To be sold by retail on the prescription of 'Psychiatrist'

VALZ

Suicidal thoughts and Behaviour

- Antidepressants increase the risk of suicidal thoughts and behaviours in patients aged 24 years and younger.
- Monitor for clinical worsening and emergence of suicidal thoughts and behaviours
- Safety and effectiveness of Vilazodone hydrochloride have not been established in paediatric patients.

1. Generic Name

Vilazodone Hydrochloride Tablets.

2. Qualitative and quantitative Composition:

VALZ 20

Each film coated tablet contains:

Vilazodone Hydrochloride….20mg

Colours: Lake Sunset Yellow & Titanium Dioxide I.P.

The excipients used are Lactose, Microcrystalline Cellulose, Hydroxypropyl Betacyclodextrin, Crospovidone, Colloidal Silicon Dioxide, Magnesium Stearate and Opadry II orange 85F530080.

VALZ 40

Each film coated tablet contains:

Vilazodone Hydrochloride….40mg

Colours: Lake Brilliant Blue & Titanium Dioxide I.P.

The excipients used are Lactose, Microcrystalline Cellulose, Hydroxypropyl Betacyclodextrin, Crospovidone, Colloidal Silicon Dioxide, Magnesium Stearate and Opadry II blue 85F505061.

3. Dosage form and strength

Dosage form: Tablets

Strength: 20mg & 40mg

4. Clinical particulars

4.1. Therapeutic indication

It is indicated for the treatment of major depressive disorders (MDD) in adults.

4.2. Posology and method of administration

Posology

Initial Treatment of Major Depressive Disorder

The recommended dose for vilazodone is 20 mg to 40 mg orally once daily with food. 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 increase to 40 mg once daily with food.

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.

Dosing in Special Populations

Pregnant Women:

Neonates exposed to serotonergic antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. When treating pregnant women with vilazodone, consider whether the potential benefits outweigh the potential risks of treatment.

Nursing Mothers:

There are no clinical data regarding the effect of vilazodone on lactation and nursing. Breastfeeding in women treated with vilazodone should be considered only if the potential benefit outweighs the potential risk.

Pediatric Patients:

The safety and efficacy of vilazodone have not been studied in pediatric patients.

Geriatric Patients:

No dose adjustment is recommended on the basis of age.

Hepatic Impairment:

No dose adjustment is recommended in patients with mild or moderate hepatic impairment. Vilazodone has not been studied in severe hepatic impairment.

Renal Impairment:

No dose adjustment is recommended in patients with mild, moderate, or severe renal impairment.

Gender:

No dose adjustment is recommended on the basis of gender.

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.

Monoamine Oxidase Inhibitors (MAOI) Antidepressant

At least 14 days must elapse between discontinuation of an MAOI antidepressant and initiation of therapy with vilazodone. In addition, at least 14 days must elapse after stopping vilazodone before starting an MAOI.

Method of administration

These should be swallowed whole with water.

4.3. Contraindications

<u>Monoamine Oxidase Inhibitors (MAOIs)</u>

Vilazodone must not be used concomitantly in patients taking MAOIs or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions have been associated with symptoms that include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Allow at least 14 days after stopping vilazodone before starting an MAOI.

4.4. Special warnings and precautions for use

<u>Clinical Worsening and Suicide Risk</u>

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. 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 reported 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) are provided in below table.

Table: Drug-placebo difference in the number of cases of suicidality per 1000 patients treated

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
Increases Compared to Placebo	
<18	14 additional cases

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
18-24	5 additional cases
Decreases Compared to Placebo	
25-64	1 fewer case
≥65	6 fewer cases

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 major depressive disorder as well as for other indications, both psychiatric and no psychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

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.

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.

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions

The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions has been reported with antidepressants alone, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs that impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation,

hallucinations, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea). Serotonin syndrome, in its most severe form can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of vilazodone with MAOIs intended to treat depression is contraindicated. If concomitant treatment of vilazodone with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of vilazodone with serotonin precursors (such as tryptophan) is not recommended. Treatment with vilazodone and any concomitant serotonergic (SSRI, serotonin–norepinephrine reuptake inhibitor [SNRI], triptan, buspirone, tramadol, etc.) or antidopaminergic drugs, including antipsychotics, 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 (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 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 reported 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 reported 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 than110 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.

Angle Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including vilazodone may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy. Avoid vilazodone, in patients with untreated anatomically narrow angles.

4.5. Drugs interactions

Central Nervous System (CNS)-Active Agents

The risk of using vilazodone in combination with other CNS-active drugs has not been systematically evaluated. Consequently, use caution when vilazodone is prescribed in combination with other CNS-active drugs.

