OXIVORT®
(VORTIOXETINE)

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COMPOSITION

Oxivort 10mg Tablets
Each film coated tablet contains:
Vortioxetine (as Hydrobromide).....10mg
Oxivort 20mg Tablets
Each film coated tablet contains:
Vortioxetine (as Hydrobromide).....20mg

(As per innovator's specs.)

SUICIDAL THOUGHTS AND BEHAVIORS
Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a trend toward reduced risk with antidepressant use in patients aged 65 and older.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber.

Vortioxetine has not been evaluated for use in pediatric patients.

DESCRIPTION
OXIVORT 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 C18 H22 N2 S, HBr with a molecular weight of 379.36 g/mol.

CLINICAL PHARMACOLOGY

Pharmacodynamics

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.

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
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 5, 10, or 20 mg/day, mean Cmax values of 9 to 33 ng/mL were observed. The 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 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.

No inhibitory or inducing effect of vortioxetine was observed in the drug-drug interaction studies for the CYP isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5. Vortioxetine is a poor P-gp substrate and inhibitor.

The major metabolite of vortioxetine is pharmacologically inactive.

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

Pharmacokinetics in special populations

Elderly
In elderly healthy subjects (aged ≥65 years; n=20), the exposure to vortioxetine increased up to 27% (Cmax and AUC) compared to young healthy control subjects (aged ≤45 years) after multiple doses of 10 mg/day. The lowest effective dose of 5 mg 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 10 mg vortioxetine once daily.

Renal impairment
Following a single dose of 10 mg vortioxetine, renal impairment estimated using the Cockcroft-Gault formula (mild, moderate, or severe; n=8 per group) 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 Cmax were 13% and 27% lower, respectively; n=8) following a single 10 mg dose of vortioxetine. No dose adjustment is needed based on renal function.

Hepatic impairment
The pharmacokinetics in subjects (N = 6-8) 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 Cmax were less than 25% lower in all groups. No dose adjustment is needed based on hepatic function.

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 10 mg/day were between those obtained in extensive metabolisers at 5 mg/day and 10 mg/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 5 to 20 mg 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 paediatric patients was similar to that observed in adult patients.

INDICATIONS

Major Depressive Disorder
OXIVORT is indicated for the treatment of major depressive disorder (MDD) in adults.

DOSAGE AND ADMINISTRATION
The starting and recommended dose of Oxivort is 10 mg vortioxetine once daily in adults less than 65 years of age.

Depending on individual patient response, the dose may be increased to a maximum of 20 mg vortioxetine once daily or decreased to a minimum of 5 mg vortioxetine once daily.
After the depressive symptoms resolve, treatment for at least 6 months is recommended for consolidation of the antidepressive response.

Treatment discontinuation
Patients treated with vortioxetine can abruptly stop taking the medicinal product without the need for a gradual reduction in dose.

Paediatric 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.

Renal or hepatic impairment
No dose adjustment is needed based on renal or hepatic function

CONTRAINDICATIONS
Hypersensitivity to vortioxetine or any components of the formulation.

The use of MAOIs intended to treat psychiatric disorders with vortioxetine or within 21days 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.

WARNING 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. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short term placebo-controlled studies of antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a trend toward reduction with antidepressants compared to placebo in adults aged 65 and older.

Serotonin Syndrome
The development of a potentially life-threatening serotonin syndrome has been reported with serotonergic antidepressants including vortioxetine, 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 vortioxetine with MAOIs 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 coadministered 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 premarketing 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
The pupillary dilation that occurs following use of many antidepressant drugs, including vortioxetine, may trigger an angle closure attack in a patient with anatomically narrow angles

who does not have a patent iridectomy.

Hyponatremia
Hyponatremia 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).

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
Immune system disorders: Anaphylactic reaction.
Metabolism and nutrition disorders: Hyponatraemia.
Psychiatric disorders: Abnormal dreams, insomnia, agitation, aggression.
Nervous system disorders: Dizziness, serotonin syndrome.
Eye disorders: Mydriasis (which may lead to acute narrow angle glaucoma).
Vascular disorders: Flushing, haemorrhage (including contusion, ecchymosis, epistaxis, gastrointestinal or vaginal bleeding).
Gastrointestinal disorders: Nausea, diarrhoea, constipation,vomiting.
Skin and subcutaneous tissue disorders: Pruritus, including pruritus generalized, night sweats, angioedema, urticaria, rash.

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 coadministered 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 coadministered 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. 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 (e.g., NSAIDs, Aspirin, and Warfarin)
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 coadministered with warfarin.

Following coadministration 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.

Coadministration 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 VORTIOXETINE
Reduce vortioxetine dose by half when a strong CYP2D6 inhibitor (e.g., bupropion, fluoxetine, paroxetine, quinidine) is coadministered. Consider increasing the vortioxetine dose when a strong CYP inducer (e.g., rifampin, carbamazepine, phenytoin) is coadministered. The maximum dose is not recommended to exceed three times the original dose.

USE IN SPECIAL POPULATIONS

Pregnancy
There are limited data from the use of vortioxetine in pregnant women. Studies in animals have shown reproductive toxicity.

The following symptoms may occur in the newborn after maternal use of a serotonergic medicinal product in the later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either discontinuation effects or excess serotonergic activity. In the majority of instances, such complications began immediately or soon (<24 hours) after delivery.

Epidemiological data suggest that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated the association of PPHN with vortioxetine treatment, this potential risk cannot be ruled out taking into account the related mechanism of action (increase in serotonin concentrations).

Vortioxetine should only be administered to pregnant women if the expected benefits outweigh the potential risk to the foetus.

Breast-feeding
Available data in animals have shown excretion of vortioxetine/ vortioxetine metabolites in milk. It is expected that vortioxetine will be excreted into human milk.

A risk to the breastfeeding child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from vortioxetine treatment taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
Fertility studies in male and female rats showed no effect of vortioxetine on fertility, sperm quality or mating performance.
Human case reports with medicinal products from the related pharmacological class of antidepressants (SSRIs) have shown an effect on sperm quality that is reversible. Impact on human fertility has not been observed so far.

Renal or hepatic impairment
No dose adjustment is needed based on renal or hepatic function

OVER DOSAGE
Ingestion of vortioxetine in clinical trials in the dose range of 40 mg to 75 mg has caused an aggravation of the following adverse reactions: nausea, postural dizziness, diarrhoea, abdominal discomfort, generalised pruritus, somnolence and flushing.

Post-marketing experience mainly concerns vortioxetine overdoses of up to 80 mg. In the majority of cases, no symptoms or mild symptoms were reported. The most frequently reported symptoms were nausea and vomiting.

There is limited experience with vortioxetine overdoses above 80 mg. Following dosages several fold higher than the therapeutic dose range, events of seizure and serotonin syndrome have been reported.

Management of overdose should consist of treating clinical symptoms and relevant monitoring. Medical follow-up in a specialised environment is recommended.

PRESENTATION
Oxivort 10mg: Pack of 14 Tablets
Oxivort 20mg: Pack of 14 Tablets

INSTRUCTIONS:
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, email us at
reports@pharmevo.biz

For more information on our products
call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
or email us at : pharmassist@pharmevo.biz

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Our dream, a healthier society

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