# PRODUCT MONOGRAPH

# [Pr]pms-TRAZODONE

Trazodone Hydrochloride Tablets, USP
50 mg, 75 mg and 100 mg

Antidepressant

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Trazodone Hydrochloride Tablets, USP

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Non medicinal Ingredients |
|---|---|---|
| Oral | Tablet/50 mg, 75 mg & 100 mg | Croscarmellose sodium, dibasic calcium phosphate, FD&C Yellow #6 (50 and 75 mg only) lactose monohydrate, magnesium stearate, microcrystalline cellulose and pregelatinized starch. |

### INDICATIONS AND CLINICAL USE

pms-TRAZODONE (trazodone hydrochloride) is of value in the symptomatic relief of depressive illness.

**Geriatrics (> 65 years of age):**
Use with caution in geriatric patients. See **WARNINGS & PRECAUTIONS: Special Population.**

**Pediatrics (< 18 years of age):**
Safety and efficacy have not been established in patients below 18 years of age. pms-TRAZODONE is not indicated in this age group.

### CONTRAINDICATIONS

Patients who are hypersensitive to trazodone or to any ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

## WARNINGS AND PRECAUTIONS

## POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM

***Pediatrics: Placebo-Controlled Clinical Trial Data***

- **Analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer antidepressants suggest that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.**

- **The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.**

***Adults and Pediatrics: Additional data***

- **There are clinical trials and post-marketing reports with SSRIs and other newer antidepressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm and harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, depersonalization. In some cases, the events occurred within several weeks of starting treatment.**

**Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.**

**An FDA meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients aged 18 to 24 years with psychiatric disorders showed an increased risk of suicidal behaviours with antidepressants compared to placebo.**

**Discontinuation Symptoms**

**At the time that a medical decision is made to discontinue an SSRI or other newer antidepressant drug, a gradual reduction in the dose, rather than an abrupt cessation, is recommended whenever possible**.

**QT Prolongation and Risk of Arrhythmias and Sudden Death**

pms-TRAZODONE is not recommended for use during the initial recovery phase of myocardial infarction. Caution should be used when administering pms-TRAZODONE to patients with cardiac disease and such patients should be closely monitored.

QT Prolongation: Trazodone is associated with QTc interval prolongation (see **ADVERSE REACTIONS, *Cardiac Disorders*** and **DRUG INTERACTIONS**). Torsade de pointes, ventricular tachycardia, and sudden death have been reported with the immediate-release form of trazodone during post-marketing use.

Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de

pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Particular care should be exercised when administering pms-TRAZODONE to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug.

Risk factors for torsade de pointes in the general population include, but are not limited to: female gender; age 65 years or older; baseline prolongation of the QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years; cardiac disease (e.g., myocardial ischemia, congestive heart failure, left ventricular hypertrophy, cardiomyopathy, conduction system disease); history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation); electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia); bradycardia; acute neurological events (e.g., intracranial or subarachnoid hemorrhage, stroke, intracranial trauma); nutritional deficits (e.g., eating disorders, extreme diets); diabetes mellitus; autonomic neuropathy.

The concomitant use of pms-TRAZODONE with drugs known to prolong the QTc interval should be avoided (see **DRUG INTERACTIONS**).

Concomitant administration of CYP3A4 inhibitors may increase trazodone plasma levels. The concomitant use of potent CYP3A4 inhibitors with pms-TRAZODONE is discouraged. If used, a lower dose of pms-TRAZODONE should be considered.

When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug.

Cardiac Disease: 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, and short episodes of ventricular tachycardia (3-4 beats). There have also been several post-marketing reports of arrhythmias in trazodone treated patients who had pre-existing cardiac disease and also in some patients who did not have preexisting cardiac disease.

**Priapism**

Rare cases of priapism (painful erections greater than 4 hours in duration) were reported in patients receiving trazodone. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

Trazodone should be used with caution in patients who have conditions that might predispose

them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease).

**The following additional warnings and precautions are listed alphabetically by body system or organ class.**

**Carcinogenesis and Mutagenesis**
See **TOXICOLOGY** for animal data.

**Cardiovascular**
Trazodone may cause hypotension including orthostatic hypotension and syncope; caution is required if it is given to patients receiving antihypertensive drugs and an adjustment in the dose of the antihypertensive medication may be required.

**Dependence/Tolerance**
Although trazodone has not been systematically studied for its potential for abuse, there is no evidence that trazodone possesses any addictive properties. Physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of trazodone.

Discontinuation 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.

**Endocrine and Metabolism**

*Hyperprolactinemia and Breast Tumors*
There is sufficient experimental evidence to conclude that chronic administration of those psychotropic drugs, such as trazodone, which increase prolactin secretion has the potential to induce mammary neoplasms in rodents under appropriate conditions. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer.

Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels or increased secretion and turnover is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; available evidence is considered too limited to be conclusive at this time.

**Genitourinary**
See **WARNINGS & PRECAUTIONS, Priapism**.

**Hematologic**

*Abnormal Bleeding*
The use of drugs that interfere with serotonin reuptake, including pms-TRAZODONE, may increase the risk of bleeding events by causing abnormal platelet aggregation. Concomitant use of acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin and other anticoagulants may add to the 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 and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of pms-TRAZODONE and NSAIDs, ASA, or other drugs that affect coagulation (see **DRUG INTERACTIONS**). Caution is advised in patients with a history of bleeding disorder or predisposing conditions (e .g. thrombocytopenia).

**Hepatic/Biliary/Pancreatic**
pms-TRAZODONE has not been studied in patients with hepatic impairment and should be used with caution in this population.