Monoamine Oxidase Inhibitors (MAOI)

Adverse reactions, some of which are serious or fatal, can develop in patients who use MAOIs or who have recently been discontinued from a MAOI and started on antidepressant(s) with pharmacological properties similar to vilazodone (e.g. SSRIs), or who have recently had SSRI therapy discontinued prior to initiation of an MAOI. Do not prescribe vilazodone concomitantly with an MAOI or within 14 days of discontinuing or starting an MAOI.

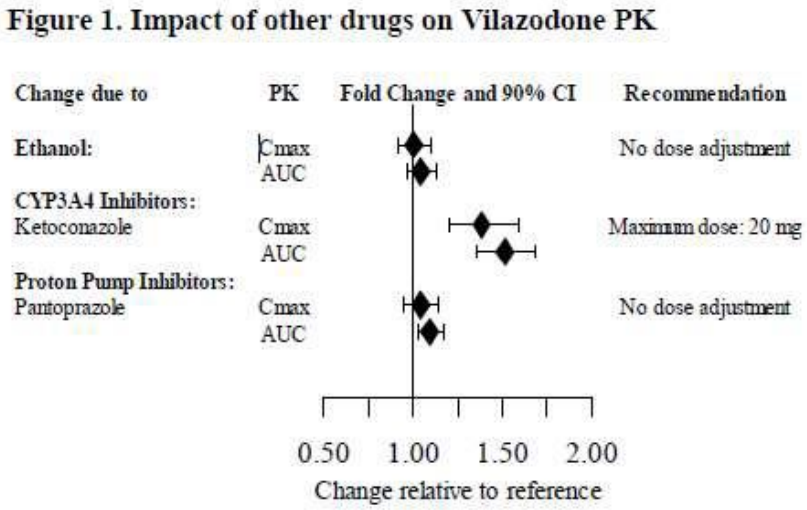
Serotonergic Drugs

Based on the mechanism of action of vilazodone and the potential for serotonin toxicity, also known as serotonin syndrome, caution is advised when vilazodone is coadministered with other drugs that may affect the serotonergic neurotransmitter systems (e.g., MAOI, SSRIs, SNRIs, triptans, buspirone, tramadol, and tryptophan products etc.).

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. Patients receiving warfarin therapy should be carefully monitored when vilazodone is initiated or discontinued.

Figure: Potential for Other Drugs to Affect Vilazodone



Inhibitors of CYP3A4

Metabolism by CYP3A4 is a major elimination pathway for vilazodone. Concomitant use of vilazodone and strong inhibitors of CYP3A4 (e.g., ketoconazole) can increase vilazodone plasma concentrations by approximately 50%. The vilazodone dose should be reduced to 20 mg if co-administered with a strong inhibitor of CYP3A4. During co-administration with moderate inhibitors of CYP3A4 (e.g., erythromycin), vilazodone dose should be reduced to 20 mg for patients with intolerable adverse events. No dose adjustment is recommended when vilazodone is co-administered with mild inhibitors of CYP3A4 (e.g., cimetidine).

Inducers of CYP3A4

Concomitant use of vilazodone with inducers of CYP3A4 has the potential to reduce vilazodone systemic exposure. However, the effect of CYP3A4 inducers on vilazodone plasma concentrations has not been evaluated.

Inhibitors of other CYP enzymes

Concomitant administration of vilazodone with inhibitors of CYP2C19 and CYP2D6 is not expected to alter plasma concentrations of vilazodone. These isoforms are minor elimination pathways in the metabolism of vilazodone. *In vitro* studies have shown that CYP1A2, CYP2A6, CYP2C9 and CYP2E1 have minimal contribution to the metabolism of vilazodone.

Potential for Vilazodone to Affect Other Drugs

Drugs metabolized by CYP1A2, CYP2C9, CYP2D6, CYP3A4 or CYP2C19

Co-administration of vilazodone with substrates for CYP1A2, CYP2C9, CYP3A4, or CYP2D6 is unlikely to result in clinically significant changes in the concentrations of the CYP substrates. A reported study in healthy subjects found that vilazodone (20 mg/day for 8-10 days) had no effect on the pharmacokinetics of caffeine, flurbiprofen, nifedipine or debrisoquine, probes for CYP1A2, CYP2C9, CYP3A4, and CYP2D6, respectively. Vilazodone co-administration with mephenytoin to healthy subjects resulted in a small (11%) increase in mephenytoin biotransformation, suggestive of a minor induction of CYP2C19.

Drugs metabolized by CYP2C8

Co-administration of vilazodone with a CYP2C8 substrate may lead to an increase in concentration of the other drug.

