg:
Each film coated tablet contains:
Vortioxetine Hydrobromide equivalent to
Vortioxetine ..... 10 mg.
Product Specs.: Innovator

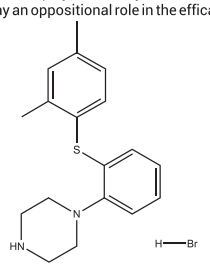
Vorti Tablet 20 mg:
Each film coated tablet contains:
Vortioxetine Hydrobromide equivalent to
Vortioxetine ..... 20 mg.

Product Specs.: Innovator

DOSAGE FORM:

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.
- 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
- Vorti has not been evaluated for use in pediatric patients.

DESCRIPTION:
Vortioxetine is a serotonergic antidepressant used for major depression disorders. Vortioxetine has been associated with a low rate of minor serum aminotransferase elevations during treatment, but has not been linked to instances of clinically apparent acute liver injury. Vortioxetine is an N-arylpiperazine in which the aryl group is specified as 2-[(2,4-dimethylphenyl) sulfanyl] phenyl. Used (as its hydrobromide salt) for treatment of major depressive disorder. It has a role as an antidepressant, an anxiolytic drug, a serotonergic agonist and a serotonergic antagonist. It is a N-arylpiperazine and an aryl sulfide. It is a conjugate base of a vortioxetine. It is classified as a serotonin modulator and simulator (SMS) as it has a multimodal mechanism of action towards the serotonin neurotransmitter system whereby it simultaneously modulates one or more serotonin receptors and inhibits the reuptake of serotonin. More specifically, vortioxetine acts via the following biological mechanisms: as a serotonin reuptake inhibitor (SRI) through inhibition of the serotonin transporter, as a partial agonist of the 5-HT1B receptor, an agonist of 5-HT1A, and an antagonist of the 5-HT3, 5-HT1D, and 5-HT7 receptors. SMSs were developed because there are many different subtypes of serotonin receptors, however, not all of these receptors appear to be involved in the antidepressant effects of SRIs. Some serotonin receptors seem to play a relatively neutral or insignificant role in the regulation of mood, but others, such as 5-HT1A auto receptors and 5-HT7 receptors, appear to play an oppositional role in the efficacy of SRIs in treating depression.



Mechanism of Action: The exact mechanism of action of vortioxetine in the treatment of depression is unknown, but is thought to occur from enhancement of central serotonergic activity secondary to potent inhibition of the serotonin transporter, a mechanism similar to the selective serotonin reuptake inhibitors (SSRIs). In addition, vortioxetine is a serotonin receptor antagonist at 5-HT3, 5-HT1D, and 5-HT7, a partial agonist at 5-HT1B, and an agonist at the 5-HT1A receptor. The contribution of these receptor activities to the overall antidepressant effect of vortioxetine has not been established. In 2 separate controlled trials, adult patients with recurrent major depressive disorder (MDD) receiving 10 to 20 mg of vortioxetine had statistically superior scores on the Digit Symbol Substitution Test (DSST) relative to patients receiving placebo. The DSST is a neuropsychological test that most specifically measures processing speed, an aspect of cognitive function that may be impaired in those with MDD. It is not known if the improvement in DSST scores observed in these studies represents a therapeutic advantage of vortioxetine over other antidepressants.

CLINICAL PHARMACOLOGY:
Pharmacokinetics: Vortioxetine is administered orally. Vortioxetine has a large volume of distribution, indicating extensive extravascular distribution. The drug is highly protein bound (98%). Oxidation is the primary metabolic route. CYP2D6 is the primary enzyme catalyzing the metabolism of vortioxetine to its major, inactive metabolite. The mean terminal half-life in normal adults is 66 hours. Approximately 59% of a dose is excreted in the urine and 26% in the feces as metabolites. Excretion of unchanged vortioxetine is negligible. Affected cytochrome P450 (CYP450) isoenzymes and drug transporters: CYP2D6. Vortioxetine is extensively metabolized primarily through oxidation via 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, inactive metabolite. Vortioxetine and its metabolites are unlikely to inhibit the following CYP enzymes and transporters based on in vitro data: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, P-gp, BCRP, BSEP, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2. According to in vitro data, vortioxetine does not induce CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5. In vivo studies indicate that vortioxetine has no clinical meaningful effect on substrates of CYP2B6, CYP2C9, or CYP2C19. Because vortioxetine is highly protein bound, coadministration with another drug that is highly protein bound may increase free concentrations of the other drug; however, in one clinical study with warfarin, no significant change in INR was observed.

INDICATIONS:
Is indicated for the treatment of **Major Depressive Disorder (MDD)** in adults.

