PRODUCT MONOGRAPH

ratio-TRAZODONE

(Trazodone Hydrochloride)

50 mg, 100 mg and 150 mg Tablets

USP

Antidepressant

Teva Canada Limited.
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Date of Preparation:
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PHARMACOLOGICAL CLASSIFICATION

Antidepressant

ACTION

The mechanism of action of trazodone hydrochloride, a psychoactive compound with sedative and antidepressant properties, is unclear in humans.

After oral administration, trazodone hydrochloride is well absorbed, with plasma levels peaking within one-half to two hours after ingestion. Food enhances, although delays somewhat, absorption. For the period from 3 to 10 hours after dosing, the mean plasma elimination half-life is 4.4 hours; and for the period from 10 to 34 hours after dosing, it is 7 to 8 hours. Metabolism of the drug is extensive, with 3 or 4 major metabolites having been identified in man. Approximately 60-70% of ^{14}C-labelled trazodone appeared in the urine within 2 days, whereas only 9-29% was excreted in the feces over 60-100 hours. At concentrations attained with therapeutic doses, trazodone is 89-95% protein bound.

A comparative, randomized, two-way, crossover, bioavailability study of two 100mg trazodone hydrochloride tablet products (Trazodone and Desyrel®) was performed in healthy adult males. The pharmacokinetic data are tabulated below:

Geometric Mean Arithmetic Mean (C.V.)			
	Trazodone (1 x 100mg)	Desyrel® (1 x 100 mg)	Percentage of Desyrel®
AUC_T (n g • h/mL)	6502 6990 (41)	5884 6287 (39)	111
AUC_I (n g • h/mL)	6905 7470 (45)	6374 6884 (44)	108
C_{MAX} (n g /mL)	992 1042 (32)	907 944 (32)	109
T_{max*} (h)	1.32 (1.17)	1.26 (0.78)	---
$T_{1/2*}$	6.95 (3.41)	7.32 (3.76)	---

*These are the arithmetic means (standard deviation).

A two-way, single dose bioavailability study of two 150 mg trazodone hydrochloride tablet products (Trazodone and Desyrel®) was conducted in normal healthy male volunteers. The pharmacokinetic data are tabulated below:

Geometric Mean Arithmetic Mean (C.V.)			
	Trazodone (2/3 x 150mg)	Desyrel® (2/3 x 150 mg)	Percentage of Desyrel®
AUC_T (n g • h/mL)	10938 11192 (25)	10721 11117 (29)	102
AUC_I	11384	11159	102

(n g • h/mL)	11763 (30)	11619 (32)	
C_{max} (n g /mL)	1510 1522 (15)	1556 1599 (26)	97
T_{max*} (h)	1.09 (0.62)	1.91 (0.89)	---
$T_{1/2*}$	7.83 (2.37)	7.51 (1.95)	---

*These are the arithmetic means (standard deviation).

INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

ratio-TRAZODONE (trazodone hydrochloride) is contraindicated in patients with a known hypersensitivity to trazodone.

WARNINGS

Priapism has occurred with the use of trazodone. Surgical intervention was required in approximately 1/3 of the cases reported, and permanent impairment of erectile function or impotence resulted in a portion of these cases. Male patients should immediately discontinue the drug and consult their physician if prolonged or inappropriate erections occur. It would be advisable for the treating physician to consult a urologist or appropriate specialist if the condition persists for more than 24 hours in order to decide on a management approach.

Recent clinical studies have shown that trazodone hydrochloride may be arrhythmogenic in some patients with pre-exisiting cardiac disease. Isolated PVC's, ventricular couplets, and in two patients, short episodes (3-4 beats) of ventricular

tachycardia are the identified arrhythmias. Several post-marketing reports of arrhythmias exist in trazodone-treated patients; in both those patients with pre-existing cardiac disease and in some patients who did not have pre-existing cardiac disease. Therefore, patients with pre-existing cardiac disease should be closely monitored, particularly for cardiac arrhythmias, until the results of prospective studies are available. ratio-TRAZODONE (trazodone hydrochloride) is not recommended for use during the initial recovery phase of myocardial infarction.

PRECAUTIONS

General:

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

In a small number of patients, episodes of grand mal seizures have been reported. Most of these patients were already receiving anticonvulsant therapy for a previously diagnosed seizure disorder.

Safety of Driving:

ratio-TRAZODONE (trazodone hydrochloride) may impair the mental and/or physical abilities required for performance of potentially hazardous tasks, such as operating an automobile or dangerous machinery. Therefore, the patient should be cautioned against engaging in such activities while impaired.

Interactions:

The response to alcohol and the effects of barbiturates and other CNS depressants may be enhanced by trazodone; patients should be cautioned accordingly.

Serum phenytoin and digoxin levels have been reportedly increased in patients

receiving trazodone concurrently with either of these two drugs. ratio-TRAZODONE should be discontinued for as long as clinically feasible prior to elective surgery since little is known about the interaction between trazodone and general anesthetics.

Administration of ratio-TRAZODONE 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 ratio-TRAZODONE is instituted, because it is not known whether an interaction will occur between ratio-TRAZODONE and MAO inhibitors.

Caution is required if ratio-TRAZODONE is given to patients receiving antihypertensive drugs, and an adjustment in the dose of antihypertensive medication may be required since trazodone may cause hypotension, including orthostatic hypotension and syncope.

Concurrent administration of electroshock therapy should be avoided because of the absence of experience.

Use in Pregnancy and Nursing Mothers:
ratio-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, because the safety and use of trazodone in pregnant women have not been established. Unless the potential benefits justify the possible risks to the child, ratio-TRAZODONE should not be administered to nursing mothers since trazodone and/or its metabolites have been detected in the milk of lactating animals.

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

Laboratory Tests:

In patients who develop sore throat, fever or other signs of infection or blood dyscrasia, it is recommended that white blood cell and differential counts be performed. If the white blood cell or absolute neutrophil count falls below normal, ratio-TRAZODONE should be discontinued.

Hyperprolactinemia and Breast Tumours:

Sufficient experimental evidence exists to conclude that the 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. It is indicated in tissue culture experiments 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.

Disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, but the clinical significance of elevated serum prolactin levels or increased secretion and turnover are unknown for most patients. An association between the chronic administration of these drugs and mammary tumourigenesis has not been found in clinical studies or epidemiologic studies conducted to date. The available evidence is considered too limited to be conclusive at this time (see TOXICOLOGY).

ADVERSE REACTIONS

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

Behavioral:

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 and cardiac arrest.

Gastrointestinal:

Nausea,vomiting, diarrhea, gastrointestinal discomfort, anorexia and increased appetite.

Endocrine:

Priapism (see WARNINGS), 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, leukocytoblastic 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

ratio-TRAZODONE (trazodone hydrochloride) overdosage 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, symptoms of drowsiness and weakness were apparent 3 hours after the ingestion of 7.5 grams (12.5 times the maximum daily dose) of trazodone hydrochloride. This patient recovered uneventfully. To date, there have been no reports of death by deliberate or accidental overdosage with trazodone alone.

As no specific antidote for trazodone hydrochloride exists, management of overdosage should be symptomatic and supportive.

A patient should be admitted to the hospital as soon as possible and the stomach emptied by gastric lavage if ingestion of an overdosage is suspected. In facilitating elimination of the drug, forced diuresis may be useful.

DOSAGE AND ADMINISTRATION

Dosage should be initiated at a low level and increased gradually. The clinical response and any evidence of intolerability should be carefully noted. It should be kept in mind that there may be a lag in therapeutic response and that increasing the dosage rapidly does not normally shorten this latent period but may increase the incidence of side effects.

Usual Adult Dosage:

The recommended initial dose is 150-200 mg a day, in two or three divided doses. In order to reduce the incidence of adverse reactions, ratio-TRAZODONE (trazodone hydrochloride) should be taken shortly after a meal or light snack. The initial dose may be increased by increments of 50 mg, usually up to 300 mg daily in divided doses, according to tolerance and response. Doses up to 400 mg daily and, rarely, up to 600

mg daily in hospitalized patients may be required in some patients. The administration of a major portion of the daily dose at bedtime or a reduction of dosage may be required in the event that drowsiness occurs.

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

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

ratio-TRAZODONE is not recommended for use in the pediatric age group because safety and effectiveness in children have not been established.

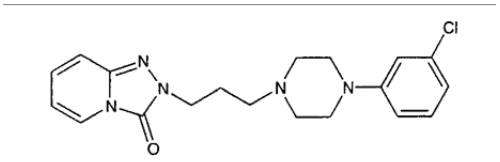
PHARMACEUTICAL INFORMATION

Drug substance:

Proper name: Trazodone Hydrochloride

Chemical name: 2-(3-(4-(m-Chlorophenyl)-1-piperazinyl)-propyl)-s-triazolo(4,3-a)pyridin-3(2H)-one monohydrochloride

Structural formula:



.HCl

Molecular formula: $C_{19}H_{22}Cl_1N_5O \bullet HCl$

Molecular weight: 408.33

Description: White to off-white crystalline powder. Soluble in chloroform and sparingly soluble in water. Melts between 231° and 234° when the melting point determination is carried out in an evacuated capillary tube; otherwise melts with decomposition over a broad range below 230°.

Stability and Storage Recommendations:

Store between 15-30°C and protect from light. Unit dose strips should be stored between 15-25°C and protected from light and high humidity.

AVAILABILITY

ratio-TRAZODONE (trazodone hydrochloride) Tablets 50 mg are light orange, round, standard convex, film-coated, single-scored tablets, with one side imprinted with "rph" and “T43” on the other side. Bottles of 100's and 500's.

ratio-TRAZODONE (trazodone hydrochloride) Tablets 100 mg are white, round, standard convex, film-coated, single-scored tablets, with one side imprinted with "rph" and “T42” on the other side. Bottles of 100's.

ratio-TRAZODONE (trazodone hydrochloride) Tablets 150 mg are light orange, rectangular-shaped, trisected and bisected compressed tablets, with one side imprinted with "rph" and “T41” on the other side. Bottles of 100's.