Induction of CYP isoforms

Vilazodone did not induce CYP1A1, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4 or 3A5 in an *in vitro* study in cultured human hepatocytes. Chronic administration of vilazodone is unlikely to induce the metabolism of drugs metabolized by these major CYP isoforms.

Drugs Highly Bound to Plasma Protein

The interaction between vilazodone and other highly protein-bound drugs has not been evaluated. Because vilazodone is highly bound to plasma protein, administration of vilazodone to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Teratogenic Effects

Pregnancy Category C

Vilazodone caused some developmental toxicity in rats, but was not teratogenic in rats or rabbits. There are no adequate and well-controlled studies of vilazodone in pregnant women. When treating pregnant women with vilazodone, carefully consider whether the potential benefits outweigh the potential risks of treatment.

No teratogenic effects were observed when vilazodone was given to pregnant rats or rabbits during the period of organogenesis at oral doses up to 200 and 36 mg/kg/day, respectively. These doses are 48 and 17 times, in rats and rabbits, respectively, the maximum recommended human dose (MRHD) of 40 mg on a mg/m2 basis. Fetal body weight gain was reduced, and skeletal ossification was delayed in both rats and rabbits at these doses; these effects were not observed at doses up to 10 times the MRHD in rats or 4 times the MRHD in rabbits. When vilazodone was administered to pregnant rats at an oral dose of 30 times the MRHD during the period of organogenesis and throughout pregnancy and lactation, the number of live born pups was decreased. There was an increase in early postnatal pup mortality, and among surviving pups there was decreased body weight, delayed maturation, and decreased fertility in adulthood. There was some maternal toxicity at this dose. These effects were not seen at 6 times the MRHD.

Nonteratogenic Effects

Neonates exposed to serotonergic antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of serotonergic antidepressants or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome. Vilazodone caused some developmental toxicity in rats, but was not teratogenic in rats or rabbits.

Labor and Delivery

The effect of vilazodone on labor and delivery in humans is unknown. Vilazodone should be used during labor and delivery only if the potential benefit outweighs the potential risk.

Nursing Mothers

Vilazodone is excreted into the milk of lactating rats. The effect of vilazodone on lactation and nursing in humans is unknown. Breast feeding in women treated with vilazodone should be considered only if the potential benefit outweighs the potential risk to the child.

Pediatric Use

Clinical studies on the use of vilazodone in pediatric patients have not been conducted; therefore, the safety and effectiveness of vilazodone in the pediatric population have not been established. Vilazodone is not approved for use in pediatric patients.

Geriatric Use

No dose adjustment is recommended on the basis of age (see Figure 2). Results from a single-dose (20 mg) pharmacokinetic study in elderly (> 65 years-old) vs. young (24-55 years-old) subjects demonstrated that the pharmacokinetics were generally similar between the two age groups. Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event. Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event.

Hepatic Impairment

Vilazodone is eliminated primarily by hepatic metabolism. In mild and moderate hepatic impairment, no dose adjustment is necessary (see Figure 2). Vilazodone has not been studied in patients with severe hepatic impairment.

Renal Impairment

In mild, moderate, and severe renal impairment, no dose adjustment is necessary.

4.7. Effects on ability to drive and use machines

Vilazodone can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how vilazodone affects you.

4.8. Undesirable effects

Clinical Studies Experience

The most commonly observed adverse reactions in vilazodone treated MDD patients in reported placebo-controlled studies (incidence ≥ 5% and at least twice the rate of placebo) were: diarrhea, nausea, vomiting, and insomnia.

The safety of vilazodone was evaluated in 2,177 patients (18-70 years of age) diagnosed with MDD who participated in clinical studies, representing 552 patient-years of exposure. In an open-label 52 week study at 40 mg daily, 599 patients were exposed to vilazodone for a total of 348 patient-years.

The information presented in these sections was derived from reported studies of vilazodone 40 mg daily in major depressive disorder including: 1) 2 placebo-controlled 8-week studies in 861 patients, including 436 receiving vilazodone; and 2) an open-label 52-week study of 599 patients. These studies included a titration period of 10 mg daily for 7 days followed by 20 mg daily for 7 days. In these reported clinical trials, vilazodone was administered with food.

Because clinical trials are conducted under widely varying conditions and varying lengths of time, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect rates observed in practice.

Adverse reactions reported as reasons for discontinuation of treatment

In the reported placebo-controlled studies of MDD there was no single adverse reaction leading to discontinuation in > 1% of the patients. Overall, 7.1% of the patients who received vilazodone discontinued treatment due to an adverse reaction, compared with 3.2% of placebo-treated patients in these studies.

