

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use trazodone hydrochloride tablets, USP safely and effectively. See full prescribing information for trazodone hydrochloride tablets, USP.

## TRAZODONE HYDROCHLORIDE tablets, USP for oral use

Initial U.S. Approval: 1981

### **WARNING: SUICIDAL THOUGHTS and BEHAVIORS** *See full prescribing information for complete boxed warning.*

- Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients (5.1)
- Closely monitor for clinical worsening and emergence of suicidal thoughts and behaviors (5.1)
- Trazodone hydrochloride tablets are not approved for use in pediatric patients (8.4)

### INDICATIONS AND USAGE

Trazodone hydrochloride tablets, USP are a selective serotonin reuptake inhibitor indicated for the treatment of major depressive disorder (MDD) (1).

### DOSAGE AND ADMINISTRATION

- Starting dose: 150 mg in divided doses daily. May be increased by 50 mg per day every three to four days. Maximum dose: 400 mg per day in divided doses (2).
- Trazodone hydrochloride tablets should be taken shortly after a meal or light snack (2).
- Tablets should be swallowed whole or broken in half along the score line, and should not be chewed or crushed (2).
- When discontinued, gradual dose reduction is recommended (2).

### DOSAGE FORMS AND STRENGTHS

- Scored tablets: 50 mg, 100 mg, 150 mg and 300 mg (3).

### CONTRAINDICATIONS

- Concomitant use of monoamine oxidase inhibitors (MAOIs), or use within 14 days of stopping MAOIs (4).

### WARNINGS AND PRECAUTIONS

- Serotonin Syndrome: Increased risk when co-administered with other serotonergic agents (e.g., SSRI, SNRI, triptans), but also when taken alone. If it occurs, discontinue trazodone hydrochloride tablets and initiate supportive treatment (5.2).
- Cardiac Arrhythmias: Increases the QT interval. Avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval (5.3).

- Orthostatic Hypotension and Syncope: Warn patients of risk and symptoms of hypotension (5.4).
- Increased Risk of Bleeding: Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), other antiplatelet drugs, warfarin, and other anticoagulants may increase this risk (5.5).
- Priapism: Cases of painful and prolonged penile erections and priapism have been reported. Immediate medical attention should be sought if signs and symptoms of prolonged penile erections or priapism are observed (5.6).
- Activation of Mania or Hypomania: Screen for bipolar disorder and monitor for mania or hypomania (5.7).
- Potential for Cognitive and Motor Impairment: Has potential to impair judgment, thinking, and motor skills. Advise patients to use caution when operating machinery (5.9).
- Angle-Closure Glaucoma: Avoid use of antidepressants, including trazodone hydrochloride tablets, in patients with untreated anatomically narrow angles (5.10)

### ADVERSE REACTIONS

Most common adverse reactions (incidence  $\geq$  5% and twice that of placebo) are: edema, blurred vision, syncope, drowsiness, fatigue, diarrhea, nasal congestion, weight loss (6).

To report SUSPECTED ADVERSE REACTIONS, contact **Torrent Pharma Inc. at 1-800-912-9561 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### DRUG INTERACTIONS

- CNS Depressants: Trazodone may enhance effects of alcohol, barbiturates, or other CNS depressants (7).
- CYP3A4 Inhibitors: Consider Trazodone dose reduction based on tolerability (2.5, 7).
- CYP3A4 Inducers: Increase in Trazodone dosage may be necessary (2.5, 7).
- Digoxin or Phenytoin: Monitor for increased digoxin or phenytoin serum levels (7).
- Warfarin: Monitor for increased or decreased prothrombin time (7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2022

## FULL PRESCRIBING INFORMATION:CONTENTS\*

### WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 Dose Selection
- 2.2 Important Administration Instructions
- 2.3 Screen for Bipolar Disorder Prior to Starting Trazodone Hydrochloride Tablets
- 2.4 Switching to or from Monoamine Oxidase Inhibitor Antidepressant
- 2.5 Dosage Recommendations for Concomitant Use with Strong CYP3A4 Inhibitors or Inducers
- 2.6 Discontinuation of Treatment with Trazodone Hydrochloride Tablets

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients
- 5.2 Serotonin Syndrome
- 5.3 Cardiac Arrhythmias
- 5.4 Orthostatic Hypotension and Syncope
- 5.5 Increased Risk of Bleeding
- 5.6 Priapism
- 5.7 Activation of Mania or Hypomania
- 5.8 Discontinuation Syndrome
- 5.9 Potential for Cognitive and Motor Impairment
- 5.10 Angle-Closure Glaucoma
- 5.11 Hyponatremia

#### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

#### 7 DRUG INTERACTIONS

- 7.1 Drugs Having Clinically Important Interactions with Trazodone Hydrochloride Tablets

#### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

#### 9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

#### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### 14 CLINICAL STUDIES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\* Sections or subsections omitted from the full prescribing information are not listed.

