140 mm

20 mm

480 mm

℞ Vilazodone Hydrochloride Tablets

Vilodon 20/40

विलोडोन २०
विलोडोन ४०

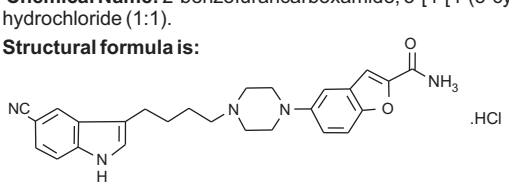
Each film coated tablet contains
Vilazodone Hydrochloride .....20 mg
Colors: Lake Sunset Yellow & Titanium Dioxide IP

Each film coated tablet contains
Vilazodone Hydrochloride .....40 mg
Colors: Lake Brilliant Blue & Titanium Dioxide IP

Route Of Administration : Oral

Chemical Name: 2-benzofurancarboxamide, 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride (1:1).

Structural formula is:



Molecular weight : 477.99 g/mol

Mechanism of Action

The mechanism of the antidepressant effect of vilazodone is not fully understood but is thought to be related to its enhancement of serotonergic activity in the CNS through selective inhibition of serotonin reuptake. Vilazodone is also a partial agonist at serotonergic 5-HT1A receptors; however, the net result of this action on serotonergic transmission and its role in vilazodone's antidepressant effect are unknown.

PHARMACOLOGY:

Pharmacodynamics

Vilazodone binds with high affinity to the serotonin reuptake site (Ki= 0.1 nM), but not to the norepinephrine (Ki=56 nM) or dopamine (Ki=37 nM) reuptake sites. Vilazodone potently and selectively inhibits reuptake of serotonin (IC = 1.6 nM). Vilazodone also binds selectively with high affinity to 5- HT receptors (IC =2.1 nM) and is a 5-HT receptor partial agonist.

Thorough QT Study: Treatment with Vilazodone did not prolong the QTc interval. The effect of vilazodone (20, 40, 60, and 80 mg) on the QTc interval was evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg), parallel-group, thorough QTc study in 157 healthy subjects.

The study demonstrated an ability to detect small effects. The upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc interval was below 10 msec, based on the individual correction method (QTcI). This is below the threshold for clinical concern. However, it is unknown whether 80 mg is adequate to represent a high clinical exposure condition.

Pharmacokinetics

Vilazodone activity is due primarily to the parent drug. The pharmacokinetics of vilazodone (5 mg – 80 mg) are dose-proportional. Accumulation of vilazodone is predictable from single dose data, does not vary with dose, and steady-state is achieved in about 3 days. Elimination of vilazodone is primarily by hepatic metabolism with a terminal half-life of approximately 25 hours. At steady-state, after daily dosing of Vilazodone 40 mg under fed conditions, the mean Cmax value is 156 ng/mL, and the mean AUC (0-24 hours) value is 1645 ng•h/mL.

Absorption

Vilazodone concentrations peak at a median of 4-5 hours (Tmax) after administration and decline with a terminal half-life of approximately 25 hours. The absolute bioavailability of vilazodone is 72% with food. Administration of Vilazodone with food (high fat or light meal) increases oral bioavailability (Cmax increased by approximately 147-160%, and AUC increased by approximately 64-85%).

Co-administration of Vilazodone with ethanol or with a proton pump inhibitor (pantoprazole) did not affect the rate or extent of vilazodone absorption. In addition, neither the Tmax nor terminal elimination rate of vilazodone was altered by co-administration with either pantoprazole or ethanol.

Absorption is decreased by approximately 25% if vomiting occurs within 7 hours of ingestion; no replacement dose is needed.

Distribution

Vilazodone is widely distributed and approximately 96-99% protein-bound.

Metabolism and Elimination

Vilazodone is extensively metabolized through CYP and non-CYP pathways (possibly by carboxylesterase), with only 1% of the dose recovered in the urine and 2% of the dose recovered in the feces as unchanged vilazodone. CYP3A4 is primarily responsible for its metabolism among CYP pathways, with minor contributions from CYP2C19 and CYP2D6. studies with human microsomes and human hepatocytes indicate that vilazodone is unlikely to inhibit or induce the metabolism of other CYP (except for CYP2C8) substrates; and an study with probe substrates for CYP2C19, 2D6 and 3A4 showed vilazodone did not alter the pharmacokinetics of the probe substrates.

However, an study with probe substrate for CYP2C19 demonstrated a minor induction of CYP2C19. Strong inhibitors of CYP3A4 (e.g., ketoconazole) can reduce the metabolism of vilazodone and increase exposure. Conversely, strong inducers of CYP3A4 (e.g., carbamazepine) can decrease vilazodone exposure.

The presence of mild or moderate renal impairment, or mild, moderate, or severe hepatic impairment did not affect the apparent clearance of vilazodone.

INDICATIONS AND USAGE:

Vilazodone is indicated for the treatment of major depressive disorder (MDD) in adults.

Major depressive disorder consists of one or more major depressive episodes. A major depressive episode (DSM-IV-TR) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest 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, or a suicide attempt or suicidal ideation.

DOSAGE AND ADMINISTRATION:

Initial Treatment of Major Depressive Disorder

The recommended dose for Vilazodone is 40 mg once daily. Vilazodone should be titrated, starting with an initial dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then an increase to 40 mg once daily. Vilazodone should be taken with food. Vilazodone blood concentrations (AUC) in the fasted state can be decreased by approximately 50% compared to the fed state, and may result in diminished effectiveness in some patients.

Maintenance/Continuation/Extended Treatment

The efficacy of Vilazodone has not been systematically studied beyond 8 weeks. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Patients should be reassessed periodically to determine the need for maintenance treatment and the appropriate dose for treatment.

Concomitant Use of CYP3A4 Inhibitors or CYP3A4 Inducers

Patients receiving concomitant CYP3A4 inhibitors:

Reduce the Vilazodone dose to 20 mg if co-administered with a strong inhibitor of CYP3A4 (e.g., ketoconazole). During co-administration with moderate inhibitors of CYP3A4 (e.g., erythromycin), the Vilazodone dose should be reduced to 20 mg for patients with intolerable adverse events. The Vilazodone dose should be readjusted to the original level when CYP3A4 inhibitors are discontinued.

Patients receiving concomitant CYP3A4 inducers:

Based on clinical response, consider increasing the dose of Vilazodone up to 2-fold when concomitantly used with strong CYP3A4 inducers (e.g., carbamazepine) for greater than 14 days. The maximum daily dose should not exceed 80 mg. If CYP3A4 inducers are discontinued, reduce the Vilazodone dose to the original level in 14 days.

Discontinuing Treatment

Discontinuation symptoms have been reported with discontinuation of serotonergic drugs such as Vilazodone. Gradual dose reduction is recommended, instead of abrupt discontinuation, whenever possible. Monitor patients for these symptoms when discontinuing Vilazodone. If intolerable symptoms occur following a dose decrease or upon discontinuation of treatment, consider resuming the previously prescribed dose and decreasing the dose at a more gradual rate.

***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 an MAOI intended to treat psychiatric disorders and initiation of therapy with Vilazodone. Conversely, at least 14 days should be allowed after stopping Vilazodone before starting an MAOI intended to treat psychiatric disorders.

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

Do not start Vilazodone 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 Vilazodone 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, Vilazodone should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 2 weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with Vilazodone 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 Vilazodone is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use.

CONTRAINDICATIONS

Monoamine Oxidase Inhibitors (MAOIs)

The use of MAOIs intended to treat psychiatric disorders with Vilazodone or within 14 days of stopping treatment with Vilazodone is contraindicated because of an increased risk of serotonin syndrome. The use of Vilazodone within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated.

Starting Vilazodone 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.

WARNINGS AND PRECAUTIONS

Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

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 18-24) with MDD and other psychiatric disorders.

140 mm

20 mm

480 mm

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 reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated).

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.

All patients being treated with anti depress ants 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, hostilit,

aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder 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 symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder 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.

Prescriptions for Vilazodone should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

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 Vilazodone is not approved for use in treating bipolar depression.

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including Vilazodone, alone but particularly with concomitant use of 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). Symptoms of serotonin syndrome were noted in 0.1% of MDD patients treated with Vilazodone in premarketing clinical trials.

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 Vilazodone with MAOIs intended to treat psychiatric disorders is contraindicated. Vilazodone 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 an MAOI such as linezolid or intravenous methylene blue in a patient taking Vilazodone. Vilazodone should be discontinued before initiating treatment with the MAOI.

If concomitant use of Vilazodone 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 Vilazodone and any concomitant serotonergic agents, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Seizures

Vilazodone has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from clinical studies. Like other antidepressants, Vilazodone should be prescribed with caution in patients with a seizure disorder.

Abnormal Bleeding

The use of drugs that interfere with serotonin reuptake inhibition, including Vilazodone, 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 (casecontrol 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 SSRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of Vilazodone and 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 Vilazodone in clinical studies. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other antidepressants. As with all antidepressants, use Vilazodone cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

Discontinuation of Treatment with Vilazodone

There have been reports of adverse events occurring upon discontinuation of serotonergic antidepressants, particularly when discontinuation is abrupt, including the following: dysphoric mood,

irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Monitor patients for these symptoms when discontinuing Vilazodone. Reduce the dose gradually whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, the dose may be decreased, but at a more gradual rate.

Hyponatremia

Although no cases of hyponatremia resulting from Vilazodone treatment were reported in the clinical studies, hyponatremia has occurred as a result of treatment with SSRIs and SNRIs. In many cases, hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk. Discontinuation of Vilazodone 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. Signs and symptoms associated with 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.

Clinical Worsening and Suicide Risk
Serotonin Syndrome
Seizure
Abnormal Bleeding
Activation of Mania/Hypomania
Discontinuation of Treatment with Vilazodone
Hyponatremia

OVER DOSAGE:

Human Experience

There is limited clinical experience regarding human over dosage with Vilazodone. Four patients and 1 patient's child experienced an overdose of Vilazodone, all recovered. The adverse reactions associated with overdose of Vilazodone at doses of 200-280 mg as observed in clinical trials included serotonin syndrome, lethargy, restlessness, hallucinations, and disorientation.

Management of Overdose

Consult a Certified Poison Control Center for up-to-date guidance and advice. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). No specific antidotes for vilazodone are known. In case of an overdose, provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in
the management of over dosage with any drug. Consider the possibility of multiple drug overdose.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be considered. Removal of vilazodone by dialysis has not been studied; however, the high volume of distribution of vilazodone suggests that dialysis will not be effective in reducing vilazodone plasma concentrations.

STORAGE:
Store below 30°C.

Keep out of reach of children

Manufactured by:
MSN Laboratories Private Limited
(Formulations Division), Plot No. 42,
Anrich Industrial Estate, Bollaram,
Sangareddy District - 502 325,
Telangana, INDIA.

B32814-00