PRODUCT MONOGRAPH

PHL-TRAZODONE
(Trazodone Hydrochloride, USP)

50 mg, 75 mg and 100 mg Tablets

Antidepressant

Pharmel Inc.
8699 8e Ave.
Montreal PQ
H1Z 2X4

Date of Preparation
February 23, 2004

Control # 089852, 089853

NAME OF DRUG

[Pr]phl-TRAZODONE

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

THERAPEUTIC CLASSIFICATION

Antidepressant

ACTION AND CLINICAL PHARMACOLOGY

The antidepressant action of trazodone appears to be associated with brain serotonin. *In vitro* studies have shown trazodone to be a selective inhibitor of serotonin uptake into isolated rat brain synaptosomes. The drug has also been found to antagonize the depletion of brain serotonin induced by fenfluramine and to inhibit uptake of serotonin by rat platelets *in vitro*. Behavioral changes induced by the serotonin precursor 5-hydroxytryptophan are potentiated by trazodone.

The action of trazodone observed in these studies is consistent with the biogenic amine theory of depression, which attributes depressive disorders to a deficiency of the neurotransmitters norepinephrine and serotonin at central receptor sites. Accordingly, antidepressant drugs owe their effects to blockade of amine reuptake by presynaptic neurons. This blockade increases the concentrations of these monoamines at postsynaptic receptor sites. Some antidepressants selectively inhibit norepinephrine reuptake; others, like trazodone, selectively block serotonin reuptake, and still others inhibit reuptake of both norepinephrine and serotonin.

A bioavailability study was performed in fourteen healthy volunteers, comparing two

different formulations of Trazodone Hydrochloride 50 mg tablets: ***phl-TRAZODONE*** *versus* ***DESYREL***, the Canadian Reference Product. The results are summarized as follows:

SUMMARY OF COMPARATIVE BIOAVAILABILITY DATA

[after single oral administration of 2 x 50 mg tablets]

phl-TRAZODONE 50 mg Tablets (Pharmel Inc., Canada)

versus

DESYREL 50 mg Tablets (Bristol-Myers Squibb Canada Inc.)

(From Measured Data)

Parameter	Geometric Mean Arithmetic Mean (C.V.%) Test	Reference	Ratio of Geometric Means (%)
AUC_T (ng·h/mL)	7944.82 8400.95 (31.13)	7854.34 8454.81 (37.02)	101.15
AUC_∞ (ng·h/mL)	8680.56 9102.16 (30.96)	8544.95 9138.98 (35.56)	101.59
C_{max} (ng/mL)	1325.20 1384.63 (32.26)	1145.81 1196.70 (32.26)	115.66
T_{max} (h)	0.85 (84.81)	1.65 (62.21)	
$T½_{el}$ (h)	6.17 (29.10)	6.08 (25.60)	

T_{max} and $T½_{el}$ -- arithmetic means (CV%)

The plasma concentration of trazodone declines in a biphasic manner. In the initial phase,

the mean plasma elimination half-life is 3 to 6 hours and the half life of the terminal phase is 5-9 hours.

When trazodone is taken shortly after food ingestion, there may be a slight increase (up to 20%) in the amount of drug absorbed, a decrease in peak plasma concentration of the drug, and the time to peak concentration when fasting is one hour and with food it is 2 hours.

Trazodone is extensively metabolized in the liver via hydroxylation, oxidation, N-Oxidation and splitting of the pyridine ring. A hydroxylated metabolite and Oxotriazolopyridinpropionic acid (the major metabolite excreted in the urine) are conjugated with glucuronic acid. The metabolite 1-m-chlorophenyl piperazine is pharmacologically active in humans, however it is unknown if any metabolites are pharmacologically active in animals. Results from animal studies indicate that trazodone does not induce its own metabolism.

Approximately 75% of trazodone is excreted in the urine via renal elimination within 72 hours and 20% is excreted in the feces via biliary elimination principally as inactive metabolites.