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## FULL PRESCRIBING INFORMATION

### WARNING: SUICIDAL THOUGHTS and BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors [see *Warnings and Precautions (5.1)*]. Trazodone hydrochloride tablets are not approved for use in pediatric patients [see *Use in Specific Populations (8.4)*].

## 1 INDICATIONS AND USAGE

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

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dose Selection

An initial dose of 150 mg/day in divided doses is suggested. The dosage should be initiated at a low-dose 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.

The dose may be increased by 50 mg/day every 3 to 4 days. The maximum dose for outpatients usually should not exceed 400 mg/day in divided doses. Inpatients (i.e., more severely depressed patients) may be given up to but not in excess of 600 mg/day in divided doses.

Once an adequate response has been achieved, dosage may be gradually reduced, with subsequent adjustment depending on therapeutic response.

### 2.2 Important Administration Instructions

Trazodone hydrochloride tablets can be swallowed whole or administered as a half tablet by breaking the tablet along the score line.

Trazodone hydrochloride tablets should be taken shortly after a meal or light snack.

### 2.3 Screen for Bipolar Disorder Prior to Starting Trazodone Hydrochloride Tablets

Prior to initiating treatment with trazodone hydrochloride tablets or another antidepressant, screen patients for a personal or family history of bipolar disorder, mania, or hypomania [see *Warnings and Precautions (5.7)*].

### 2.4 Switching to or from Monoamine Oxidase Inhibitor Antidepressant

At least 14 days must elapse between discontinuation of a monoamine oxidase inhibitor (MAOI) antidepressant and initiation of trazodone hydrochloride tablets. In addition, at least 14 days must elapse after stopping trazodone hydrochloride tablets before starting an MAOI antidepressant [see *Contraindications (4)*, *Warnings and Precautions (5.2)*].

## **2.5 Dosage Recommendations for Concomitant Use with Strong CYP3A4 Inhibitors or Inducers**

### Coadministration with Strong CYP3A4 Inhibitors

Consider reducing trazodone dose based on tolerability when trazodone is coadministered with a strong CYP3A4 inhibitor [see *Drug Interactions (7.1)*].

### Coadministration with Strong CYP3A4 Inducers

Consider increasing trazodone dose based on therapeutic response when trazodone is coadministered with a strong CYP3A4 inducer [see *Drug Interactions (7.1)*].

## **2.6 Discontinuation of Treatment with Trazodone Hydrochloride Tablets**

Adverse reactions may occur upon discontinuation of trazodone hydrochloride tablets [See *Warnings and Precautions (5.8)*]. Gradually reduce the dosage rather than stopping trazodone hydrochloride tablets abruptly whenever possible.

## **3 DOSAGE FORMS AND STRENGTHS**

50 mg Tablets, white to off white, round, biconvex, uncoated tablets debossed with “13” bisect “30” on one side and plain on other side.

100 mg Tablets, white to off white, round, biconvex, uncoated tablets debossed with “13” bisect “31” on one side and plain on other side.

150 mg Tablets, white to off white, oval, flat faced beveled edge uncoated tablets with a full bisect and two partial trisects. Debossed “13” bisect “32” on one side and “50 50 50” on other side.

300 mg white to off white, oval, flat faced beveled edge uncoated tablets with a full bisect and two partial trisects. Debossed “13” bisect “33” on one side and “100 100 100” on other side with middle “100” perpendicular to others.

## **4 CONTRAINDICATIONS**

Trazodone hydrochloride tablets are contraindicated in:

- Patients taking, or within 14 days of stopping, monoamine oxidase inhibitors (MAOIs), including MAOIs such as linezolid or intravenous methylene blue, because of an increased risk of serotonin syndrome [see *Warnings and Precautions (5.2)*, *Drug Interactions (7.1)*].

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients**

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and over 4,400 pediatric patients, the incidence of suicidal thoughts and behaviors in pediatric and young adult patients was greater in antidepressant-treated patients than in placebo-treated patients. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1,000 patients treated are provided in Table 1.

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 antidepressant drug effect on suicide.

**Table 1: Risk Differences of the Number of Cases of Suicidal Thoughts or Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Patients**

Age Range (years)	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1,000 Patients Treated
	Increases Compared to Placebo
< 18	14 additional patients
18 - 24	5 additional patients
	Decreases Compared to Placebo
25 - 64	1 fewer patient
≥ 65	6 fewer patients

It is unknown whether the risk of suicidal thoughts and behaviors in pediatric and young adult patients extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants delay the recurrence of depression.

