For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

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Trazodone Hydrochloride

Trazodone Hydrochloride Tablets U.S.P. 50 mg / 100 mg

COMPOSITION

Trazodone Hydrochloride 50mg

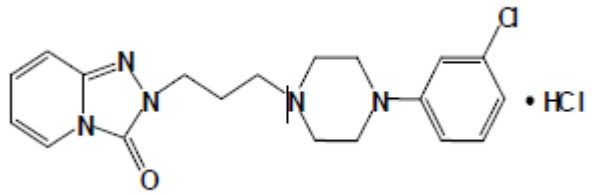
Each uncoated Tablet contains:
Trazodone Hydrochloride U.S.P. 50 mg
Excipients q.s.

Trazodone Hydrochloride 100mg

Each uncoated Tablet contains:
Trazodone Hydrochloride U.S.P. 100 mg
Excipients q.s.

DESCRIPTION

Trazodone hydrochloride is a triazolopyridine. It is a white, odorless crystalline powder which is freely soluble in water. Trazodone is formulated as the hydrochloride salt, which is chemically designated as 2-[3-[4-(*m*-Chlorophenyl)-1-piperazinyl]propyl]-*s*-triazolo[4,3-*a*]pyridin-3(2*H*)-one monohydrochloride. Trazodone Hydrochloride has the empirical formula $C_{19}H_{22}ClN_5O \cdot HCl$ representing a molecular weight of 408.32. Structural Formula:



CLINICAL PHARMACOLOGY

Pharmacodynamic

Preclinical studies have reported that trazodone selectively inhibits neuronal reuptake of serotonin and acts as an antagonist at 5-HT-$_{2A/2C}$ serotonin receptors.

Trazodone is not a monoamine oxidase inhibitor and, unlike amphetamine-type drugs, does not stimulate the central nervous system. Trazodone antagonizes alpha 1-adrenergic receptors, a property which may be associated with postural hypotension.

Pharmacokinetic

Absorption

In humans, trazodone hydrochloride is well absorbed after oral administration without selective localization in any tissue. When trazodone hydrochloride is taken shortly after ingestion of food, there may be an increase in the amount of drug absorbed, a decrease in maximum concentration and a lengthening in the time to maximum concentration. Peak plasma levels occur approximately one hour after dosing when trazodone hydrochloride is taken on an empty stomach or two hours after dosing when taken with food.

Metabolism
In vitro studies in human liver microsomes show that trazodone is metabolized to an active metabolite, m-chlorophenylpiperazine (mCPP) by cytochrome P450 3A4 (CYP3A4). Other metabolic pathways that may be involved in metabolism of trazodone have not been well characterized.

Elimination
In some patients trazodone may accumulate in the plasma.

Drug-Drug Interactions
In vitro drug metabolism studies reveal that trazodone is a substrate of the cytochrome P450 3A4 (CYP3A4) enzyme and trazodone metabolism can be inhibited by the CYP3A4 inhibitors ketoconazole, ritonavir, and indinavir. The effect of short-term administration of ritonavir (200 mg twice daily, 4 doses) on the pharmacokinetics of a single dose of trazodone (50 mg) has been studied in 10 healthy subjects. The C_{max} of trazodone increased by 34%, the AUC increased 2.4-fold, the half-life increased by 2.2-fold, and the clearance decreased by 52%. Adverse effects including nausea, hypotension, and syncope were observed when ritonavir and trazodone were co-administered.

Carbamazepine induces CYP3A4. Following co-administration of carbamazepine 400 mg/day with trazodone 100 mg to 300 mg daily, carbamazepine reduced plasma concentrations of trazodone (as well as mCPP) by 76 and 60%, respectively, compared to precarbamazepine values.

For those patients who responded to trazodone, one-third of the inpatients and one-half of the outpatients had a significant therapeutic response by the end of the first week of treatment. Three-fourths of all responders demonstrated a significant therapeutic effect by the end of the second week. One-fourth of responders required 2–4 weeks for a significant therapeutic response.