Common adverse reactions in reported placebo-controlled MDD studies

Below table shows the incidence of common adverse reactions that occurred in ≥ 2% of vilazodone-treated MDD patients (and greater than in placebo-treated patients) in the reported placebo-controlled studies.

Table: Incidence of common adverse reactions

System Organ Class **Preferred Term**	**Vilazodone 40 mg/day N = 436**	**Placebo N = 433**
Gastrointestinal disorders		
Diarrhea	28	9
Nausea	23	5
Dry mouth	8	5
Vomiting	5	1
Dyspepsia	3	2
Flatulence	3	2
Gastroenteritis	3	<1
Nervous system disorders		
Dizziness	9	5
Somnolence	3	2
Paresthesia	3	1
Tremor	2	0
Psychiatric disorders		
Insomnia	6	2
Abnormal dreams	4	1
Libido decreased	4	<1
Restlessness *	3	<1
Orgasm abnormal**	3	0
General disorders		

System Organ Class Preferred Term	Vilazodone 40 mg/day N = 436	Placebo N = 433
Fatigue	4	3
Feeling jittery	2	<1
Cardiac disorders		
Palpitations	2	<1
Musculoskeletal and connective tissue disorders		
Arthralgia	3	2
Reproductive system and breast disorders		
Delayed ejaculation***	2	0
Erectile dysfunction***	2	1
Metabolism and nutrition disorders		
Arthralgia	**3**	**2**
Reproductive system and breast disorders		
Delayed ejaculation***	**2**	**0**
Erectile dysfunction***	**2**	**1**
Increased appetite	**2**	**1**

*Includes restlessness, akathisia, and restless legs syndrome
**Includes orgasm abnormal and anorgasmia
***Male patients only (Placebo n=182; Vilazodone n=170)

Table: Sexual Adverse Reactions: Percentage in the Placebo-Controlled Studies

	Males		Females	
Preferred Term	Vilazodone N= 170	Placebo N= 182	Vilazo done N=266	Placebo N=251
Decreased libido	5	0	3	<1
Abnormal orgasm*	4	0	2	0
Delayed ejaculation	2	0	–	–

Erectile dysfunction	2	1	–	–
Sexual dysfunction	2	0	<1	<1

*Includes anorgasmia

Laboratory Tests

Vilazodone has not been associated with any clinically important changes in laboratory test parameters in serum chemistry (including liver function tests), Hematology and urinalysis, as measured in reported placebo-controlled studies. These studies include analysis of (1) mean change from baseline and (2) the proportion of patients meeting criteria for potentially clinically significant changes from baseline. Results from a 52-week open-label study were consistent with the findings from the placebo-controlled studies.

ECG

Vilazodone has not been associated with any clinically significant effect on ECG parameters, including QT, QTc, PR and QRS intervals, or with any arrhythmogenic potential. ECGs were evaluated in a thorough QTc study at doses up to 80 mg daily with food and in the placebo-controlled studies.

Vital Signs

Vilazodone has not been associated with any clinically significant effect on vital signs, including systolic and diastolic blood pressure and heart rate, as measured in in reported studies placebo-controlled studies. These reported studies included analyses of (1) change from baseline, and (2) the proportion of patients meeting criteria for potentially clinically significant changes from baseline. Results from a 52-week open-label study were consistent with the findings from the placebo-controlled studies.

Weight

Vilazodone had no effect on body weight as measured by the mean change from baseline in the 8-week, reported placebo-controlled studies. The mean changes in weight were +0.16 kg in the Vilazodone group and +0.18 kg in the placebo group. The proportions of patients with a weight gain > 7% were 0.9% in the Vilazodone group and 1.2% in the placebo group.

Other adverse reactions observed in clinical studies

The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Reactions are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients:

Cardiac disorders: infrequent: ventricular extrasystoles

Eye disorders: frequent: vision blurred, dry eye; infrequent: cataracts

General disorders: infrequent: feeling abnormal

Metabolism and nutrition disorders: frequent: decreased appetite

Nervous System: frequent: sedation, migraine; infrequent: dysgeusia

Psychiatric disorders: infrequent: panic attack, mania

Renal and Urinary disorder: infrequent: pollakiuria

Skin and subcutaneous tissue disorders: frequent: hyperhidrosis, night sweats

Reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

4.9. Overdose

Human Experience

There is limited clinical experience regarding human overdosage with Vilazodone. 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

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 overdosage with any drug. 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.

5. Pharmacological properties

5.1. 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.

5.2. Pharmacodynamic properties

Pharmacodynamic effects: 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 (IC50= 1.6 nM). Vilazodone also binds selectively with high affinity to 5-HT1A receptors (IC50=2.1 nM) and is a 5-HT1A 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.