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing trazodone hydrochloride tablets, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

## 5.2 Serotonin Syndrome

Serotonin-norepinephrine reuptake inhibitors (SNRIs) and SSRIs, including trazodone, can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is **increased 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, i.e., MAOIs [see Contraindications (4), Drug Interactions (7.1)]. Serotonin syndrome can also occur when these drugs are used alone.**

Serotonin syndrome signs and 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 gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of trazodone with MAOIs is contraindicated. In addition, do not initiate trazodone in a patient being treated with MAOIs such as linezolid or intravenous methylene blue. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection). If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking trazodone hydrochloride tablets, discontinue trazodone before initiating treatment with the MAOI [see Contraindications (4), Drug Interactions (7.1)].

Monitor all patients taking trazodone for the emergence of serotonin syndrome. Discontinue treatment with trazodone and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of trazodone with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms.

### **5.3 Cardiac Arrhythmias**

Clinical studies indicate that trazodone hydrochloride may be arrhythmogenic in patients with preexisting cardiac disease. Arrhythmias identified include isolated PVCs, ventricular couplets, tachycardia with syncope, and torsade de pointes. Postmarketing events, including torsade de pointes have been reported at doses of 100 mg or less with the immediate-release form of trazodone. Trazodone should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval. Trazodone 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) may cause cardiac arrhythmias [*see Adverse Reactions (6.2)*].

Trazodone prolongs the QT/QTc interval. The use of trazodone should be avoided in patients with known QT prolongation or in combination with other drugs that are inhibitors of CYP3A4 (e.g., itraconazole, clarithromycin, voriconazole), or known to prolong QT interval including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), certain antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and certain antibiotics (e.g., gatifloxacin). Concomitant administration of drugs may increase the risk of cardiac arrhythmia [*see Drug Interactions (7.1)*].

### **5.4 Orthostatic Hypotension and Syncope**

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

### **5.5 Increased Risk of Bleeding**

Drugs that interfere with serotonin reuptake inhibition, including trazodone, increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), other antiplatelet drugs, warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to drugs that interfere with serotonin reuptake have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages.

Inform patients about the risk of bleeding associated with the concomitant use of trazodone and antiplatelet agents or anticoagulants. For patients taking warfarin, carefully monitor coagulation indices when initiating, titrating, or discontinuing trazodone.

## **5.6 Priapism**

Cases of priapism (painful erections greater than 6 hours in duration) have been 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 4 hours, whether painful or not, should immediately discontinue the drug and seek emergency medical attention [*see Adverse Reactions (6.2), Overdosage (10)*].

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).

## **5.7 Activation of Mania or Hypomania**

In patients with bipolar disorder, treating a depressive episode with trazodone or another antidepressant may precipitate a mixed/manic episode. Activation of mania/hypomania has been reported in a small proportion of patients with major affective disorder who were treated with antidepressants. Prior to initiating treatment with trazodone, screen patients for any personal or family history of bipolar disorder, mania, or hypomania [*see Dosage and Administration (2.3)*].

## **5.8 Discontinuation Syndrome**

Adverse reactions after discontinuation of serotonergic antidepressants, particularly after abrupt discontinuation, include: nausea, sweating, dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), tremor, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. A gradual reduction in dosage rather than abrupt cessation is recommended whenever possible [*See Dosage and Administration (2.6)*].

## **5.9 Potential for Cognitive and Motor Impairment**

Trazodone hydrochloride tablets 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.

## **5.10 Angle-Closure Glaucoma**

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

## **5.11 Hyponatremia**

Hyponatremia may occur as a result of treatment with SNRIs and SSRIs, including trazodone. Cases with serum sodium lower than 110 mmol/L have been reported. 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. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

In patients with symptomatic hyponatremia, discontinue trazodone and institute appropriate medical intervention. Elderly patients, patients taking diuretics, and those who are volume-depleted may be at greater risk of developing hyponatremia with SSRIs and SNRIs [see *Use in Specific Populations* (8.5)].

## 6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Suicidal Thoughts and Behavior in Children, Adolescents and Young Adults [see *Boxed Warning and Warnings and Precautions* (5.1)]
- Serotonin Syndrome [see *Warnings and Precautions* (5.2)]
- Cardiac Arrhythmias [see *Warnings and Precautions* (5.3)]
- Orthostatic Hypotension and Syncope [see *Warnings and Precautions* (5.4)]
- Increased risk of Bleeding [see *Warnings and Precautions* (5.5)]
- Priapism [see *Warnings and Precautions* (5.6)]
- Activation of Mania or Hypomania [see *Warnings and Precautions* (5.7)]
- Discontinuation Syndrome [see *Warnings and Precautions* (5.8)]
- Potential for Cognitive and Motor Impairment [see *Warnings and Precautions* (5.9)]
- Angle-Closure Glaucoma [see *Warnings and Precautions* (5.10)]
- Hyponatremia [see *Warnings and Precautions* (5.11)]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted 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.

**Table 2: Common Adverse Reactions Occurring in  $\geq 2\%$  of Trazodone Hydrochloride Tablets-treated Patients and Greater than the Rate of Placebo-Treated Patients as Observed in Controlled Clinical Studies**

	Inpatients		Outpatients	
	Trazodone Hydrochloride Tablets N=142	Placebo N=95	Trazodone Hydrochloride Tablets N=157	Placebo N=158
<b>Allergic</b>				
Skin Condition/Edema	3%	1%	7%	1%
<b>Autonomic</b>				
Blurred Vision	6%	4%	15%	4%
Constipation	7%	4%	8%	6%
Dry Mouth	15%	8%	34%	20%



<b>Cardiovascular</b>				
Hypertension	20%	1%	1%	*
Hypotension	7%	1%	4%	0
Syncope	3%	2%	5%	1%
<b>CNS</b>				
Confusion	5%	0	6%	8%
Decreased Concentration	3%	2%	1%	0
Disorientation	2%	0	*	0
Dizziness/Light-Headedness	20%	5%	28%	15%
Drowsiness	24%	6%	41%	20%
Fatigue	11%	4%	6%	3%
Headache	10%	5%	20%	16%
Nervousness	15%	11%	6%	8%
<b>Gastrointestinal</b>				
Abdominal/Gastric Disorder	4%	4%	6%	4%
Diarrhea	0	1%	5%	1%
Nausea/Vomiting	10%	1%	13%	10%
<b>Musculoskeletal</b>				
Aches/Pains	6%	3%	5%	3%
<b>Neurological</b>				
Incoordination	5%	0	2%	*
Tremors	3%	1%	5%	4%
<b>Other</b>				
Eyes Red/Tired/Itching	3%	0	0	0
Head Full-Heavy	3%	0	0	0
Malaise	3%	0	0	0
Nasal/Sinus Congestion	3%	0	6%	3%
Weight Gain	1%	0	5%	2%
Weight Loss	*	3%	6%	3%

Other adverse reactions occurring at an incidence of <2% with the use of trazodone hydrochloride in the controlled clinical studies: akathisia, allergic reaction, anemia, chest pain, delayed urine flow, early menses, flatulence, hallucinations/delusions, hematuria, hypersalivation, hypomania, impaired memory, impaired speech, impotence, increased appetite, increased libido, increased urinary frequency, missed periods, muscle twitches, numbness, paresthesia, retrograde ejaculation shortness of breath, and tachycardia/palpitations. Occasional sinus bradycardia has occurred in long-term studies.

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of trazodone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure:

**Blood and lymphatic system disorders:** hemolytic anemia, leukocytosis

**Cardiac disorders:** cardiospasm, congestive heart failure, conduction block, orthostatic hypotension and syncope, palpitations, bradycardia, atrial fibrillation, myocardial infarction, cardiac arrest, arrhythmia, ventricular ectopic activity, including ventricular tachycardia and QT prolongation. Prolonged QT interval, torsade de pointes, and ventricular tachycardia have been reported at doses of 100 mg per day or less [see *Warnings and Precautions (5.3)*].

**Endocrine disorders:** inappropriate ADH syndrome

**Eye disorders:** diplopia

**Gastrointestinal disorders:** increased salivation, nausea/vomiting

**General disorders and administration site conditions:** chills, edema, unexplained death, weakness

**Hepatobiliary disorders:** cholestasis, jaundice, hyperbilirubinemia, liver enzyme alterations

**Investigations:** increased amylase

**Metabolism and nutrition disorders:** methemoglobinemia

**Nervous system disorders:** aphasia, ataxia, cerebrovascular accident, extrapyramidal symptoms, grand mal seizures, paresthesia, tardive dyskinesia, vertigo

**Psychiatric disorders:** abnormal dreams, agitation, anxiety, hallucinations, insomnia, paranoid reaction, psychosis, stupor

**Renal and urinary disorders:** urinary incontinence, urinary retention

**Reproductive system and breast disorders:** breast enlargement or engorgement, clitorism, lactation, priapism [see *Warnings and Precautions (5.6)*]

**Respiratory, thoracic and mediastinal disorders:** apnea

**Skin and subcutaneous tissue disorders:** alopecia, hirsutism, leukonychia, pruritus, psoriasis, rash, urticaria

**Vascular disorders:** vasodilation

## 7 DRUG INTERACTIONS

### 7.1 Drugs Having Clinically Important Interactions with Trazodone Hydrochloride Tablets

**Table 3: Clinically Important Drug Interactions with Trazodone Hydrochloride Tablets**

<b>Monoamine Oxidase Inhibitors (MAOIs)</b>	
Clinical Impact:	The concomitant use of MAOIs and serotonergic drugs including trazodone increases the risk of serotonin syndrome.
Intervention:	Trazodone is contraindicated in patients taking MAOIs, including MAOIs such as linezolid or intravenous methylene blue [see <i>Contraindications (4)</i> , <i>Dosage and Administration (2.3, 2.4)</i> , and <i>Warnings and Precautions (5.2)</i> ].
Examples:	isocarboxazid, moclobemide, phenelzine, selegiline, tranylcypromine
<b>Other Serotonergic Drugs</b>	
Clinical Impact:	The concomitant use of serotonergic drugs including trazodone and other serotonergic drugs increases the risk of serotonin syndrome.
Intervention:	Monitor patients for signs and symptoms of serotonin syndrome, particularly during trazodone initiation. If serotonin syndrome occurs, consider discontinuation of trazodone and/or concomitant serotonergic drugs [see <i>Warnings and Precautions (5.2)</i> ].
Examples:	triptans, antidepressants (tricyclic and serotonin uptake inhibitors), fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort

<b>Antiplatelet Agents and Anticoagulants</b>	
Clinical Impact:	Serotonin release by platelets plays an important role in hemostasis. The concurrent use of an antiplatelet agent or anticoagulant with trazodone may potentiate the risk of bleeding.
Intervention:	Inform patients of the increased risk of bleeding with the concomitant use of trazodone and antiplatelet agents and anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio (INR) when initiating or discontinuing trazodone [see <i>Warnings and Precautions (5.5)</i> ].
Examples:	warfarin, rivaroxaban, dabigatran, clopidogrel
<b>Strong CYP3A4 Inhibitors</b>	
Clinical Impact:	The concomitant use of trazodone and strong CYP3A4 inhibitors increased the exposure of trazodone compared to the use of trazodone alone.
Intervention:	If trazodone is used with a potent CYP3A4 inhibitor, the risk of adverse reactions, including cardiac arrhythmias, may be increased and a lower dose of trazodone should be considered [see <i>Dosage and Administration (2.5)</i> , <i>Warnings and Precautions (5.3)</i> ].
Examples:	itraconazole, ketoconazole, clarithromycin, indinavir
<b>Strong CYP3A4 Inducers</b>	
Clinical Impact:	The concomitant use of trazodone and strong CYP3A4 inducers decreased the exposure of trazodone compared to the use of trazodone alone.
Intervention:	Patients should be closely monitored to see if there is a need for an increased dose of trazodone when taking CYP3A4 inducers [see <i>Dosage and Administration (2.5)</i> ].
Examples:	rifampin, carbamazepine, phenytoin, St. John's wort
<b>Digoxin and Phenytoin</b>	
Clinical Impact:	Digoxin and phenytoin are narrow therapeutic index drugs. Concomitant use of trazodone can increase digoxin or phenytoin concentrations.
Intervention:	Measure serum digoxin or phenytoin concentrations before initiating concomitant use of trazodone. Continue monitoring and reduce digoxin or phenytoin dose as necessary.
Examples:	digoxin, phenytoin
<b>Central Nervous System (CNS) Depressants</b>	
Clinical Impact:	Trazodone may enhance the response CNS depressants.
Intervention:	Patients should be counseled that trazodone may enhance the response to alcohol, barbiturates, and other CNS depressants.
Examples:	alcohol, barbiturates
<b>QT Interval Prolongation</b>	
Clinical Impact:	Concomitant use of drugs that prolong the QT interval may add to the QT effects of trazodone and increase the risk of cardiac arrhythmia.
Intervention:	Avoid the use of trazodone in combination with other drugs known to prolong QTc [see <i>Warnings and Precautions (5.3)</i> ].
Examples:	Class 1A antiarrhythmics: quinidine, procainamide, disopyramide; Class 3 antiarrhythmics: amiodarone, sotalol; Antipsychotics: ziprasidone, chlorpromazine, thioridazine; Antibiotics: gatifloxacin

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/>

#### Risk Summary

Published prospective cohort studies, case series, and case reports over several decades with trazodone use in pregnant women have not identified any drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes (*see Data*). Trazodone hydrochloride has been shown to cause increased fetal resorption and other adverse effects on the fetus in the rat when given at dose levels approximately 7.3 to 11 times the maximum recommended human dose (MRHD) of 400 mg/day in adults on a mg/m<sup>2</sup> basis. There was also an increase in congenital anomalies in the rabbit at approximately 7.3 to 22 times the MRHD on a mg/m<sup>2</sup> basis (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

#### Clinical Considerations

##### *Disease-associated maternal and/or embryofetal risk*

A prospective, longitudinal study followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. The women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

#### Data

##### *Human Data*

While available studies cannot definitively establish the absence of risk, published data from prospective cohort studies, case series, and case reports over several decades have not identified an association with trazodone use during pregnancy and major birth defects, miscarriage, or other adverse maternal or fetal outcomes. All available studies have methodological limitations, including small sample size and inconsistent comparator groups.