INDICATION
Trazodone hydrochloride tablets are indicated for the treatment of major depressive disorder (MDD) in adults**.**

DOSAGE AND ADMINISTRATION
The dosage should be initiated at a low level and increased gradually, noting the clinical response and any evidence of intolerance. Occurrence of drowsiness may require the administration of a major portion of the daily dose at bedtime or a reduction of dosage. Trazodone hydrochloride tablets should be taken shortly after a meal or light snack. Symptomatic relief may be seen during the first week, with optimal antidepressant effects typically evident within two weeks. Twenty-five percent of those who respond to trazodone require more than two weeks (up to four weeks) of drug administration.

CONTRAINDICATION

Monoamine Oxidase Inhibitors (MAOIs)

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

Starting trazodone 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

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 trials of antidepressant drugs (SSRIs and others) reported 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 placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (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 1,000 patients treated) are provided in following table.

Age Range	**Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated**
	Increases Compared to Placebo
< 18	14 additional cases
18 – 24	5 additional cases

	Decreases Compared to Placebo
25 – 64	1 fewer case
≥ 65	6 fewer cases

No suicides reported in any of the pediatric trials. There were suicides in the adult trials, 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 trials 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 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.

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 health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for trazodone should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Serotonin Syndrome
The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including trazodone, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, busipirone, 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, and 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 trazodone with MAOIs intended to treat psychiatric disorders is contraindicated. Trazodone 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 trazodone. Trazodone should be discontinued before initiating treatment with the MAOI.

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

Angle Closure Glaucoma
The pupillary dilation that occurs following use of many antidepressant drugs including trazodone may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Screening Patients for Bipolar Disorder and Monitoring for Mania/Hypomania
A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed 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 for clinical worsening and suicide risk 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 trazodone is not approved for use in treating bipolar depression.

QT Prolongation and Risk of Sudden Death
Trazodone is known to prolong the QT/QTc interval. Some drugs that prolong the QT/QTc interval can cause Torsades de Pointes with sudden, unexplained death. The relationship of QT prolongation is clearest for larger increases (20 msec and greater), but it is possible that smaller

QT/QTc prolongations may also increase risk, especially in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or a genetic predisposition to prolonged QT/QTc.

Although Torsades de Pointes has not been observed with the use of Trazodone Hydrochloride at recommended doses in premarketing trials, experience is too limited to rule out an increased risk. However, there have been postmarketing reports of Torsades de Pointes with the immediate-release form of trazodone (in the presence of multiple confounding factors), even at doses of 100 mg per day or less.

Use in Patients with Heart Disease
Trazodone hydrochloride is not recommended for use during the initial recovery phase of myocardial infarction. Caution should be used when administering trazodone to patients with cardiac disease and such patients should be closely monitored, since antidepressant drugs (including trazodone hydrochloride) may cause cardiac arrhythmias.

QT prolongation has been reported with trazodone therapy. Clinical studies in patients with pre-existing cardiac disease indicate that trazodone may be arrhythmogenic in some patients in that population. Arrhythmias identified include isolated PVCs, ventricular couplets, tachycardia with syncope, and Torsades de Pointes. Postmarketing events have been reported at doses of 100 mg or less with the immediate-release form of trazodone.

Concomitant administration of drugs that prolong the QT interval or that are inhibitors of CYP3A4 may increase the risk of cardiac arrhythmia.

Orthostatic Hypotension and Syncope
Hypotension, including orthostatic hypotension and syncope has been reported in patients receiving trazodon.. Concomitant use with an antihypertensive may require a reduction in the dose of the antihypertensive drug.

Abnormal Bleeding
Postmarketing data have reported an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal (GI) bleeding. While no association between trazodone and bleeding events, in particular GI bleeding, was shown, patients should be cautioned about potential risk of bleeding associated with the concomitant use of trazodone and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding. Other bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages.