**Interactions with Medications that Alter CYP3A4 Metabolism**
Concomitant use of pms-TRAZODONE with CYP3A4 inhibitors may increase trazodone plasma levels (see **WARNINGS AND PRECAUTIONS, QT Prolongation and Risk of Arrhythmias and Sudden Death**, and **DRUG INTERACTIONS**). The concomitant use of potent CYP3A4 inhibitors with pms-TRAZODONE is discouraged. If used, a lower dose of pms-TRAZODONE should be considered.

*In vitro* drug metabolism studies suggest that there is a potential for drug interactions when trazodone is given with CYP3A4 inhibitors. Ritonavir, a potent CYP3A4 inhibitor, increased the $C_{max}$, AUC, and elimination half-life, and decreased clearance of trazodone after administration of ritonavir twice daily for 2 days. 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 also lead to substantial increases in trazodone plasma concentrations with a potential for adverse effects.

Carbamazepine, a CYP3A4 inducer, reduced plasma concentrations of trazodone when coadministered. Patients should be closely monitored to see if there is a need for an increased dose of trazodone when taking both drugs (see **DRUG INTERACTIONS**).

**Laboratory Tests**
It is recommended that white blood cell and differential counts should be performed in patients who develop sore throat, fever or other signs of infection or blood dyscrasia. Trazodone should be discontinued if the white blood cell or absolute neutrophil count falls below normal.

**Neurologic**

*Serotonin Syndrome*
On rare occasions serotonin syndrome or neuroleptic malignant syndrome-like events have occurred in association with trazodone treatment, particularly when given in combination with

other serotonergic or neuroleptic and antipsychotic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with pms-TRAZODONE should be discontinued if patients develop a combination of symptoms possibly including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs and mental status changes (confusion, irritability, extreme agitation progressing to delirium and coma). Supportive symptomatic treatment should be initiated. Due to the risk of serotonergic syndrome or neuroleptic malignant syndrome, pms-TRAZODONE should not be used in combination with MAO inhibitors or serotonin precursors (such as L-tryptophan, oxitriptan) and should be used with caution in patients receiving other serotonergic drugs (e.g., triptans, lithium, tramadol, St. John's Wort, SSRIs, most tricyclic antidepressants) or neuroleptics/antipsychotics (see **DRUG INTERACTIONS**).

*Seizures*
Episodes of grand mal seizures have been reported in a small number of patients. The majority of these patients were already receiving anticonvulsant therapy for a seizure disorder. As with other antidepressants, pms-TRAZODONE should be introduced cautiously in patients who have a history of seizures or in patients with unstable epilepsy. Treatment should be discontinued in any patient who develops seizures or for whom there is an increase in seizure frequency.

*Cognitive and motor disturbances*
Trazodone may impair the mental or physical abilities required for performance of potentially hazardous tasks, such as operating an automobile or machinery. Patients should be cautioned not to engage in such activities until they are reasonably certain that pms-TRAZODONE does not affect them adversely.

*CNS Depressants*
Trazodone may enhance the response to alcohol and the effects of barbiturates and other CNS depressants and patients should be cautioned accordingly.

**Psychiatric**

*Suicide*
The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of patients should accompany initial drug therapy, and consideration should be given to the need for hospitalization of high risk patients. The risk of suicide attempt must be considered, especially in depressed patients; the smallest quantity of drug, consistent with good patient management, should be provided to reduce the risk of overdose with this drug (see **WARNINGS AND PRECAUTIONS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**).

*Activation of Mania/Hypomania*
pms-TRAZODONE should be used with caution in patients with a history of mania/hypomania and should be discontinued in any patient entering a manic phase. Depression may be the initial presentation of bipolar disorder. Patients with bipolar disorder may be at an increased risk of experiencing manic episodes when treated with antidepressants alone. Therefore, the decision to initiate symptomatic treatment of depression should only be made after patients have been adequately assessed to determine if they are at risk for bipolar disorder.

## Renal

*Hyponatremia*
Hyponatremia has been reported with the use of antidepressants, probably due to syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elderly patients and patients taking diuretics or who are otherwise volume-depleted may be at greater risk of developing hyponatremia. Discontinuation of pms-TRAZODONE should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Symptoms may include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls.

*Renal Impairment*
pms-TRAZODONE has not been studied in patients with renal impairment and should be used with caution in this population.

## Sexual Function/Reproduction
See **WARNINGS AND PRECAUTIONS: Priapism**.

## Special Populations

**Pregnant Women:**
There are no adequate and well-controlled studies in pregnant women. In two studies using the rat, trazodone has been shown to cause increased fetal resorption and other adverse effects on the fetus 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. pms-TRAZODONE should not be used in women of childbearing potential unless, in the opinion of the physician, the expected benefits justify the potential risk to the fetus.

***Trazodone Hydrochloride Treatment during Pregnancy – Effects on Newborns***
Postmarketing reports indicate that some neonates exposed to trazodone, SSRIs or other newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Most often, such complications begin immediately or soon (< 24 hours) after delivery. When treating a pregnant woman with pms-TRAZODONE during later stages of pregnancy, the physician should carefully consider the potential risks and benefits of treatment.

**Nursing Women:**
Trazodone and its metabolites have been detected in the milk of lactating animals; it should not be administered to nursing mothers unless the potential benefits justify the possible risks to the child.

**Pediatrics (<18 years of age):**
The safety and effectiveness of trazodone in children below the age of 18 have not been established. pms-TRAZODONE should not be used in that population.

**Geriatrics (>65 years of age):**
Trazodone should be used with caution in geriatric patients and lower initial and maintenance doses should be considered (see DOSAGE AND ADMINISTRATION).

Elderly patients receiving antidepressants may be at increased risk of clinically significant hyponatremia.

## ADVERSE REACTIONS

**The following adverse reactions are listed alphabetically by body system or organ class.**

Blood and the lymphatic system disorders: Blood dyscrasias (agranulocytosis, leucopenia, anemia)

Cardiac disorders: Orthostatic hypotension, syncope, hypertension, tachycardia, bradycardia, palpitations, shortness of breath, apnea, arrhythmias (including Torsade de Pointes, PVCs, ventricular couplets, ventricular tachycardia), prolonged P-R interval, atrial fibrillation, myocardial infarction, cardiac arrest and conduction block.

Endocrine disorders: Syndrome of Inappropriate Antidiuretic Hormone Secretion.

Gastrointestinal disorders: Nausea, vomiting, dry mouth, increased salivation, constipation, diarrhea, dyspepsia, stomach pain, gastroenteritis, paralytic ileus.

Genitourinary: Priapism (see WARNINGS & PRECAUTIONS), decreased libido, increased libido (rarely), retrograde ejaculation, inhibition of ejaculation, menstrual irregularities.

Hepato-biliary disorders: Hepatic function abnormalities (including jaundice and hepatocellular damage), intrahepatic cholestasis.

Immune system disorders: Allergic reactions, including skin rash, itching, edema, and, rarely, hemolytic anemia, methemoglobinemia, liver enzyme alterations, leukocytoclastic vasculitis, purpuric maculopapular eruptions, photosensitivity, fever and obstructive jaundice.

Metabolism and nutrition disorders: Hyponatremia, weight loss, anorexia, increased appetite.

Nervous system disorders: Serotonin syndrome, convulsion, neuroleptic malignant syndrome, dizziness, vertigo, headache, drowsiness, restlessness, decreased alertness, tremor, blurred vision, memory disturbance, myoclonus, aphasia, paresthesia, dystonia, taste altered.

Psychiatric disorders: Suicidal ideation or suicidal behaviours, confusional state, insomnia, disorientation, mania, anxiety, nervousness, agitation (very occasionally exacerbating to delirium), delusion, aggressive reaction, hallucinations, nightmares, withdrawal syndrome.

Respiratory disorders: Nasal congestion, dyspnea.

Skin and subcutaneous tissue disorders: Rash, pruritus, hyperhidrosis.

## DRUG INTERACTIONS

### Drug-Drug Interactions

*CYP 3A4 Inhibitors and Inducers*
*In vitro* studies reveal that trazodone is a substrate of the cytochrome P450 3A4 enzyme (CYP3A4) and trazodone metabolism can be inhibited by CYP3A4 inhibitors (e.g. ritonavir, ketoconazole). The effect of short-term administration of ritonavir (200 mg twice daily for four 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. If trazodone is used with a potent CYP3A4 inhibitor, a lower dose of trazodone should be considered.

Prolongation of the QTc interval by pms-TRAZODONE is anticipated to be increased in the presence of CYP3A4 inhibitors. Drugs that inhibit CYP3A4 include ketoconazole, itraconazole, voriconazole, clarithromycin, erythromycin, atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, and amiodarone. The concomitant use of these drugs with pms-TRAZODONE is discouraged. If used concomitantly with a CYP3A4 inhibitor, pms-TRAZODONE should be started at a low dose and patients monitored closely.

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 pre-carbamazepine values.

*Drugs with a QTc prolongation effect*
The concomitant use of pms-TRAZODONE with another QTc-prolonging drug is discouraged. If used concomitantly with these drugs, pms-TRAZODONE should be started at a low dose and patients monitored closely. Drugs that have been associated with QTc interval prolongation or torsade de pointes include, but are not limited to, the examples in the following list. Drugs classes are listed if some class members have been implicated in QTc prolongation or torsade de pointes:

Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide); Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide); Class 1C antiarrhythmics (e.g., flecainide, propafenone); antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone); antidepressants (e.g., SSRI, venlafaxine, tricyclic/tetracyclic antidepressants); opioids (e.g., methadone); macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, tacrolimus); quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin); pentamidine; antimalarials (e.g., quinine, chloroquine); azole antifungals (e.g., ketoconazole, fluconazole, voriconazole); domperidone; 5-hydroxytryptamine receptor antagonists (e.g., dolasetron, ondansetron); tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, lapatinib); histone deacetylase inhibitors (e.g., vorinostat); beta-2 agonists (e.g., salmeterol, formoterol).

*Drugs with effect on electrolytes*
The use of pms-TRAZODONE is discouraged with drugs that can disrupt electrolyte levels, including: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high dose corticosteroids. If used concomitantly with these drugs, pms-TRAZODONE should be started at a

low dose and patients monitored closely.

*Digoxin and Phenytoin.*
Increased serum digoxin or phenytoin levels have been reported to occur in patients receiving trazodone concurrently with either of these drugs.

*Serotonergic drugs*
Based on the mechanism of action of trazodone and the potential for serotonin syndrome, pms-TRAZODONE should not be used in combination with a MAO inhibitor or within 14 days of discontinuing treatment with a MAO inhibitor; similarly, at least 14 days should be allowed after stopping pms-TRAZODONE before starting treatment with a MAO inhibitor. Caution is advised when pms-TRAZODONE is co-administered with other drugs that may affect neurotransmitter systems, such as tryptophan, triptans, SSRIs, lithium, fentanyl, tramadol, or St. John's Wort (see WARNINGS AND PRECAUTIONS, Serotonin Syndrome).

*Drugs that affect coagulation or bleeding*
Due to a possible association between serotonin modulating drugs and gastrointestinal bleeding, 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 (see WARNINGS AND PRECAUTIONS, Abnormal Bleeding).

*Warfarin*
There have been reports of increased and decreased prothrombin time occurring in warfarinized patients who take trazodone.

*CNS depressant*s
Trazodone may enhance the response to alcohol and the effects of barbiturates and other CNS depressants and patients should be cautioned accordingly.

*General anesthetics*
Little is known about the interaction between trazodone and general anesthetics. As a precaution, pms-TRAZODONE should be discontinued for as long as clinically feasible prior to elective surgery.

**Drug-Non-drug Therapy Interactions**
Electroconvulsive therapy (ECT): The efficacy and safety of the concurrent use of pms-TRAZODONE and ECT have not been studied.

**Drug-Food Interactions**
Grapefruit, grapefruit juice, and products containing grapefruit extracts should not be used during treatment with pms-TRAZODONE because of the potential to inhibit CYP3A4 and increase plasma levels of trazodone.

**Drug-Herb Interactions**
Pharmacodynamic interactions between trazodone and St. John's Wort may occur and may result in an increase in undesirable effects (see WARNINGS AND PRECAUTIONS: Neurologic; Serotonin Syndrome).

**Drug-Laboratory Interactions**
Interactions with laboratory tests have not been established.

**Drug-Lifestyle Interactions**
Trazodone may enhance the response to alcohol and the effects of barbiturates and other CNS depressants and patients should be cautioned accordingly.

## DOSAGE AND ADMINISTRATION

**Dosing Considerations**
Dosage should be initiated at a low level and increased gradually. It should be kept in mind that there may be a lag in the therapeutic response. Increasing the dosage rapidly does not normally shorten this latent period and may increase the incidence of side effects.

**Recommended Dose and Dosage Adjustment**

**Adults**
The recommended initial dose is 150–200 mg daily, in two or three divided doses. pms-TRAZODONE should be taken shortly after a meal or light snack in order to reduce the incidence of adverse reactions. The dose may be increased according to tolerance and response by increments of 50 mg, usually up to 300 mg daily in divided doses. In some patients, doses up to 400 mg daily and, rarely, up to 600 mg daily, may be required. Occurrence of drowsiness may require the administration of a major portion of the daily dose at bedtime or a reduction of dosage.

Once an adequate response has been achieved, the dosage may be gradually reduced, with adjustment depending on therapeutic response. During prolonged maintenance therapy the dosage should be kept at the lowest effective level.

**Discontinuation of Treatment**
Patients should be monitored for discontinuation symptoms when discontinuing treatment with pms-TRAZODONE. The dose should be gradually reduced whenever possible.

**Geriatrics (>65 years of age)**
If used in the elderly, doses not exceeding half the recommended adult dosage should be used, with adjustments made depending on tolerance and response.

**Pediatrics**
pms-TRAZODONE is not indicated for use in children under 18 years of age.

## OVERDOSAGE

Fatal overdoses have occurred mostly in patients ingesting trazodone and other CNS depressant drugs concurrently (alcohol; chloral hydrate; diazepam; amobarbital; chlordiazepoxide; or meprobamate).

The most severe reactions reported with overdose of trazodone alone have been priapism, respiratory arrest, coma, seizures, ECG changes (including QTc prolongation and torsade de pointes) and death. The reactions reported most frequently have been drowsiness and vomiting. Also reported were bradycardia, transient first-degree heart block, ataxia and hyponatremia. Overdosage may cause an increase in incidence or severity of any of the reported adverse reactions.

Treatment of Overdosage:
There is no specific antidote for trazodone. Treatment should be symptomatic and supportive. Ensure adequate airway, oxygenation and ventilation. Continuous ECG and vital signs monitoring are recommended. Monitor fluids and electrolyte status in symptomatic patients. Induction of emesis is not recommended. Any patient suspected of having taken a potentially life-threatening overdose should have the stomach emptied by gastric lavage, with appropriate airway protection, if it can be performed soon after ingestion. Forced diuresis may be useful in facilitating elimination of the drug.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

## ACTION AND CLINICAL PHARMACOLOGY

Trazodone's antidepressant mechanism of action in man is not fully understood, but is thought to be related to its potentiation of serotonergic activity in the CNS. It is also called a Serotonin 2A/2C Antagonist and Serotonin Reuptake Inhibitor (SARI).

Preclinical studies have shown that trazodone functions as an antagonist at 5-HT2A and 5-HT2C receptors and as a weak inhibitor of serotonin reuptake.

Trazodone's active metabolite, m-chlorophenylpiperazine (mCPP) functions as a potent 5-HT2C agonist and as a partial agonist at several of the other subtypes of serotonin receptors.

Trazodone is a potent α1-adrenergic receptor antagonist with relatively weak α2-adrenergic receptor activity and its main actions at adrenergic receptors are dominated by antagonism of α1-adrenergic receptor subtypes. Trazodone has weak action at a variety of other neurotransmitter receptors, ion channels and transporters.

Cardiac conduction effects of trazodone in the anesthetized dog are qualitatively dissimilar and quantitatively less pronounced than those seen with tricyclic antidepressants. Trazodone is not a monoamine oxidase inhibitor and, unlike amphetamine-type drugs, does not stimulate the central nervous system.

### Pharmacokinetics

**Absorption:**
Trazodone hydrochloride is well absorbed after oral administration with peak plasma levels obtained within one-half to two hours after ingestion. Absorption is somewhat delayed and enhanced by food.

**Distribution:**
Trazodone is 89-95% protein bound *in vitro* at concentrations attained with therapeutic doses.

**Metabolism:**
*In vitro* studies in human liver microsomes show that trazodone is metabolized to an active metabolite, mCPP, by cytochrome P450 3A4 (CYP3A4). Other metabolic pathways that may be involved in 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**
Approximately 60-70% of $^{14}$C-labelled trazodone was found to be excreted in the urine within two days and 9-29% in feces over 60-100 hours. In some patients trazodone may accumulate in the plasma.

**Special Populations and Conditions**

**Pediatrics (< 18 years of age):** The safety and efficacy of trazodone in patients below the age of 18 years have not been evaluated.

**Geriatrics (> 65 years of age):** pms-TRAZODONE should be used with caution in geriatric patients (see DOSAGE AND ADMINISTRATION).

**Hepatic Insufficiency:** pms-TRAZODONE has not been studied in patients with hepatic impairment and should be used with caution in this population.

**Renal Insufficiency:** pms-TRAZODONE has not been studied in patients with renal insufficiency and should be used with caution in this population.

## STORAGE AND STABILITY

Store between 15°C and 30°C. Protect from light.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

**50 mg**: Each salmon, round, biconvex tablet debossed with “TRAZO” over “50" on one side and a score line on the other side, contains trazodone hydrochloride 50 mg equivalent to 45.5 mg trazodone base, and the following non medicinal ingredients: croscarmellose sodium, dibasic calcium phosphate, FD&C Yellow #6, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. Available in HDPE bottles of 100, 250 and 500.

**75 mg**: Each salmon, round, biconvex tablet debossed with “TRAZO” over “75" on one side and nothing on the other side, contains trazodone hydrochloride 75 mg equivalent to 68.25 mg trazodone base, and the following non medicinal ingredients: croscarmellose

sodium, dibasic calcium phosphate, FD&C Yellow #6, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. Available in HDPE bottles of 100, 250 and 500.

**100 mg**: Each white, round, biconvex tablet debossed with “TRAZO” over “100" on one side and a score line on the other side, contains trazodone hydrochloride 100 mg equivalent to 91 mg trazodone base, and the following non medicinal ingredients: croscarmellose sodium, dibasic calcium phosphate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. Available in HDPE bottles of 100 and 500.

# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug Substance

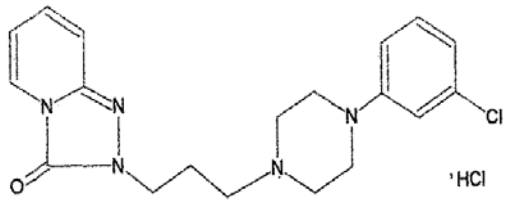
Proper name: Trazodone Hydrochloride

Chemical name: 2-{3-[4-(3-chlorophenyl)-1-piperazinyl] propyl}
-1,2,4-triazolo-[4,3-a]pyridin- 3(2H)-one monohydrochloride

Molecular formula: $C_{19}H_{22}ClN_5O$ HCl

Molecular mass: 408.32 g/mol

Structural Formula:




Physicochemical properties:

Description:

White, odorless crystals (plates) with a bitter taste. The melting point for trazodone free base is 96°C. The hydrochloride salt melts with decomposition in the range 222-228°C. Under vacuum decomposition does not occur and a melting range of 231-232.5°C is reported. Trazodone Hydrochloride is sparingly soluble in chloroform and in water. The reported pKa for trazodone in 50% ethanol is 6.14. This value was obtained potentiometrically using a glass-calomel electrode.

## CLINICAL TRIALS

### Comparative Bioavailability Studies

A single-dose comparative bioavailability study was conducted between two different formulations of trazodone hydrochloride. The study compared a 100 mg dose (2 x 50 mg tablets) of pms-TRAZODONE (trazodone hydrochloride tablets) manufactured by Pharmascience Inc. versus DESYREL® (trazodone hydrochloride tablets) manufactured by Bristol Inc., administered to fourteen healthy volunteers. The pharmacokinetic parameters are summarized below:

| Trazodone (2 x 50 mg) From measured data Geometric Mean Arithmetic Mean (CV %) | | | | |
|---|---|---|---|---|
| **Parameters** | **Test *** | **Reference†** | **% Ratio of Geometric Means** | **95% Confidence Interval** |
| $AUC_{0-T}$ (ng.hr/mL) | 7944.82<br>8400.95 (31.13) | 7854.34<br>8454.81 (37.02) | 101.0% | 92.8-109.9 |
| $AUC_{0-\infty}$ (ng.hr/mL) | 8680.56<br>9102.16 (30.96) | 8544.95<br>9138.98 (35.56) | 101.59% | --- |
| $C_{max}$ (ng/mL) | 1325.20<br>1384.63 (32.26) | 1145.81<br>1196.70 (32.26) | 116.2% | 100.1-134.8 |
| $T_{max}$ § (hours) | 0.85 (84.81) | 1.65 (62.21) | ---- | --- |
| T½e ¶ (hours) | 6.17 (29.10) | 6.08 (25.60) | ---- | --- |
| | | | | |

*: pms-TRAZODONE (trazodone hydrochloride) tablets by Pharmascience Inc.
†: DESYREL® (trazodone hydrochloride) tablets manufactured by Bristol Inc. were purchased in Canada.
§: Expressed as the median (range) only
¶: Expressed as the arithmetic mean (CV%) only

## DETAILED PHARMACOLOGY

The pharmacological profile of trazodone differs significantly from that of other known psychopharmacological agents.

Trazodone impedes the membrane uptake of serotonin. Small doses of the drug impede the depletion of brain serotonin, by fenfluramine, but doses of 50 mg/kg do not affect the concentration of serotonin in the rat brain. In experimental studies, trazodone is a weak inhibitor of

noradrenalin re-uptake but is practically inactive against 1-dopa, histamine and acetylcholine. It has no known monoamine oxidase inhibiting activity.

Trazodone exhibits CNS depressant properties, causing decreased motor activity in cats, rats and mice and increasing the hexobarbital-induced sleeping time in mice. It also inhibits conditioned avoidance responding in rats at doses which do not influence the unconditioned response ($ED_{50}$ = 19.5 mg/kg p.o.). Trazodone has no anticonvulsant, anti-reserpine or cataleptogenic effects and its muscle relaxant activity is very weak.

In mice, responses to painful stimuli are suppressed by doses at which motor activity is unaffected (10 mg/kg p.o.), and oxotremorine-, clonidine- and nicotine-induced tremors are significantly inhibited by 12.5 mg/kg i.p. Trazodone protects grouped mice against amphetamine-induced toxicity, but does not inhibit the stereotyped behaviour due to amphetamine or apomorphine.

In rats, infusion of trazodone produces first a fall in mean blood pressure, followed by ECG changes only as a consequence of the hypotension produced. In anesthetized dogs, graded doses between 1 and 30 mg/kg i.v. demonstrated no effect on the bundle of His conduction and no evidence of heart block or rhythm disturbance other than the slowing of normal sinus rhythm, while 0.5 to 5 mg/kg imipramine slowed impulse conduction as well as atrial transmission. The effect of trazodone on the sleep-wakefulness cycle in rats was comparable to that of similar doses of imipramine: 10 mg/kg p.o. reduced and 160 mg/kg completely suppressed REM sleep.

## TOXICOLOGY

Acute Toxicity

The acute toxicity of trazodone has been examined in the mouse, rat, rabbit and dog. Summarized $LD_{50}$ values are presented in the following table.

| **$LD_{50}$ in mg/kg (95% confidence limits)** | | | | |
|---|---|---|---|---|
| **Route** | **Species** | | | |
| | **Mouse** | **Rat** | **Rabbit** | **Dog** |
| Intravenous | 91 (82–101) | 91 (86–96) | 52 | 40 |
| Intraperitoneal | 210 (189–233) | 178 (162–196) | - | - |
| Oral | 610 (540–689) | 690 (616–733) | 560 | 500 |

Signs of toxicity included dyspnea, salivation, ptosis, aggressivity, hypoactivity, prostration and clonic convulsions.

Subacute and Chronic Toxicity

In several subacute studies in rats, 100 to 450 mg/kg/day p.o. for one to four months produced a decrease in body weight gain and slight liver enlargement in males as the main toxic effects. The highest dose also caused some deaths. In dogs, 50 and 100 mg/kg/day p.o. for one month produced tremors, vomiting and clonic convulsions.

One of two dogs receiving 100 mg/kg died after 3 weeks. In a 6-month rat study, administration of approximately 250 mg/kg/day in the diet resulted in significantly greater liver weights than in control rats and in slightly lower weight gain in males. Dogs receiving 5 and 25 mg/kg/day for 6 months showed no toxic effects.

An eighteen-month study was carried out in rats using doses of 0, 30, 100 and 300 mg/kg/day p.o. A decrease in body weight gain was seen in all treated groups and males at the highest dose level showed significantly reduced food intake. No behavioral or pathologic effects were observed at the lowest dose level, while rats at the 100 mg/kg dose exhibited some lethargy and salivation immediately following dosing. At the highest dose level, there was excessive salivation and the animals became inactive, assuming a prone position for approximately 3 hours after dosing. Occasional body tremors were also seen. Tolerance developed to all these reactions within 30 weeks.

Beagle dogs were given oral doses of 0, 10 and 40 mg/kg/day for one year; however, after 8 weeks the highest dose was reduced to 30 mg/kg/day following the death of 3/10 animals in the group. No abnormal signs were observed at the 10 mg/kg level. In the 20 mg/kg group, one animal was found prostrate and panting on one occasion and another was unexpectedly found dead near the end of the study. 40 mg/kg produced occasional transient ataxia, excessive salivation and convulsions. Following the three deaths and the reduction of dosage to 30 mg/kg, a fourth death occurred 16 weeks later, subsequent to convulsions. A fifth animal became hypersensitive to touch and aggressive during the final 6 months of the study. Hematological and biochemical analyses were normal apart from one case of transient anemia in the 20 mg/kg group and slightly elevated SGPT values in 2/6 high dose dogs during the final 3 months.

Groups of 6 rhesus monkeys received 0, 20, 40, and 80 mg/kg/day of trazodone by gavage for one year. The only effects noted were a slight dose-related decrease in activity and tremors in 3 high dose monkeys. Both effects decreased during the study.

Reproductive Studies

A number of reproductive studies were performed. Fertility and general reproductive performance of male and female rats were not affected by doses of up to 250 mg/kg/day. At 300 mg/kg, the birth weight of pups was significantly reduced.

In one rat study, 100 and 210 mg/kg/day p.o. was given during days 10-15 and 6-15 of gestation respectively, and another study, 150 to 450 mg/kg/day p.o. during days 9-14 of gestation. At 100 mg/kg only a sedative effect on dams was noted. 150 mg/kg and higher doses produced increased sedation, decreased maternal and fetal weights, and retarded ossification. 300 and 450 mg/kg resulted in a significant increase in resorption and stillborn feti in addition to retarded fetal growth. Also noted were isolated cases of branched rib, separated thoracic arch, umbilical hernia, and exencephalia.

Peri-and postnatal effects of up to 300 mg/kg/day of trazodone were examined in rats. The only effects observed were reduced birth and weaning weights of offspring in the highest dosage group.

When doses approximately 30 - 50 times the proposed maximum human dose were administered

to rats, trazodone was shown to cause increased fetal resorption and other adverse effects on the fetus. There was also an increase in congenital anomalies in one of three rabbit studies at approximately 15 - 50 times the maximum human dose.

Carcinogenicity Studies

A two-year carcinogenicity study was performed in rats at dose levels of 0, 40 and 80 mg/kg/day. Larger numbers of female rats in both treatment groups died sooner than controls and most deaths were related to the presence of pituitary tumors. The incidence of palpable masses (mammary tumors, cysts, etc.) also was increased in both treatment groups at 12, 13, and 14 months. The observations may be related to the effects of trazodone on prolactin secretion. (Acute administration caused an increase in prolactin blood levels; chronic administration did not; however, turnover was not studied. A neuroleptic, used as a positive control, produced similar results). The relative incidences of male rats with pituitary tumors were reversed; however, early deaths due to nephritis and other causes might have influenced these observations.

## REFERENCES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2. Feighner, John P.: Trazodone, A Triazolopyridine Derivative, in Primary Depressive Disorder. J. of Clinical Psychiatry. Volume 41, No. 7: 250-255, 1980.

3. Gamble Donald E. and Peterson Linda G. : Trazodone Overdose: Four Years of Experience From Voluntary Reports. J. of Clnical Psychiatry. Volume 47, No. 11: 544-546, 1986.

4. DESYREL™ Canadian Product Monograph. Bristol-Myers Squibb Canada. Revised October 29, 2004. Control No. 094864.

## PART III: CONSUMER INFORMATION

**[Pr]pms-TRAZODONE**
**Trazodone Hydrochloride Tablets, USP**

**This leaflet is part III of a three-part "Product Monograph" published when pms-TRAZODONE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about pms-TRAZODONE. Contact your doctor or pharmacist if you have any questions about the drug.**

## ABOUT THIS MEDICATION

**What the medication is used for:**
pms-TRAZODONE (trazodone hydrochloride) is an antidepressant used to treat the symptoms of depression in adults over 18 years old.

**What it does:**
pms-TRAZODONE belongs to a group of medicines called antidepressants. Depression is thought to be caused by an imbalance of certain chemicals that occur naturally in the brain. pms-TRAZODONE works to correct the imbalance in one of these chemicals (serotonin). This may help ease emotional and physical symptoms of depression.

**When it should not be used:**
**Do not use pms-TRAZODONE if:**
- you are allergic to trazodone or any other ingredients of this medicine. (see What the non medicinal ingredients are).

**What the medicinal ingredient is:**
Trazodone hydrochloride

**What the non medicinal ingredients are:**
Croscarmellose sodium, dibasic calcium phosphate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and the following:
**50 mg & 75 mg** also contain: FD&C Yellow #6

**What dosage forms it comes in:**
**Tablets:** 50 mg, 75 mg & 100 mg

## WARNINGS AND PRECAUTIONS

**pms-TRAZODONE is not for use in children and adolescents under 18 years of age.**

**During treatment with these types of medications, it is important that you and your doctor have good ongoing communication about how you are feeling.**

**New or Worsened Emotional or Behavioural Problems**
Particularly in the first weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience new or worsened feelings of agitation, hostility or anxiety, or thoughts about suicide, or harm to others. Suicidal thoughts and actions can occur in any age group but may be more likely in patients 18 to 24 years old. Should this happen to you, or to those in your care**, talk to your doctor immediately**. Close observation by a doctor is necessary in this situation. **Do not discontinue your medication on your own**.

**BEFORE you use pms-TRAZODONE talk to your doctor or pharmacist if you:**
- have a history or a family history of heart problems, including: heart disease, heart attack, QT prolongation, arrhythmias (irregular heart beat), or a family history of sudden cardiac death at age younger than 50 years
- have liver problems
- have kidney problems
- have or have had fainting or dizziness
- have electrolyte disturbances (e.g., low blood potassium or magnesium levels) or conditions that could lead to electrolyte disturbances (e.g., vomiting, diarrhea, dehydration)
- have an eating disorder or are following a strict diet
- have diabetes, especially with associated nerve disorders
- have or have had abnormal bleeding
- have bipolar disorder
- have blood pressure problems
- have had breast tumours
- have had pituitary tumours
- have conditions that might predispose you to priapism, (painful erections greater than 4 hours in duration) such as sickle cell anemia, multiple myeloma, or leukemia, or if you have any anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease)
- are taking or have recently taken any prescription, non-prescription, or natural/herbal medications (see Interactions with this Medication)
- are pregnant, thinking about becoming pregnant or breastfeeding
- are older than 65 years of age

Do not drive or operate any tools or machines until you know how pms-TRAZODONE affects you.

**Effects on Newborns**
Some newborns whose mothers took certain antidepressants, such as trazodone, during pregnancy have shown such symptoms as breathing and feeding difficulties, jitteriness and constant crying. In most cases, the antidepressant was taken during the third trimester of pregnancy. These symptoms normally resolve over time. However, if your baby experiences any of these symptoms, contact your doctor as soon as you can.