In vitro, trazodone is 89-95% bound to plasma proteins at plasma trazodone concentrations of 100-150 ng/mL.

INDICATIONS AND CLINICAL USE

phI-TRAZODONE (trazodone hydrochloride tablets) are indicated for the treatment of depression.

CONTRAINDICATIONS

Known hypersensitivity to trazodone.

WARNINGS

Recent 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 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-treated patients who have pre-existing cardiac disease and in some patients who did not have pre-existing cardiac disease.

Until the results of prospective studies are available, patients with pre-existing cardiac disease should be closely monitored, particularly for cardiac arrhythmias. Trazodone is not recommended for use during the initial recovery phase of myocardial infarction.

Priapism:
Priapism has been reported in some patients taking trazodone. In some instances surgical intervention has been necessary. Priapism usually occurs within the first two to three weeks of treatment, and it is often preceded by abnormally prolonged or inappropriate penile erections. Patients should be advised to discontinue trazodone immediately if such abnormalities are experienced.

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.

Although a cause and effect relationship has not been established, episodes of grand mal seizures have been reported in a small number of patients. The majority of these patients were already receiving anti-convulsant therapy for a previously diagnosed seizure disorder.

Safety of Driving:
Since trazodone 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.

Interactions:
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 concurrently with either of those two drugs. Little is known about the interaction between trazodone and general anesthetics; therefore, prior to elective surgery, trazodone should be discontinued for as long as clinically feasible.

Because it is not known whether an interaction will occur between trazodone and MAO inhibitors, administration of 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 trazodone is instituted.

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.

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

Use in Pregnancy and Nursing Mothers:
Since the safety and use of trazodone in pregnant women has not been established, it should not be used in women of child-bearing potential unless, in the opinion of the physician, the expected benefits justify the potential risk to the fetus. Since trazodone 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 in children below the age of 18 has 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 should be discontinued if the white blood cells or absolute neutrophil count falls below normal.

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 have 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 are 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.

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, dystonia, tingling of extremities, paresthesia, weakness, grand mal seizures, (see PRECAUTIONS) and, rarely, impaired speech, muscle twitching and numbness.

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, arryhthmias, prolonged P-R interval, atrial fibrillation, bradycardia, ventricular ectopic activity, myocardial infarction, and cardiac arrest.

Gastrointestinal:
Nausea, vomiting, diarrhea, gastro-intestinal 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, leukocytoclastic vasculitis, purpuric maculopapular eruptions, photosensitivity, fever and obstructive jaundice.

Miscellaneous:
Aching joints and muscles, peculiar taste, hyper salivation, chest pain, hematuria, red, tired and itchy eyes.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage of trazodone 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. Recovery was uneventful. Deaths by deliberate or accidental overdosage have not yet been reported.

There is no specific antidote for trazodone. 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. phl-TRAZODONE (trazodone hydrochloride tablets) 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.

Maintenance Dose:
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 is not recommended in the pediatric age group.

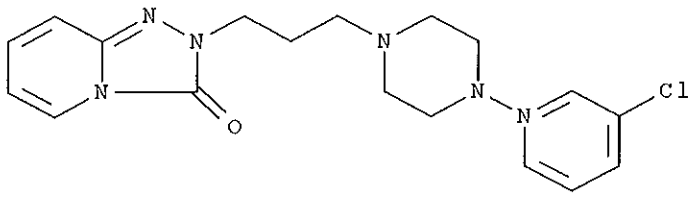
PHARMACEUTICAL INFORMATION

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

Structural Formula:



Molecular Formula: $C_{19}H_{22}ClN_5O$ HCl Molecular Weight: 408.33

Elemental Composition:
C–55.89%; H–5.68%; Cl–17.36%; N–17.15%; O–3.92%

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.

Stability and Storage Recommendations:
phl-TRAZODONE (trazodone hydrochloride tablets) should be stored at room temperature (15-30°C). Protect from light.

AVAILABILITY OF DOSAGE FORMS

phl-TRAZODONE 50 mg tablets: orange, biconvex tablets, scored and identified "TRAZODONE" on one side and "pms/50" on the other side. Each tablet contains trazodone hydrochloride 50 mg equivalent to 45.5 mg trazodone base. Bottles of 100, 250 and 500.

phl-TRAZODONE 75 mg tablets: salmon, biconvex tablets, scored and identified "TRAZODONE" on one side and "pms/75" on the other side. Each tablet contains trazodone hydrochloride 75 mg equivalent to 68.25 mg trazodone base. Bottles of 100, 250 and 500.

phl-TRAZODONE 100 mg tablets: white, biconvex tablets, scored and identified "TRAZODONE" on one side and "pms/100" on the other side. Each tablet contains trazodone hydrochloride 100 mg equivalent to 91 mg trazodone base. Bottles of 100 and 500.

PHARMACOLOGY

Like many neuroleptics, trazodone reduces spontaneous motor activity and emotional responses such as aggressive and exploratory behaviour and also blocks responses to painful stimuli and conditioned avoidance reflexes at doses which do not alter the unconditional responses.

At higher doses, conditioned defence responses are blocked by trazodone and group toxicity to amphetamine is reduced. However, unlike neuroleptics, trazodone has only weak hypothermic activity, does not inhibit apomorphine or amphetamine-induced stereotype behaviour or possess cataleptogenic activity, even in higher doses.

Trazodone shows an anxiolytic effect at low doses, with muscle relaxation, muscle hypotonia and reduced activity but psychosedative action at higher doses. This sedative effect is related to a flat dose-response curve, and like benzodiazepines trazodone causes fast activity in the EEG but differs in its action on the sleep cycle since trazodone depresses REM sleep without changing Stages III and IV sleep. Trazodone reduces spontaneous and elicited aggression but lacks anticonvulsant effects.

In animals, trazodone seems to be devoid of catecholamine potentiating action, which is thought to be responsible for the cardiotoxicity of tricyclic anti-depressants; after intravenous infusion, trazodone does not induce the typical electrocardiographic changes of the tricyclic antidepressants and cardiac conduction effects in the anesthetized dog are qualitatively dissimilar and quantitatively less pronounced than those seen with tricyclic antidepressants. Intravenous trazodone in anesthetized dog caused a significant lowering of arterial blood pressure at 0.3 mg/kg, slowed heart rate at 3 mg/kg, and reduced myocardial contractility at 3–10 mg/kg. Trazodone has been given to patients with hypertension, ischemic heart disease, and hyperthyroidism. Electro-cardiograms were unchanged.

Earlier work suggested that the central action of trazodone may be serotoninergic. Thus trazodone has been reported to potentiate behavioural changes induced by 5-HTP in the presence of a MAOI and block 5-HT uptake by brain synaptosomes and platelets selectively since catecholamines are only affected at relatively high doses.

Furthermore, fenfluramine induced hyperthermia is reduced by trazodone while apomorphine induced hyperthermia is enhanced. *In vitro*, trazodone also inhibits the uptake of 5-HT by platelets following fenfluramine induced depletion of 5-HT and antagonizes a decrease in brain 5-HT induced by fenfluramine.

Pharmacokinetics and Dynamics

Absorption:
Following oral administration to man, trazodone is rapidly absorbed from the GI tract, without selective localization in any tissue.

Following oral ingestion of a single 100 mg trazodone dose, average maximum plasma concentrations of 1.61 µg/mL and 1.66 µg/mL were reported for capsule and liquid formulation respectively.

The rate and extent of absorption are affected by the presence of food and when trazodone is taken shortly after the ingestion of food, there may be a slight increase (up to 20%) in the amount of drug absorbed, a decrease in peak plasma concentration of the drug and a lengthening of the time to reach the peak plasma concentration.

Peak plasma concentrations of trazodone occur approximately 1 hour after oral administration when the drug is taken on an empty stomach or 2 hours after oral administration when taken with food.