Interaction with MAOIs
In patients receiving serotonergic drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal reactions including hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuation in vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued antidepressant treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of serotonergic

antidepressants and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that trazodone should not be used in combination with an MAOI or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping trazodone before starting an MAOI.

Priapism

Rare cases of priapism (painful erections greater than 6 hours in duration) were reported in men receiving trazodone. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Men who have an erection lasting greater than 6 hours, whether painful or not, should immediately discontinue the drug and seek emergency medical attention.Trazodone should be used with caution in men who have conditions that might predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia), or in men with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease).

Hyponatremia

Hyponatremia may occur as a result of treatment with antidepressants. In many cases, this 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 antidepressants. Also, patients taking diuretics or who are otherwise volume-depleted can be at greater risk. Discontinuation of trazodone should be considered 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.

Potential for Cognitive and Motor Impairment

Trazodone may cause somnolence or sedation and may impair the mental and/or physical ability required for the performance of potentially hazardous tasks. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Discontinuation Symptoms

Withdrawal symptoms including anxiety, agitation and sleep disturbances, have been reported with trazodone. Clinical experience suggests that the dose should be gradually reduced before complete discontinuation of the treatment.

DRUG INTERACTION

Monoamine Oxidase Inhibitors (MAOIs)

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

Central Nervous System (CNS) Depressants
Trazodone may enhance the response to alcohol, barbiturates, and other CNS depressants.

Cytochrome P450 3A4 Inhibitors
In vitro drug metabolism studies suggest that there is a potential for drug interactions when trazodone is given with cytochrome P450 3A4 (CYP3A4) inhibitors. The effect of short-term administration of ritonavir (200 mg twice daily, 4 doses) on the pharmacokinetics of a single dose of trazodone (50 mg) has been studied in 10 healthy subjects. The Cmax of trazodone increased by 34%, the AUC increased 2.4-fold, the half-life increased by 2.2-fold, and the clearance decreased by 52%. Adverse effects including nausea, hypotension, and syncope were observed when ritonavir and trazodone were co-administered. It is likely that ketoconazole, indinavir, and other CYP3A4 inhibitors such as itraconazole may lead to substantial increases in trazodone plasma concentrations with the potential for adverse effects. If trazodone is used with a potent CYP3A4 inhibitor, the risk of cardiac arrhythmia may be increased and a lower dose of trazodone should be considered.

Cytochrome P450 Inducers (e.g., carbamazepine)
Carbamazepine induces CYP3A4. Following co-administration of carbamazepine 400 mg per day with trazodone 100 mg to 300 mg daily, carbamazepine reduced plasma concentrations of trazodone and mchlorophenlypiperazine (an active metabolite) by 76% and 60% respectively, compared to precarbamazepine values. Patients should be closely monitored to see if there is a need for an increased dose of trazodone when taking both drugs.

Digoxin and Phenytoin
Increased serum digoxin or phenytoin levels have been reported in patients receiving trazodone concurrently with either of these drugs. Monitor serum levels and adjust dosages as needed.

NSAIDs, Aspirin, or Other Drugs Affecting Coagulation or Bleeding
Due to a possible association between serotonin modulating drugs and gastrointestinal bleeding, patients should be monitored for and cautioned about the potential risk of bleeding associated with the concomitant use of trazodone and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding.

Warfarin
There have been reports of altered (either increased or decreased) prothrombin times in taking both warfarin and trazodone.

USE IN SPECIFIC POPULATIONS
Pregnancy Category C
Trazodone has been shown to cause increased fetal resorption and other adverse effects on the fetus in two studies using the rat when given at dose levels approximately 30–50 times the proposed maximum human dose. There was also an increase in congenital anomalies in one of three rabbit studies at approximately 15 – 50 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. Trazodone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Trazodone and/or its metabolites have been found in the milk of lactating rats, suggesting that the drug may be secreted in human milk. Caution should be exercised when trazodone is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in the pediatric population have not been established trazodone should not be used in children or adolescents.