## INTERACTIONS WITH THIS MEDICATION

**There are medications that may cause pms-TRAZODONE to be less effective, or may cause you to have side effects or drug reactions.**

**The following list includes some, but not all, of the drugs that may interact with pms-TRAZODONE:**
- Other antidepressants, such as SSRIs, SNRIs, certain tricyclics, drugs used to treat schizophrenia (e.g. olanzapine, risperidone),

or bipolar depression (e.g. lithium).
- Other drugs that affect serotonin, such as lithium, drugs containing tryptophan, St. John's Wort, triptans (used to treat migraine)
- Drugs that alter CYP3A4 metabolism (e.g., ritonavir, ketoconazole, indinavir, itraconazole, carbamazepine)
- Certain medicines used to treat pain, such as opioids.
- Medicines which may affect blood clotting and increase bleeding such as aspirin, other non-steroidal anti-inflammatory drugs (e.g. ibuprofen), warfarin.
- Antibiotics and antifungals such clarithromycin, erythromycin, ciprofloxacin, ketoconazole, fluconazole
- Some heart medications to treat irregular heart rate, high blood pressure, diuretics (water pills), digoxin
- Barbiturates
- Phenytoin
- Drugs to treat nausea and vomiting (e.g., ondansetron, dolasetron, domperidone)
- Laxatives or enemas
- Pentamidine

Consumption of grapefruit, grapefruit juice, or products containing grapefruit extracts should be avoided while taking pms-TRAZODONE.

Do not drink alcohol while taking pms-TRAZODONE.

## PROPER USE OF THIS MEDICATION

It is very important that you take your medication exactly as your doctor has instructed. Never exceed the prescribed dose.

pms-TRAZODONE should be taken shortly after a meal or light snack

**Usual Adult Dose:**
- 150 mg to 200 mg daily, in two or three divided doses.
- Doses may be increased by increments of 50 mg, usually up to 300 mg daily in divided doses.

**Elderly (65 years of age or older):**
Doses should not exceed half the recommended adult dosages.

**Discontinuing the medication:**
Continue to take pms-TRAZODONE for as long as your doctor recommends. Do not suddenly stop taking or change the dose of your medicine without talking to your doctor first. See the section SIDE EFFECTS AND WHAT TO DO ABOUT THEM for more information.

**Overdose:**

If you think you have taken too much pms-TRAZODONE, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**
Take the next dose at the usual time. Do not take a double dose to make up for the missed dose.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, pms-TRAZODONE can cause side effects, although not everybody gets them. For most patients these side effects are likely to be minor and temporary. However, some may be serious. Talk to your doctor if you experience side effects and they worry you, as the dose may have to be adjusted.

The most common side effects of pms-TRAZODONE are:
- Headache
- Drowsiness, sedation
- Dry mouth
- Dizziness (light-headedness)
- Nausea
- Fatigue
- Diarrhea
- Constipation
- Back pain
- Blurred vision

**Other effects may include the following:**
Heart pounding, heart racing, ringing in the ears, vomiting, weakness, feeling jittery, disturbance in attention, tingling sensation, musculoskeletal stiffness, erectile dysfunction (in men), tremors, hot flashes, sore throat, changes in blood sugar, decreased appetite, changes in sense of taste, sweating, nervousness, urinary urgency, excessively frequent urination, confusion, memory problems, painful menstrual periods.

***This is not a complete list of side effects. If you develop any other unusual side effects while taking pms-TRAZODONE, please talk to your doctor.***

**Effect on the hormone Prolactin**
In women, medicines of this type may cause changes in the regularity of their monthly periods or leakage of milk from the breast even if they are not pregnant. In some men, after prolonged treatment, there may be some diminished sexual function and breast enlargement may be experienced. Tell your doctor if you experience any of these symptoms.

**Discontinuation Symptoms**
Even if you have side effects, contact your doctor before stopping or reducing your dosage of pms-TRAZODONE. Discontinuation symptoms including anxiety, agitation and sleep disturbances, have been reported with trazodone. Tell your doctor immediately if you have these or any other symptoms. Your doctor may adjust the dosage of pms-TRAZODONE to reduce the symptoms.

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|---|---|---|---|---|
| **Symptom/effect** | | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | | **Only if severe** | **In all cases** | |
| Common | Low blood pressure: feeling dizzy, lightheaded | | ✓ | |
| Uncommon | Fainting | | | ✓ |
| Rare | Painful erection lasting more than 4 hours | | | ✓ |
| | Uncontrollable movements of the body or face | | ✓ | |
| | Inability to urinate | | ✓ | |
| Unknown | Allergic reactions (red skin, hives, itching, swelling of the lips, face, tongue, throat, trouble breathing) | | | ✓ |
| | Bruising or unusual bleeding from the skin or other areas | | ✓ | |
| | Low sodium level in blood (symptoms of tiredness, weakness, confusion combined with achy, stiff or uncoordinated muscles) | | ✓ | |
| | Mania/Hypomania (elevated or irritable mood, decreased need for sleep, racing thoughts) | | ✓ | |
| | Convulsions | | | ✓ |

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|---|---|---|---|---|
| **Symptom/effect** | | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | | **Only if severe** | **In all cases** | |
| Unknown | Serotonin Syndrome (a combination of most or all of the following: confusion, restlessness, sweating, shaking, sudden jerking of the muscles, hallucinations, fast heartbeat) | | | ✓ |
| | Heart rhythm problem (dizziness, palpitations or fast heartbeat, fainting) | | | ✓ |
| | Akathisia (feeling restless and unable to sit or stand still) | | ✓ | |
| | Dark-coloured, tarry stools | | ✓ | |
| | Sore throat, fever, general feeling of being unwell | | ✓ | |
| See warnings and precautions | Thoughts of death or suicide | | | ✓ |
| | New or worsened emotional or behavioural problems | | ✓ | |

## HOW TO STORE IT

Store between 15°C and 30°C. Protect from light.

Do not use pms-TRAZODONE after the expiry date. All expired medications should be returned to your pharmacist.

Keep this and all medicines in a safe place away from children.

**Reporting Side Effects**
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
**3 ways to report**:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9
    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting Pharmascience Inc. at 1-888-550-6060.

This leaflet was prepared by
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