##### *Animal Data*

No teratogenic effects were observed when trazodone was given to pregnant rats and rabbits during the period of organogenesis at oral doses up to 450 mg/kg/day. This dose is 11 and 22 times, in rats and rabbits, respectively, the maximum recommended human dose (MRHD) of 400 mg/day in

adults on a mg/m<sup>2</sup> basis. Increased fetal resorption and other adverse effects on the fetus in rats at 7.3 to 11 times the MRHD and increase in congenital anomalies in rabbits at 7.3 to 22 times the MRHD on a mg/m<sup>2</sup> basis were observed. No further details on these studies are available.

## **8.2 Lactation**

### Risk Summary

Data from published literature report the transfer of trazodone into human milk. There are no data on the effect of trazodone on milk production. Limited data from postmarketing reports have not identified an association of adverse effects on the breastfed child.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for trazodone and any potential adverse effects on the breastfed child from trazodone or from the underlying maternal condition.

## **8.4 Pediatric Use**

Safety and effectiveness in the pediatric population have not been established. Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients [*see Boxed Warning, Warnings and Precautions (5.1)*].

## **8.5 Geriatric Use**

Reported clinical literature and experience with trazodone has 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.

Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse reaction [*see Warnings and Precautions (5.11)*].

## **8.6 Renal Impairment**

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

## **8.7 Hepatic Impairment**

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

## **9 DRUG ABUSE AND DEPENDENCE**

### **9.1 Controlled Substance**

Trazodone hydrochloride tablets are not a controlled substance.

### **9.2 Abuse**

Although trazodone hydrochloride has not been systematically studied in preclinical or clinical studies for its potential for abuse, no indication of drug-seeking behavior was seen in the clinical studies with trazodone hydrochloride.

## 10 OVERDOSAGE

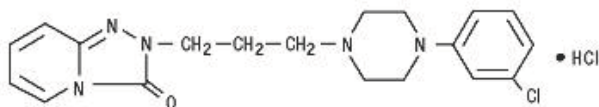
Death from overdose has occurred in patients ingesting trazodone and other CNS depressant drugs concurrently (alcohol; alcohol and chloral hydrate and diazepam; amobarbital; chlordiazepoxide; or meprobamate).

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.

There is no specific antidote for trazodone hydrochloride overdose. In managing overdosage, consider the possibility of multiple drug involvement. For current information on the management of poisoning or overdose, contact a poison control center (1-800-222-1222 or [www.poisson.org](http://www.poisson.org)).

## 11 DESCRIPTION

Trazodone hydrochloride tablets for oral administration contain trazodone hydrochloride, a selective serotonin reuptake inhibitor and 5HT<sub>2</sub> receptor antagonist. Trazodone hydrochloride is a triazolopyridine derivative designated as 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-a]pyridin-3(2*H*)-one hydrochloride. It is a white odorless crystalline powder which is freely soluble in water. The structural formula is represented as follows:



**Molecular Formula:** C<sub>19</sub>H<sub>22</sub>ClN<sub>5</sub>O · HCl

**Molecular Weight:** 408.33

Each tablet, for oral administration, contains 50 mg, 100 mg, 150 mg or 300 mg of trazodone hydrochloride, USP. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, pregelatinized maize starch, sodium lauryl sulfate, and sodium starch glycolate.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism of trazodone's antidepressant action is not fully understood, but is thought to be related to its enhancement of serotonergic activity in the CNS. Trazodone is both a selective serotonin reuptake inhibitor (SSRI) and a 5HT<sub>2</sub> receptor antagonist and the net result of this action on serotonergic transmission and its role in trazodone's antidepressant effect is unknown.

### 12.2 Pharmacodynamics

Preclinical studies have shown that trazodone selectively inhibits neuronal reuptake of serotonin (K<sub>i</sub> = 367 nM) and acts as an antagonist at 5-HT<sub>2A</sub> (K<sub>i</sub> = 35.6 nM) serotonin receptors. Trazodone is also an antagonist at several other monoaminergic receptors including 5-HT<sub>2B</sub> (K<sub>i</sub> = 78.4 nM), 5-HT<sub>2C</sub> (K<sub>i</sub> = 224 nM), α<sub>1A</sub> (K<sub>i</sub> = 153 nM), α<sub>2C</sub> (K<sub>i</sub> = 155 nM) receptors and it is a partial agonist at 5-HT<sub>1A</sub> (K<sub>i</sub> = 118 nM) receptor.

