

PRODUCT MONOGRAPH

Pr MYLAN-TRAZODONE

TRAZODONE HYDROCHLORIDE TABLETS, USP

50 mg, 100 mg, 150 mg

ANTIDEPRESSANT

Mylan Pharmaceuticals ULC
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ANTIDEPRESSANT

ACTION AND CLINICAL PHARMACOLOGY

Trazodone hydrochloride is a psychoactive compound with sedative and antidepressant properties. Its mechanism of action in humans is not clear.

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. 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, m-chlorophenylpiperazine (mCPP) by cytochrome P450 3A4 (CYP3A4). Other metabolic pathways that may be involved in metabolism of trazodone have not been well characterized.

Elimination

Approximately 60-70% of ¹⁴C-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 hydrochloride may accumulate in the plasma.

The pharmacokinetic profile of Mylan-Trazodone (Mylan Pharmaceuticals ULC) in comparison to Desyrel (Bristol Laboratories Canada) is summarized below:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA
Mylan-Trazodone
 (100 mg)
 From measured data
 Geometric Mean
 Arithmetic Mean (CV%)

PARAMETER (means)	Mylan-Trazodone Mylan Pharmaceuticals ULC	DESYREL Bristol Labs Canada	RATIO OF Geometric Means
AUC _T (ng.hr/mL)	9068.47 9468.41 (32%)	8987.33 9478.83 (34%)	100
AUC _I (ng.hr/mL)	9417.57 9885.49 (35%)	9278.08 9863.72 (38%)	100
C _{max} (ng/mL)	1213.47 1236.17 (20%)	1185.23 1210.61 (21%)	102
T _{max} (h)	1.86 (44%)	2.29 (54%)	
T _{1/2} (h)	5.6	6.0	

The T_{max} and T_{1/2} parameters are expressed as the arithmetic means.

Drug-Drug Interactions

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

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

INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

Known hypersensitivity to trazodone.

WARNINGS

Trazodone has been associated with the occurrence of priapism. In approximately 1/3 of the cases reported, surgical intervention was required and, in a portion of these cases, permanent impairment of erectile function or impotence resulted. Male patients with prolonged or inappropriate erections should immediately discontinue the drug and consult their physician. If the condition persists for more than 24 hours, it would be advisable for the treating physician to consult a urologist or appropriate specialist in order to decide on a management approach.

Caution should be used when administering MYLAN-TRAZODONE to patients with cardiac disease, and such patients should be closely monitored, since antidepressant drugs (including trazodone hydrochloride) have been associated with the occurrence of cardiac arrhythmias. Recent clinical studies in patients with pre-existing cardiac disease indicate that trazodone hydrochloride may be arrhythmogenic in some patients in that population. Arrhythmias identified include isolated premature ventricular contractions (PVC's), ventricular couplets, and in two patients short episodes (3-4 beats) of ventricular tachycardia. There have also been several post-marketing reports of arrhythmias in trazodone hydrochloride treated patients who have pre-existing cardiac disease and in some patients who did not have pre-existing cardiac disease. MYLAN-TRAZODONE is not recommended for use during the initial recovery phase of myocardial infarction.

PRECAUTIONS

General: The possibility of suicide in depressed patients remains during treatment and until significant remission occurs. Therefore, the number of tablets prescribed at any one time should take into account this possibility and patients with suicide ideation should never have access to large quantities of trazodone.

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 previously diagnosed seizure disorder.

Safety of Driving: Since trazodone hydrochloride may impair the mental and/or physical abilities required for performance of potentially hazardous tasks, such as operating an automobile or machinery, the patient should be cautioned not to engage in such activities while impaired.

Drug Interactions: *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 or nefazodone may lead to substantial increases in trazodone plasma concentrations with the potential for adverse effects. If trazodone is used with a potent CYP3A4 inhibitor, a lower dose of trazodone should be considered.

Carbamazepine reduced plasma concentrations of trazodone when co-administered. Patients should be closely monitored to see if there is a need for an increased dose of trazodone when taking both drugs.

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

Increased serum digoxin and phenytoin levels have been reported to occur in patients receiving trazodone hydrochloride concurrently with either of those two drugs. Little is known about the interaction between trazodone hydrochloride and general anesthetics; therefore prior to elective surgery, trazodone hydrochloride should be discontinued for as long as clinically feasible.

Because it is not known whether an interaction will occur between trazodone hydrochloride and MAO inhibitors, administration of trazodone hydrochloride should be initiated very cautiously with gradual increase in dosage as required, if an MAO inhibitor is given concomitantly or has been discontinued shortly before medication with trazodone hydrochloride is instituted.

Trazodone hydrochloride 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.

Because of the absence of experience, concurrent administration of electroshock therapy should be avoided.

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

Use in Pregnancy and Nursing Mothers: Since the safety and use of trazodone hydrochloride in pregnant women has not been established, it 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. Since trazodone hydrochloride and/or 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.

Use in Children: The safety and effectiveness of trazodone hydrochloride in children below the age of 18 have not been established.

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, and trazodone hydrochloride should be discontinued if the white blood cell or absolute neutrophil count falls below normal.

Hyperprolactinemia and Breast Tumours: There is sufficient experimental evidence to conclude that chronic administration of those psychotropic drugs, such as trazodone, which increases 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 (see TOXICOLOGY).