The DIVIDOSE tablet design makes dosage adjustments easy. Each tablet can be broken accurately to provide any of the following dosages.

PHARMACOLOGY

Trazodone differs significantly from other known psychopharmacological agents in pharmacological profile.

Trazodone impedes the uptake of serotonin by the membrane. The depletion of brain serotonin by fenfluramine is impeded with small doses of the drug, but doses of 50 mg/kg do not affect the concentration of serotonin in the rat brain. Trazodone is a weak inhibitor of noradrenaline re-uptake in experimental studies but is practically inactive against 1-dopa, histamine and acetylcholine. It is not known to inhibit monoamine oxidase.

Trazodone exhibits CNS depressant activities, with motor activity being decreased in cats, rats and mice, and hexobarbital-induced sleeping time being increased in mice. At

doses which do not influence the unconditioned response (ED_{50}=19.5 mg/kg p.o.), trazodone also inhibits conditioned avoidance responding in rats. Trazodone has very weak muscle relaxant activity, but has no anticonvulsant, anti-reserpine or cataleptogenic effects.

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

The infusion of trazodone in rats produces first a fall in mean blood pressure, followed by ECG changes only as a consequence of the hypotension produced. There was no effect on His bundle conduction nor evidence of heart block or rhythm disturbance other than the slowing of normal sinus rhythm when anesthetized dogs were administered graded doses of trazodone between 1 and 30 mg/kg i.v. Doses of 0.5 to 5 mg/kg imipramine, however, slowed impulse conduction as well as atrial transmission. Similar doses of trazodone and imipramine had comparable effects on the sleep-wakefulness cycle in rats; REM sleep was reduced with 10 mg/kg p.o. and completely suppressed with 160 mg/kg.

TOXICOLOGY

Acute Toxicity:

LD_{50} in mg/kg (95% Confidence Limits)

	Species			
Route	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, prostation and clonic convulsions.

Subacute and Chronic Toxicity:

Several subacute studies were conducted in rats using doses ranging from 100 to 450 mg/kg/day p.o. for one to four months. The main toxic effects observed were decreased body weight gain and slight liver enlargement in males. There were some deaths at the highest dose. Tremors, vomiting and clonic convulsions were produced in dogs given 50 and 100 mg/kg/day p.o. for one month.

Of two dogs receiving 100 mg/kg, one died after 3 weeks. Administration of approximately 250 mg/kg/day in the diet of rats for 6 months resulted in significantly greater liver weights than in control rats and slightly lower weight gain in males. No toxic effects were evident in dogs receiving 5 and 25 mg/kg/day for 6 months.

Rats were given doses of 0, 30, 100 and 300 mg/kg/day p.o for 18 months. All treated

groups demonstrated decreased body weight gain, and males in the highest dose group showed significantly reduced food intake. Rats at the 100 mg/kg dose exhibited some lethargy and salivation immediately following dosing, but at the lowest dose level, no behavioral or pathologic effects were observed. There was excessive salivation and the animals became inactive, assuming a prone position for approximately 3 hours after dosing with the highest dose. There were occasional body tremors also. Within 30 weeks, tolerance developed to all these reactions.

Oral doses of 0, 10, 20 and 40 mg/kg/day were given to beagle dogs for one year. Following the death of 3/10 animals in the highest dose group, the dose was reduced to 30 mg/kg/day after 8 weeks. There were no abnormal signs at the 10 mg/kg level. One animal in the 20 mg/kg group was found prostate and panting on one occasion and another was unexpectedly found dead near the end of the study. Occasional transient ataxia, excessive salivation and convulsions were produced with 40 mg/kg. Upon reducing the dosage to 30 mg/kg following the three deaths, a fourth death occurred 16 weeks later, subsequent to convulsions. During the final 6 months of the study, a fifth animal became hypersensitive to touch and aggressive. Apart from one case of transient anemia in the 20 mg/kg group and slightly elevated SGPT values in 2 of the high dose dogs during the final 3 months, hematological and biochemical analyses were normal.

Trazodone was administered in doses of 0, 20, 40, and 80 mg/kg/day by gavage for one year to groups of 6 rhesus monkeys. A slight, dose-related decrease in activity and tremors in 3 high dose monkeys were the only effects noted. Both these effects decreased during the study.

Reproductive Studies:

Fertility and general reproductive performance of male and female rats were unaffected by doses of up to 250 mg/kg/day. The birth weight of pups was significantly reduced at 300 mg/kg.

Two rat studies were conducted: one in which rats were given 100 and 210 mg/kg/day

p.o. during days 10-15 and 6-15 of gestation, respectively; and another in which doses of 150 - 450 mg/kg/day p.o. were given during days 9-14 of gestation. Only a sedative effect on dams was noted at 100 mg/kg. Increased sedation, decreased maternal and fetal weights and retarded ossification were produced at doses of 150 mg/kg and higher. A significant increase in resorptions and stillborn fetuses, in addition to retarded fetal growth, occurred with 300 and 450 mg/kg. Isolated cases of branched rib, separated thoracic arch, umbilical hernia and exencephalia were also noted.

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

Carcinogenicity Studies:

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

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