Trazodone antagonizes alpha 1-adrenergic receptors, a property which may be associated with postural hypotension.

### **12.3 Pharmacokinetics**

#### ***Absorption***

In humans, trazodone hydrochloride is 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 2 hours after dosing when taken with food.

#### ***Metabolism***

*In vitro* studies in human liver microsomes show that trazodone is metabolized, via oxidative cleavage, to an active metabolite, m-chlorophenylpiperazine (mCPP) by CYP3A4. Other metabolic pathways that may be involved in the metabolism of trazodone have not been well characterized. Trazodone is extensively metabolized; less than 1% of an oral dose is excreted unchanged in the urine.

#### ***Elimination***

In some patients trazodone may accumulate in the plasma

#### ***Protein Binding***

Trazodone is 89 to 95% protein bound *in vitro* at concentrations attained with therapeutic doses in humans.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### **Carcinogenesis**

No drug- or dose-related occurrence of carcinogenesis was evident in rats receiving trazodone in daily oral doses up to 7.3 times the maximum recommended human dose (MRHD) of 400 mg/day in adults on a mg/m<sup>2</sup> basis.

#### **Mutagenesis**

No genotoxicity studies were conducted with trazodone.

#### **Impairment of Fertility**

Trazodone has no effect on fertility in rats at doses up to 7.3 times the MRHD in adults on a mg/m<sup>2</sup> basis.

## **14 CLINICAL STUDIES**

The efficacy and safety of trazodone hydrochloride were established from inpatient and outpatient trials of the trazodone immediate release formulation in the treatment of major depressive disorder.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Trazodone Hydrochloride Tablets, USP 50 mg are available for oral administration as white to off white, round, biconvex, uncoated tablets debossed with “13” bisect “30” on one side and plain on other side.

Bottles of 30	NDC 13668-330-30
Bottles of 100	NDC 13668-330-01
Bottles of 500	NDC 13668-330-05
Bottles of 1,000	NDC 13668-330-10

Trazodone Hydrochloride Tablets, USP 100 mg are available for oral administration as white to off white, round, biconvex, uncoated tablets debossed with “13” bisect “31” on one side and plain on other side.

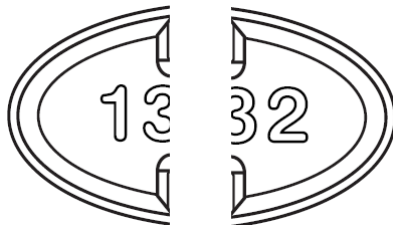
Bottles of 30	NDC 13668-331-30
Bottles of 100	NDC 13668-331-01
Bottles of 500	NDC 13668-331-05
Bottles of 1,000	NDC 13668-331-10

Trazodone Hydrochloride Tablets, USP 150 mg are available for oral administration as white to off white, oval, flat faced beveled edge uncoated tablets with a full bisect and two partial trisects. Debossed “13” bisect “32” on one side and “50 50 50” on other side.

Bottles of 30	NDC 13668-332-30
Bottles of 100	NDC 13668-332-01
Bottles of 500	NDC 13668-332-05
Bottles of 1,000	NDC 13668-332-10

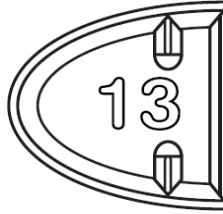
Directions for using the correct score when breaking the tablet, please refer to the following:

- For 50 mg, break the score on either the left or right side of the tablet (one-third of a tablet).

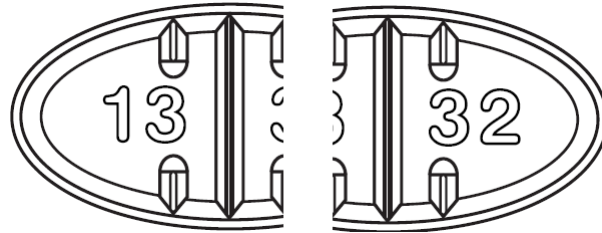


- For 75 mg, break the score down the middle of the tablet (one-half of a tablet).

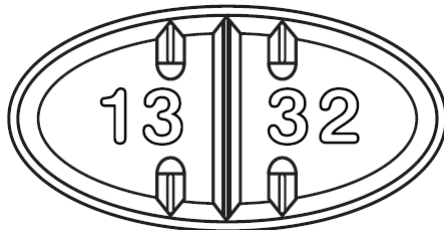




- For 100 mg, break the score on either the left or right side of the tablet (two-thirds of a tablet).



- For 150 mg, use the entire tablet.



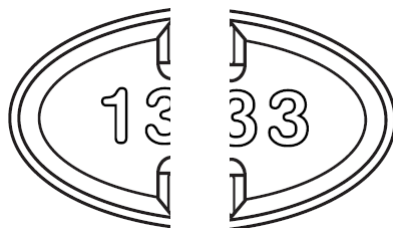
Trazodone Hydrochloride Tablets, USP 300 mg are available for oral administration as white to off white, oval, flat faced beveled edge uncoated tablets with a full bisect and 2 partial trisects. Debossed "13" bisect "33" on one side and "100 100 100" on other side with middle "100" perpendicular to others.

Bottles of 100

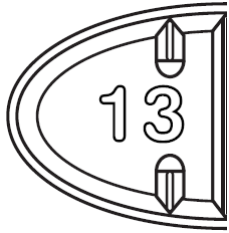
NDC 13668-333-01

Directions for using the correct score when breaking the tablet, please refer to the following:

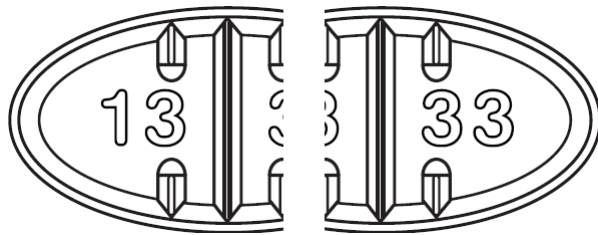
- For 100 mg, break the score on either the left or right side of the tablet (one-third of a tablet).



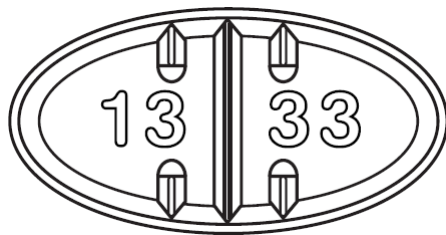
- For 150 mg, break the score down the middle of the tablet (one-half of a tablet).



- For 200 mg, break the score on either the left or right side of the tablet (two-thirds of a tablet).



- For 300 mg, use the entire tablet.



Store at 20° to 25°C (68° to 77°F). Excursions permitted between 15° to 30°C (59° to 86°F) [*see USP Controlled Room Temperature*].

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

### Suicidal Thoughts and Behaviors

Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dosage is adjusted up or down and instruct them to report such symptoms to the healthcare provider [*see Box Warning and Warnings and Precautions (5.1)*].

### Dosage and Administration

Advise patients that trazodone hydrochloride tablets should be taken shortly after a meal or light snack. Advise patients regarding the importance of following dosage titration instructions [*see Dosage and Administration (2)*].

### Serotonin Syndrome

Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of trazodone with other serotonergic drugs including triptans, tricyclic antidepressants, fentanyl,

lithium, tramadol, tryptophan, buspirone, 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). Patients should contact their health care provider or report to the emergency room if they experience signs or symptoms of serotonin syndrome [see *Warnings and Precautions (5.2) and Drug Interactions (7)*].

#### Activation of Mania/Hypomania

Advise patients and their caregivers to observe for signs of activation of mania/hypomania and instruct them to report such symptoms to the healthcare provider [see *Warnings and Precautions (5.7)*].

#### Increased Risk of Bleeding

Inform patients about the concomitant use of trazodone with aspirin, NSAIDs, other antiplatelet drugs, warfarin, or other anticoagulants because the combined use of drugs that interfere with serotonin reuptake and these medications has been associated with an increased risk of bleeding. Advise them to inform their health care providers if they are taking or planning to take any prescription or over-the-counter medications that increase the risk of bleeding [see *Warnings and Precautions (5.5)*].

#### Discontinuation Syndrome

Advise patients not to abruptly discontinue trazodone hydrochloride tablets and to discuss any tapering regimen with their healthcare provider. Adverse reactions can occur when trazodone hydrochloride tablets is discontinued [see *Warnings and Precautions (5.8)*].

#### Concomitant Medications

Advise patients to inform their health care providers if they are taking, or plan to take any prescription or over-the-counter medications since there is a potential for interactions [see *Drug Interactions (7.1)*].

#### Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy with trazodone hydrochloride tablets. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to trazodone hydrochloride tablets during pregnancy [see *Use in Special Populations (8.1)*].



#### **Manufactured by:**

TORRENT PHARMACEUTICALS LTD., Indrad-382 721, Dist. Mehsana, INDIA.

#### **For:**

TORRENT PHARMA INC., Basking Ridge, NJ 07920.