ADVERSE REACTIONS

The most common adverse reactions encountered are drowsiness, nausea/vomiting, headache and dry mouth. Adverse reactions reported include the following:

Behavioural: drowsiness, fatigue, lethargy, retardation, lightheadedness, dizziness, difficulty in concentration, confusion, impaired memory, disorientation, excitement, agitation, anxiety, tension, nervousness, restlessness, insomnia, nightmares, anger, hostility, and, rarely, hypomania, visual distortions, hallucinations, delusions and paranoia.

Neurologic: tremor, headache, ataxia, akathisia, muscle stiffness, slurred speech, retarded speech, vertigo, tinnitus, tingling of extremities, paresthesia, weakness, grand mal seizures, (see PRECAUTIONS) and, rarely, impaired speech, muscle twitching numbness, dystonia and involuntary movements.

Autonomic: dry mouth, blurred vision, diplopia, miosis, nasal congestion, constipation, sweating, urinary retention, increased urinary frequency, and incontinence.

Cardiovascular: orthostatic hypotension, hypertension, tachycardia, palpitations, shortness of breath, apnea, syncope, arrhythmias, prolonged P-R interval, atrial fibrillation, bradycardia, ventricular ectopic activity (including ventricular tachycardia), myocardial infarction, cardiac arrest and conduction block.

Gastrointestinal: nausea, vomiting, diarrhea, gastrointestinal discomfort, anorexia and increased appetite.

Endocrine: Priapism (see PRECAUTIONS), decrease and, more rarely, increase in libido, weight gain and loss and, rarely, menstrual irregularities, retrograde ejaculation, and inhibition of ejaculation.

Allergic or Toxic: skin rash, itching, edema, and, rarely, hemolytic anemia, methemoglobinemia, liver enzyme alterations, and obstructive jaundice, leukocytoclastic vasculitis, purpuric maculopapular eruptions, photosensitivity and fever.

Miscellaneous: aching joints and muscles, peculiar taste, hypersalivation, chest pain, hematuria, red, tired and itchy eyes.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage of trazodone hydrochloride may cause an increase in incidence or severity of any of the reported adverse reactions, e.g. hypotension and excessive sedation. In one known suicide attempt, the patient presented with symptoms of drowsiness and weakness three hours after ingesting 7.5 grams (12.5 times the maximum daily dose) of trazodone hydrochloride. Recovery was uneventful. Death by deliberate or accidental overdosage with trazodone alone has not yet been reported. For management of a suspected drug overdose, contact your regional Poison Control Centre.

There is no specific antidote for trazodone hydrochloride. Management of overdosage should, therefore, be symptomatic and supportive. Any patient suspected of having taken an overdosage should be admitted to hospital as soon as possible and the stomach emptied by gastric lavage. Forced diuresis may be useful in facilitating elimination of the drug.

DOSAGE AND ADMINISTRATION

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance. 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.

Usual Adult Dosage: The recommended initial dose is 150-200 mg daily, in two or three divided doses. MYLAN-TRAZODONE (trazodone hydrochloride) should be taken shortly after a meal or light snack in order to reduce the incidence of adverse reactions. The initial 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 in hospitalized patients, 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.

Use in the Elderly: If used in the elderly, doses not exceeding half the recommended adult dosage should be used, with adjustments made depending on tolerance and response.

Because safety and effectiveness in children have not been established trazodone hydrochloride is not recommended in the pediatric age group.

AVAILABILITY

Mylan-Trazodone 50 mg

Pale orange, round, biconvex tablet embossed with “G” over TZ5" on one side and scored on the other. Mylan-Trazodone tablets are available in plastic bottles of 100's and 250's.

Mylan-Trazodone 100 mg

White, round, biconvex tablet embossed with “G” over “TZ10" on one side and scored on the other. Mylan-Trazodone tablets are available in plastic bottles of 100's.

Mylan-Trazodone 150 mg

Pale orange, round, biconvex embossed with GTZ15 on one side and scored on the other.

Mylan-Trazodone tablets are available in plastic bottles of 100's.

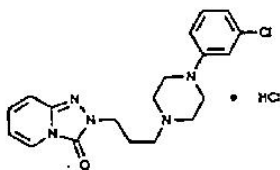
COMPOSITION

Mylan-Trazodone tablets contain:

Trazodone hydrochloride, USP, Croscarmellose sodium, Lactose, Magnesium Stearate, Cellulose, Povidone.

PHARMACEUTICAL INFORMATION

Proper name:	Trazodone hydrochloride
Chemical group:	Triazolopyridine
Chemical name:	1,2,4-Triazolo-4,3-a-pyridin-3(2H)-one,2-3-4-(3-chlorophenyl)-1-piperazinyl-, monohydro-chloride.
Molecular Formula:	$C_{19}H_{22}ClN_5O \cdot HCl$
Structural Formula:	



Molecular Weight: 408.33

Description: Trazodone hydrochloride USP - white to off-white crystalline powder.

Melts between 231 and 234° C when the melting point determination is carried out in an evacuated capillary tube; otherwise melts with decomposition over a broad range below 230° C.

Solubility: Sparingly soluble in chloroform and in water.

Other Characteristics: Trazodone is not chemically related to tricyclic, tetracyclic, or other known antidepressants.

Storage requirements: Trazodone should be stored in tight, light-resistan

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 His bundle 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

LD₅₀ 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 behavioural 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 of 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.

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.

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