5.3. Pharmacokinetic properties

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.

Absorption

Vilazodone concentrations peak at a median of 4-5 hours (Tmax) after Vilazodone administration and decline with a terminal half-life of approximately 25 hours. The absolute bioavailability of vilazodone is 72% with food. Vilazodone AUC and Cmax in the fasted state can be decreased by approximately 50% and 60%, respectively, compared to the fed state. Administration without food can result in inadequate drug concentrations and may reduce effectiveness.

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 coadministration 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. In vitro studies indicate that vilazodone is unlikely to inhibit or induce the metabolism of substrates for CYP1A1, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4 or 3A5, except for CYP2C8. The effect of vilazodone on CYP2C8 activity has not been tested in vivo. The presence of mild or moderate renal impairment, or mild or moderate hepatic impairment did not affect the apparent clearance of vilazodone.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Carcinogenesis

Carcinogenicity studies were conducted in which B6C3F1mice and Wistar rats were given oral doses of vilazodone up to 135 and 150 mg/kg/day, respectively, for 2 years. These doses are approximately 16.5 and 36 times the maximum recommended human dose (MRHD) of 40 mg, respectively, on a mg/m2 basis

In mice, the incidence of hepatocellular carcinomas was increased in males at 16.5 times the MRHD; this finding was not observed at 5.5 times the MRHD. The incidence of malignant mammary gland tumors was numerically increased in females at 5.5 and 16.5 times the

MRHD, with statistical significance at 16.5 the MHRD; this finding was not observed at 1.8 times the MRHD. Elevated prolactin levels were observed in a 2-week study of vilazodone administered at 5.5 and 33 times the MRHD. Increases in prolactin levels are known to cause mammary tumors in rodents. In the rat study, vilazodone was not carcinogenic in either sex at doses up to 36 times the MRHD.

Mutagenesis

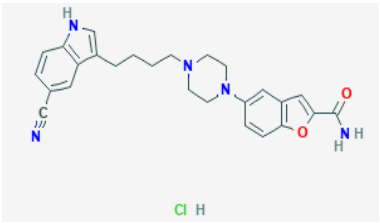
Vilazodone was not mutagenic in the in vitro bacterial reverse mutation assay (Ames test). Vilazodone was negative in the in vitro V79/HGRPT mammalian cell forward mutation assay. Vilazodone was clastogenic in two in vitro mammalian cell chromosome aberration assays. However, vilazodone was negative for clastogenic activity in both an in vivo rat bone marrow chromosome aberration assay and a micronucleus test. Vilazodone was also negative in an in vivo/in vitro unscheduled DNA synthesis assay in rats.

Impairment of Fertility

Treatment of rats with vilazodone at a dose of 125 mg/kg, which is 30 times the MRHD of 40 mg on a mg/m2 basis, caused impairment of male fertility with no effect on female fertility. Impaired male fertility was not observed at 6 times the MRHD.

7. Description

Vilazodone Hydrochloride is 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl]-1-benzofuran-2-carboxamide; hydrochloride having molecular weight of 478 g/mol and molecular formula of $C_{26}H_{28}ClN_5O_2$. The chemical structure is as below:



VALZ 20

Vilazodone Hydrochloride Tablets are blue coloured, oval shaped, biconvex film coated tablets debossed with “20” on one side and plain surface on other side. The excipients used are Lactose, Microcrystalline Cellulose, Hydroxypropyl Betacyclodextrin, Crospovidone, Colloidal Silicon Dioxide, Magnesium Stearate and Opadry II orange 85F530080.

VALZ 40

Vilazodone Hydrochloride Tablets are orange coloured, oval shaped, biconvex film coated tablets debossed with “40” on one side and plain surface on other side. The excipients used are Lactose, Microcrystalline Cellulose, Hydroxypropyl Betacyclodextrin, Crospovidone, Colloidal Silicon Dioxide, Magnesium Stearate and Opadry II blue 85F505061.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

VALZ is available in blister strip of 10 tablets.

8.4. Storage and handing instructions

Store below 30°C, protected from light and moisture..

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Manufactured in India by:

MSN Laboratories Private Limited

Formulation Division, Unit-II,

Sy.No. 1277, 1319 to 1324, Nandigama (Village & Mandal),

Rangareddy (District), Telangana – 509228, India

11. Details of permission or licence number with date

Mfg Lic No. 5/MN/TS/2014/F/G issued on 20.08.2015

12. Date of revision

FEB-2026

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/VALZ 20, 40mg /FEB 2026/04/PI