Geriatric Use
Of 202 patients treated with trazodone Hydrochloride in the clinical trial, there were 9 patients older than 65. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical literature and experience with trazodone have not identified differences in responses between elderly and younger patients. However, as experience in the elderly with trazodone Hydrochloride is limited, it should be used with caution in geriatric patients.

Antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients who may be at greater risk for this adverse reaction.

Renal Impairment
Trazodone has not been studied in patients with renal impairment. Trazodone should be used with caution in this population.

Hepatic Impairment
Trazodone has not been studied in patients with hepatic impairment. Trazodone should be used with caution in this population

ADVERSE EFFECTS

- Clinical Worsening and Suicide Risk.
- Serotonin Syndrome or NMS-like Reactions.
- QT Prolongation and Risk of Sudden Death.
- Orthostatic Hypotension.
- Abnormal bleeding events.
- Priapism
- Hyponatremia
- Cognitive and Motor Impairment.
- Discontinuation symptoms

The most common adverse reactions (reported in ≥5% and at twice the rate of placebo) are: somnolence/sedation, dizziness, constipation, vision blurred.

Table presents the summary of adverse events (AEs) leading to discontinuation of trazodone Hydrochloride treatment with an incidence of at least 1% and at least twice that for placebo.

AEs with discontinuation as action taken (≥1% incidence and incidence 2x placebo)	
	Trazodone Hydrochloride **N = 202**
Somnolence/Sedation	8 (4.0%)
Dizziness	7 (3.5%)
Confusional state	2 (1.0%)
Coordination abnormal	2 (1.0%)
Headache	2 (1.0%)
Nausea	2 (1.0%)
Balance disorder / Gait disturbance	2 (1.0%)

Clinical Studies Experience
The data described below reflects exposure in a clinical trial of 406 patients, including 204 exposed to placebo and 202 exposed to trazodone. Patients were between 18-80 years of age and 69.3% and 67.5% of patients had at least one previous episode of depression in the last 24 months in the placebo and active-treated group, respectively. In individual patients, doses were flexible and ranged from 150 to 375 mg per day. The mean daily dose during the 6-week treatment period was 310 mg. The tablets were administered orally and were given once a day for a total duration of 8 weeks, including the titration period.

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

Following Table presents the summary of all treatment emergent AEs that occurred at an incidence of ≥ 5% in the trazodone group, whether considered by the clinical investigator to be related to the study drug or not.

Most Common Treatment Emergent Adverse Events (≥ 5% of Patients on Active Treatment		
Preferred Term	**Placebo N = 204**	**Trazodone N = 202**
Somnolence/Sedation	39 (19%)	93(46%)
Headache	55 (27%)	67(33%)
Dry mouth	26 (13%)	51(25%)
Dizziness	25 (12%)	50(25%)
Nausea	26 (13%)	42(21%)
Fatigue	17 (8%)	30(15%)
Diarrhea	23 (11%)	19 (9%)
Constipation	4 (2%)	16 (8%)
Back pain	7 (3%)	11 (5%)
Vision blurred	0 (0%)	11 (5%)

Sexual Dysfunction Adverse events related to sexual dysfunction (regardless of causality) were reported by 4.9% and
1.5% of patients treated with Trazodone Hydrochloride and placebo, respectively. In the Trazodone Hydrochloride group, ejaculation disorders occurred in 1.5% of patients, decreased libido occurred in 1.5% of patients, and erectile dysfunction and abnormal orgasm < 1% of patients.

Vital Signs and Weight
There were no notable changes in vital signs (blood pressure, respiratory rate, pulse) or weight in either treatment group.

Following is a list of treatment-emergent adverse reactions with an incidence of ≥ 1% to < 5% (i.e., less common) in patients treated with Trazodone Hydrochloride. This listing is not intended to include reactions (i) already listed in previous tables or elsewhere in the labeling (ii) for which the association with treatment is remote, (iii) which were so general as to be uninformative, and (iv) which were not considered to have significant clinical implications. Reactions are classified by body-system using the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in less than 1/100 patients.