DOSAGE AND ADMINISTRATION:
- The recommended starting dose is 10 mg administered orally once daily without regard to meals
- The dose should then be increased to 20 mg/day, as tolerated
- Consider 5 mg/day for patients who do not tolerate higher doses
- Can be discontinued abruptly. However, it is recommended that doses of 15 mg/day or 20 mg/day be reduced to 10 mg/day for one week prior to full discontinuation if possible
- The maximum recommended dose is 10 mg/day in known CYP2D6 poor metabolizers

WARNINGS & PRECAUTIONS:
Serotonin Syndrome: Has been reported with serotonergic antidepressants (SSRIs, SNRIs, and others), when taken alone, but especially when co-administered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort). If such symptoms occur, discontinue and initiate supportive treatment. If concomitant use with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

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.

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression.
All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these.

Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Screening patients for bipolar disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that vortioxetine is not approved for use in treating bipolar depression.
The concomitant use of vortioxetine with MAOIs (Monoamine Oxidase Inhibitors) intended to treat psychiatric disorders is contraindicated. Vortioxetine should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a MAOI such as linezolid or intravenous methylene blue in a patient taking vortioxetine. Vortioxetine should be discontinued before initiating treatment with the MAOI. If concomitant use of vortioxetine 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 vortioxetine 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 vortioxetine, 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 vortioxetine 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 vortioxetine cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.
Angle closure glaucoma: Has occurred as a result of treatment with serotonergic drugs. In many cases, hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). One case with serum sodium lower than 110 mmol/L was reported in a subject treated with vortioxetine in a premarketing clinical study. Elderly patients may be at greater risk of developing hyponatremia with a serotonergic antidepressant. Also, patients taking diuretics or who are otherwise volume-depleted can be at greater risk. Discontinuation of vortioxetine in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. More severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

ADVERSE REACTIONS:
The following adverse reactions are discussed in greater detail in other sections of the label.
- Hypersensitivity
- Clinical Worsening and Suicide Risk *(see Warnings and Precautions)*
- Serotonin Syndrome *(see Warnings and Precautions)*
- Abnormal Bleeding *(see Warnings and Precautions)*
- Activation of Mania/Hypomania *(see Warnings and Precautions)*
- Angle Closure Glaucoma *(see Warnings and Precautions)*
- Hyponatremia *(see Warnings and Precautions)*

SPECIAL POPULATIONS:
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 [see Clinical Considerations]. Advise a pregnant woman of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.
Clinical considerations: Disease-associated maternal and/or embryo/fetal risk - A prospective, longitudinal study followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. The women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risks of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.
Fetal/Neonatal adverse reactions: Exposure to serotonergic antidepressants, including vortioxetine, in late pregnancy may lead to an increased risk for neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding, and/or persistent pulmonary hypertension of the newborn (PPHN). Monitor neonates who were exposed to vortioxetine in the third trimester of pregnancy for PPHN and drug discontinuation syndrome.

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.

DRUG INTERACTIONS:
CNS Active Agents:
- **Monoamine Oxidase Inhibitors**
- **Serotonergic Drugs**
- ***Other CNS active agents:*** No clinically relevant effect was observed on steady-state lithium exposure following co-administration with multiple daily doses of vortioxetine. Multiple doses of vortioxetine did not affect the pharmacokinetics or pharmacodynamics (composite cognitive score) of Reference ID: 4337698 Page 12 of 32 diazepam. A clinical study has shown that vortioxetine (single dose of 20 or 40 mg) did not increase the impairment of mental and motor skills caused by alcohol (single dose of 0.6 g/kg).

Drugs that interfere with hemostasis: Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are co-administered with warfarin. Following co-administration of stable doses of warfarin (1 to 10 mg/day) with multiple daily doses of vortioxetine, no significant effects were observed in INR, prothrombin values or total warfarin (protein bound plus free drug) pharmacokinetics for both R- and S-warfarin. Co-administration of aspirin 150 mg/day with multiple daily doses of vortioxetine had no significant inhibitory effect on platelet aggregation or pharmacokinetics of aspirin and salicylic acid. Patients receiving other drugs that interfere with hemostasis should be carefully monitored when vortioxetine is initiated or discontinued.
Potential for other drugs to affect vortioxentine: Reduce vortioxetine dose by half when a strong CYP2D6 inhibitor (e.g., bupropion, fluoxetine, paroxetine, quinidine) is co-administered. Consider increasing the vortioxetine dose when a strong CYP inducer (e.g., rifampin, carbamazepine, phenytoin) is co-administered. The maximum dose is not recommended to exceed three times the original dose.

INSTRUCTIONS:
- Store below 30°C.
- Protect from heat, sunlight and moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

Vorti Tablet 5 mg	:	Pack of 2 x 7 tablets.
Vorti Tablet 10 mg	:	Pack of 2 x 7 tablets.
Vorti Tablet 20 mg	:	Pack of 2 x 7 tablets.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATIONS PLEASE CONTACT:

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