Following oral administration of multiple doses of trazodone (25 mg 2 or 3 times daily), steady-state plasma concentrations of the drug are usually attained within 4 days and exhibit wide inter-patient variation.

Following oral administration of a singly 25 mg dose of radiolabeled trazodone to healthy adults in one study, mean peak plasma drug concentrations of 650 and 480 ng/mL occurred at 1.5 and 2.5 hours after ingestion, in the fasted and nonfasted state, respectively.

Following oral administration of single doses of 25, 50 or 100 mg of trazodone to healthy, fasted adults in another study, mean peak plasma trazodone concentrations were 490,

860 and 1620 ng/mL, respectively. The areas under the plasma concentration-time curves (AUCs) were 3.44, 5.95, and 11.19 µg/mL, for the 25, 50, and 100 mg doses, respectively.

Distribution:
Trazodone is a weak base with a pKa of 6.14, and therefore it exists mostly in the unionized form at physiological pH.

Following oral administration of trazodone in animals, the drug and its metabolites are distributed mainly into the liver, kidneys, small intestine, lungs, adrenal glands, and pancreas, with lower concentrations being distributed into adipose tissue, heart, and skeletal muscle.

Trazodone crosses the blood-brain barrier in animals, and concentrations of the drug in the brain are higher than those in plasma during the first 8 hours after oral ingestion.

In vitro, trazodone is 89-95% bound to plasma proteins at plasma trazodone concentrations of 100-150 ng/mL.

Excretion of trazodone in human breast milk has been studied and found to be very small. The average milk/plasma ratios was 0.142, therefore, exposure of babies to trazodone via breast milk would be minimal.

Elimination:
Plasma concentrations of trazodone decline in a biphasic manner. The half-life of trazodone in the initial phase is about 3-6 hours and the half-life in the terminal phase is about 5-9 hours. The clearance of trazodone from the body shows wide inter-individual variation.

Metabolism:
Trazodone is extensively metabolized via hydroxylation, N-oxidation and hydrolysis. Hydroxylation occurs in the benzene ring (4-hydroxyphenyl metabolite) and in the triazolopyridine ring (dihydrodiol) while N-oxidation occurs on a piperazine nitrogen (N-oxide). A hydrolytic reaction results in the formation of 3-oxo-1,2,4-triazolo[4,3-a]- pyridin-2-yl propionic acid and 1-m- chlorophenylpiperazine, a pharmacologically active metabolite.

Small concentrations of 1-m-chloro-phenylpiperazine, approximately 1% of trazodone plasma concentrations, have been reported in man.

Excretion:
Approximately 70-75% of an oral dose of the drug is excreted in urine within 72 hours of administration, most as metabolites.

Only less than 1% of the dose is recovered in urine as unchanged drug. The remainder of an oral dose is excreted in feces, involving biliary excretion, mainly as trazodone metabolites.

Results from animal studies indicate that trazodone does not induce its own metabolites.

TOXICOLOGY

Acute Toxicity:

LD_{50} in mg/kg (95% confidence limits)

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, prostration and clonic convulsions.

Subacute Toxicity:
Oral doses of 25, 50 and 100 mg/kg daily or 5 and 50 mg/kg subcutaneously for 3 weeks were without adverse effects in rats. Intraperitoneal doses of 5 and 50mg/kg daily for 3 weeks caused a marked decrease in weight gain and adhesions of the peritoneal cavity. Oral doses of 100 to 450 mg/kg daily for 1 month resulted in reduced feed intake and decreased weight gain.

Doses of 4, 12 and 36 mg/kg intraperitoneally for 6 weeks resulted in no consistent drug-related toxicity, although hypoactivity, ptosis and mild ataxia occurred with the highest dose.

A 6-month study in rats in which trazodone was mixed with the normal diet at a concentration of 0.1 and 0.25% showed reduced weight gain and some increase in liver weight with the higher dosage, but doses of up to 25 mg/kg daily for 6 months in dogs resulted in no drug-related changes. Intravenous administration of 1. 5 and 10 mg/kg daily for 4 weeks resulted in occasional tonic-clonic seizures in 2 dogs given 5 mg/kg and in all of those given 10 mg/kg.

Chronic Toxicity:
Doses of 30, 100 and 300 mg/kg daily were given to rats for 78 weeks. At the higher dosages, there was reduced weight gain, lethargy during the first 4 weeks, and salivation.

At 30 mg/kg, there was a lower incidence of pituitary adenomas in the males and of mammary gland tumours in the females. At 100 mg/kg, there was a lower incidence of pituitary enlargement and of subcutaneous tissue masses. In a second study, doses of 40 and 80 mg/kg daily were given for 91 weeks followed by a 13-week observation period. There were no distinct or consistent increases in the numbers of rats developing neoplasms, nor were there any unusual types of neoplasms. There were, however, treatment-related transient increases in non-neoplastic mammary changes such as glandular or ductal dilatation.

One-year studies in beagle dogs (10 to 30 mg/kg) and monkeys (20 to 80 mg/kg) revealed no organ toxicity attributable to trazodone, although convulsions and death occurred in some female dogs at the high dose level.

Reproductive Studies:
Trazodone was administered orally to rats and rabbits during the middle portion of pregnancy at levels ranging from 15 to 450 mg/kg daily. There were no findings to indicate a dysmorphogenic effect except at 450 mg/kg daily, which was lethal to the dam.

Treatment at 10 to 300 mg/kg daily of both male and female rats prior to and during mating, with the females continually treated during pregnancy and lactation, exhibited no

adverse effects on fertility, mating, pregnancy or postpartum measurements other than lighter pup weights at birth for the high dose group.

Dosage levels of 10 to 300 mg/kg daily were given to pregnant rats during the last 6 to 7 days of pregnancy and throughout lactation. There were no adverse effects on pregnancy, survival of the offspring or maternal care of the offspring, except for lighter pup weights at the high dose level at birth and 21 days of age.

Carcinogenicity Studies in Rats:
Trazodone has been administered for 2 years with the feed at concentrations corresponding to 40 or 80 mg/kg/day. There was no evidence of carcinogenesis.

REFERENCES

PRECLINICAL

R.N. Brogden, R.D. Heel, T.M. Speight, and G.S. Avery. Trazodone: A review of its pharmacological properties and therapeutic use in depression and anxiety. Drugs: 21:401-429, 1981.

J.E. Byrne, A.W. Gomoll. Differential effects of trazodone and imipramine on intracardiac conduction in the anesthetized dog Arch.int.Pharmacodynn, 259:259-270, 1982.

G.W. Dec, M.A. Jenike, T.A. Stern Trazodone-Digoxin interaction in an animal model J Clin Psychopharmacol,Vol.4/No.3,1984

J.D. Fernstrom, C.M. VanItallie, M.H. Fernstrom
Effects of acute and chronic trazodone administration on serum prolactin levels in adult female rats. Life Sciences, 33:2559-2565, 1983.

S. Garattini, G. de Gaetano, R. Samanin, S. Bernasconi and M.C. Roncaglioni. Effects of trazodone on serotonin in the brain and platelets of the rats. Biochemical, Pharmacology, 25:13-16, 1976.

A.W. Gomoll, J.E. Byrne, D. Deitchman Hemodynamic and cardiac actions of trazodone and imipramine in the anesthetized dog Life Sciences, Vol.24:1841-1948, 1979.

R. Lisciani, A. Campana, P. Scorza Barcellona Comparative cardiovascular toxicity of trazodone and imipramine in the rat Arch.Toxicol.,Suppl.1:169-172, 1978.

M.Massotti, A.Scotti de Carolis, V.G. Longo. Effects of Trazodone on behavior and brain amine content of mice Current Therapeutic Research, Vol. 19, No.1, 1976.

B. Silvestrini, V. Cioli, S. Burberi and B. Catanese. Pharmacological properties of AF 1161, a new psychotropic drug. Int. J. Neuropharmacol., 7:587-599, 1968.

B. Silvestrini, R. Lisciani and M. DeGregorio
Trazodone in Pharmacological and Biochemical properties of drug substance, Vol II.p.94.

E.Stefanini, F.Fadda, L.Medda, G.L. Gessa Selective inhibition of serotonin uptake by trazodone, a new antidepressant agent Life Sciences, Vol.18:1459-1466, 1976.

M. Wielosz, A. d'All'olio, G. de Gaetano, and S. Garattini.
Effects of two non tricyclic antidepressant drugs on [^{14}C]5-hydroxy tryptamine uptake by rat platelets. J. Pharm. Pharmac., 29:546-549, 1977.

CLINICAL:

AHFS Drug Informatio 91. ed: McEvoy, G.K., United States: American Society of Hospital Pharmacists 1261-1264, 1991.

R.J. Branconnier, J.O. Cole Effects of acute administration of trazodone and amitriptyline on cognition, cardiovascular function and salivation in the normal geriatric Journal of Clinical Psychopharmacology, Vol. 1, No. 6 Suppl., 1981

J.O. Cole, A.F. Schatzberg, C. Sniffin, J. Zolner and J.P. Cole Trazodone in treatment-resistant depression: An open study Journal of Clinical Psychopharmacology, Vol. 1, No. 6 Suppl., 1981

L.F. Fabre, John P. Feighner Long-term therapy for depression with trazodone. J. Clin. Psychiatry, 44:17-21, 1983.

J.P. Feighner, Charles H. Merideth and Gordon Hendrickson Maintenance antidepressant therapy: A double-blind comparison of trazodone and imipramine. Journal of Clinical Psychopharmacology, Vol. 1, No. 6 Suppl., 1981

S.Gershon, R. Newton Lack of anticholinergic side effects with a new antidepressent - trazodone J.Clin. Psychiatry: 41:3, March 1980

S. Gershon, J.Mann, R. Newton, B.J. Gunther Evaluation of trazodone in the treatment of endogenous depression: Results of a multicenter double-blind study. Journal of Clinical Psychopharmacology, Vol. 1, No. 6 Suppl., 1981

H.L. Goldberg, R.J. Finnerty Trazodone in the treatment of neurotic depression J.Clin.Psychiatry: 41:12, Dec.1980

H.L. Goldberg, K.Rickels, R.Finnerty Treatment of neurotic depression with a new antidepressant Journal of Clinical Psychopharmacology, Vol. 1, No. 6 Suppl., 1981

A.W. Harcus, A.E. Ward, S.I. Ankier, and G.R. Kimber. A comparative bioavailability study of molipaxin capsules and a trazodone liquid formulation in normal volunteers. J. Clin. and Hosp. Pharm., 8:125-132, 1983.

J.J. Kellams, M.H. Kalpper, J.G.Small. Trazodone, a new antidepressant: Efficacy and safety in endogenous depression. Clin.Psychiatry; 40:390-395, 1979

J.J.Mann, A.Georgotas, R.Newton, S.Gershon. A controlled study of trazodone, imipramine and placebo in outpatients with endogenous depression Journal of Clinical Psychopharmacology, Vol. 1, No. 2, 1981.

M.Hecht Orzack, J.O. Cole, L. Friedman, M. Bird, J.McEachern
Weight changes in antidepressants: A comparison of amitriptyline and trazodone Neuropsychobiology 15,1:28-30 (1986)

USP DI 1988. Drug Information for the Health Care Professional. United States Pharmacopeial Convention, Inc. Volume 1B eighth edition 2114-2115, 1988.

R.K. Verbeeck, S.G. Ross, and E.A. McKenna. Excretion of trazodone in breast milk. Br. J. Clin. Pharmac., 22:367-370, 1986.