Ear and Labyrinth Disorders:
Infrequent*:* hypoacusis, tinnitus, vertigo

Eye Disorders:
Frequent*:* visual disturbance; *Infrequent:* dry eye, eye pain, photophobia

Gastrointestinal Disorders:
Frequent**:** abdominal pain, vomiting; *Infrequent:* reflux esophagitis

General Disorders and Administration Site Conditions:
Frequent**:** edema; *Infrequent:* gait disturbance

Immune System Disorders:
I*nfrequent:* hypersensitivity

Musculoskeletal and Connective Tissue Disorders:
*Frequent***:** musculoskeletal complaints, myalgia; *Infrequent:* muscle twitching

Nervous System Disorders:
*Frequent***:** coordination abnormal, dysgeusia, memory impairment, migraine, paraesthesia, tremor; *Infrequent:* amnesia, aphasia, hypoesthesia, speech disorder

Psychiatric Disorders:
*Frequent***:** agitation, confusional state, disorientation

Renal and Urinary Disorders:
*Frequent***:** micturition urgency; *Infrequent:* bladder pain, urinary incontinence

Respiratory, Thoracic and Mediastinal Disorders:
*Frequent***:** dyspnea

Skin and Subcutaneous Tissue Disorders:
*Frequent***:** night sweats; *Infrequent:* acne, hyperhidrosis, photosensitivity reaction

Vascular Disorders:
Infrequent: flushing

Postmarketing Experience
Spontaneous reports regarding trazodone hydrochloride received from postmarketing experience include the following: abnormal dreams, agitation, alopecia, anxiety, aphasia, apnea, ataxia, breast enlargement or engorgement, cardiospasm, cerebrovascular accident, chills, cholestasis, clitorism, congestive heart failure, diplopia, edema, extrapyramidal symptoms, grand mal seizures, hallucinations, hemolytic anemia, hirsutism, hyperbilirubinemia, increased amylase, increased salivation, insomnia, leukocytosis, leukonychia, jaundice, lactation, liver enzyme alterations, methemoglobinemia, nausea/vomiting (most frequently), paresthesia, paranoid reaction, priapism *and* Patient Counseling Information, pruritus, psoriasis, psychosis, rash, stupor, inappropriate ADH syndrome, tardive dyskinesia, unexplained death, urinary incontinence, urinary retention, urticaria, vasodilation, vertigo, and weakness.

Cardiovascular system effects which have been reported include the following: conduction block, orthostatic hypotension and syncope, palpitations, bradycardia, atrial fibrillation, myocardial infarction, cardiac arrest, arrhythmia, ventricular ectopic activity, including ventricular tachycardia and QT prolongation. In postmarketing surveillance, prolonged QT interval, Torsades de pointes, and ventricular tachycardia have been reported with the immediate-release form of trazodone at doses of 100 mg per day or less.

OVERDOSE

Human Experience

Death from overdose has occurred in patients ingesting trazodone and other CNS depressant drugs concurrently (alcohol; alcohol and chloral hydrate and diazepam; amobarbital; chlordiazepoxide; or meprobamate).

The most severe reactions reported to have occurred with overdose of trazodone alone have been priapism, respiratory arrest, seizures, and ECG changes, including QT prolongation. The reactions reported most frequently have been drowsiness and vomiting. Overdosage may cause an increase in incidence or severity of any of the reported adverse reactions.

Management of Overdose

There is no specific antidote for trazodone Hydrochloride overdose. Treatment should consist of those general measures employed in the management of overdosage with any drug effective in the treatment of major depressive disorder. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients. Activated charcoal should be administered. Forced diuresis may be useful in facilitating elimination of the drug.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store at a temperature not exceeding 30°C.
Keep out of reach of Children

PRESENTATIONS

Trazodone Hydrochloride Tablets 50 mg and 100 mg available in Alu-Alu blister Strips of 10 tablets.

MARKETED BY:

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA