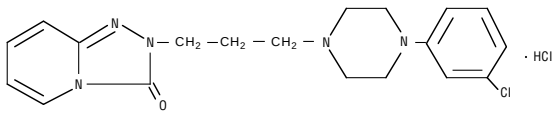
DESYREL®
(Trazodone Hydrochloride)

DESCRIPTION

DESYREL (trazodone hydrochloride) is an antidepressant chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents. Trazodone hydrochloride is a triazolopyridine derivative designated as 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-a]pyridin-3(2H)-one hydrochloride. It is a white odorless crystalline powder which is freely soluble in water. Its molecular weight is 408.3. The empirical formula is $C_{19}H_{22}ClN_5O \cdot HCl$ and the structural formula is represented as follows:



DESYREL is supplied for oral administration in 50 mg, 100 mg, 150 mg and 300 mg tablets.

DESYREL Tablets, 50 mg, contain the following inactive ingredients: dibasic calcium phosphate, castor oil, microcrystalline cellulose, ethylcellulose, FD&C Yellow No. 6 (aluminum lake), lactose, magnesium stearate, povidone, sodium starch glycolate, and starch (corn).

DESYREL Tablets, 100 mg, contain the following inactive ingredients: dibasic calcium phosphate, castor oil, microcrystalline cellulose, ethylcellulose, lactose, magnesium stearate, povidone, sodium starch glycolate, and starch (corn).

DESYREL Tablets, 150 mg, contain the following inactive ingredients: microcrystalline cellulose, FD&C Yellow No. 6 (aluminum lake), magnesium stearate, pregelatinized starch, and stearic acid.

DESYREL Tablets, 300 mg, contain the following inactive ingredients: microcrystalline cellulose, yellow ferric oxide, magnesium stearate, sodium starch glycolate, pregelatinized starch, and stearic acid.

CLINICAL PHARMACOLOGY

The mechanism of DESYREL's antidepressant action in man is not fully understood. In animals, DESYREL selectively inhibits serotonin uptake by brain synaptosomes and potentiates the behavioral changes induced by the serotonin precursor, 5-hydroxytryptophan. Cardiac conduction effects of DESYREL in the anesthetized dog are qualitatively dissimilar and quantitatively less pronounced than those seen with tricyclic antidepressants. DESYREL is not a monoamine oxidase inhibitor and, unlike amphetamine-type drugs, does not stimulate the central nervous system.

In man, DESYREL is well absorbed after oral administration without selective localization in any tissue. When DESYREL is taken shortly after ingestion of food, there may be an increase in the amount of drug absorbed, a decrease in maximum concentration and a lengthening in the time to maximum concentration. Peak plasma levels occur approximately one hour after dosing when DESYREL is taken on an empty stomach or two hours after dosing when taken with food. Elimination of DESYREL is biphasic, consisting of an initial phase (half-life 3–6 hours) followed by a slower phase (half-life 5–9 hours), and is unaffected by the presence or absence of food. Since the clearance of DESYREL from the body is sufficiently variable, in some patients DESYREL may accumulate in the plasma.

For those patients who responded to DESYREL, one-third of the inpatients and one-half of the outpatients had a significant therapeutic response by the end of the first week of treatment. Three-fourths of all responders demonstrated a significant therapeutic effect by the end of the second week. One-fourth of responders required 2–4 weeks for a significant therapeutic response.

INDICATIONS AND USAGE

DESYREL is indicated for the treatment of depression. The efficacy of DESYREL has been demonstrated in both inpatient and outpatient settings and for depressed patients with and without prominent anxiety. The depressive illness of patients studied corresponds to the Major Depressive Episode criteria of the American Psychiatric Association's Diagnostic and Statistical Manual, III.[a]

Major Depressive Episode implies a prominent and relatively persistent (nearly every day for at least two weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least four of the following eight symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigability, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicidal ideation or attempts.

CONTRAINDICATIONS

DESYREL is contraindicated in patients hypersensitive to DESYREL.

WARNINGS

TRAZODONE HAS BEEN ASSOCIATED WITH THE OCCURRENCE OF PRIAPISM. IN MANY OF THE CASES REPORTED, SURGICAL INTERVENTION WAS REQUIRED AND, IN A SOME 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.

The detumescence of priapism and drug-induced penile erections has been accomplished by both pharmacologic, e.g., the intracavernosal injection of alpha-adrenergic stimulants such as epinephrine and norepinephrine, as well as surgical procedures.[b-g] Any pharmacologic or surgical procedure utilized in the treatment of priapism should be performed under the supervision of a urologist or a physician familiar with the procedure and should not be initiated without urologic consultation if the priapism has persisted for more than 24 hours.

DESYREL (trazodone hydrochloride) is not recommended for use during the initial recovery phase of myocardial infarction.

Caution should be used when administering DESYREL to patients with cardiac disease, and such patients should be closely monitored, since antidepressant drugs (including DESYREL) have been associated with the occurrence of cardiac arrhythmias. Recent clinical studies in patients with pre-existing cardiac disease indicate that DESYREL may be arrhythmogenic in some patients in that population. Arrhythmias identified include isolated PVCs, ventricular couplets, and in two patients short episodes (3–4 beats) of ventricular tachycardia.

PRECAUTIONS

General

The possibility of suicide in seriously depressed patients is inherent in the illness and may persist until significant remission occurs. Therefore, prescriptions should be written for the smallest number of tablets consistent with good patient management.

Hypotension, including orthostatic hypotension and syncope, has been reported to occur in patients receiving DESYREL. Con-comitant administration of antihypertensive therapy with DESYREL may require a reduction in the dose of the antihypertensive drug.

Little is known about the interaction between DESYREL and general anesthetics; therefore, prior to elective surgery, DESYREL should be discontinued for as long as clinically feasible.

As with all antidepressants, the use of DESYREL should be based on the consideration of the physician that the expected benefits of therapy outweigh potential risk factors.

Information for Patients

Because priapism has been reported to occur in patients receiving DESYREL, patients with prolonged or inappropriate penile erection should immediately discontinue the drug and consult with the physician (see WARNINGS).

Antidepressants may impair the mental and/or physical ability required for the performance of potentially hazardous tasks, such as operating an automobile or machinery; the patient should be cautioned accordingly.

DESYREL may enhance the response to alcohol, barbiturates, and other CNS depressants.

DESYREL should be given shortly after a meal or light snack. Within any individual patient, total drug absorption may be up to 20% higher when the drug is taken with food rather than on an empty stomach. The risk of dizziness/lightheadedness may increase under fasting conditions.

Laboratory Tests

Occasional low white blood cell and neutrophil counts have been noted in patients receiving DESYREL. These were not considered clinically significant and did not necessitate discontinuation of the drug; however, the drug should be discontinued in any patient whose white blood cell count or absolute neutrophil count falls below normal levels. White blood cell and differential counts are recommended for patients who develop fever and sore throat (or other signs of infection) during therapy.

Drug Interactions

Increased serum digoxin or phenytoin levels have been reported to occur in patients receiving DESYREL concurrently with either of those two drugs.

It is not known whether interactions will occur between mono-amine oxidase (MAO) inhibitors and DESYREL. Due to the absence of clinical experience, if MAO inhibitors are discontinued shortly before or are to be given concomitantly with DESYREL, therapy should be initiated cautiously with gradual increase in dosage until optimum response is achieved.

Therapeutic Interactions

Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

No drug- or dose-related occurrence of carcinogenesis was evident in rats receiving DESYREL in daily oral doses up to 300 mg/kg for 18 months.

Pregnancy Category C

DESYREL has been shown to cause increased fetal resorption and other adverse effects on the fetus in two studies using the rat 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. There are no adequate and well-controlled studies in pregnant women. DESYREL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

DESYREL and/or its metabolites have been found in the milk of lactating rats, suggesting that the drug may be secreted in human milk. Caution should be exercised when DESYREL is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Because the frequency of adverse drug effects is affected by diverse factors (e.g., drug dose, method of detection, physician judgment, disease under treatment, etc.) a single meaningful estimate of adverse event incidence is difficult to obtain. This problem is illustrated by the variation in adverse event incidence observed and reported from the inpatients and outpatients treated with DESYREL. It is impossible to determine precisely what accounts for the differences observed.

Clinical Trial Reports

The table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of DESYREL® (trazodone hydrochloride).

The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors often differ from those which prevailed in the clinical trials. These incidence figures, also, cannot be compared with those obtained from other clinical studies involving related drug products and placebo as each group of drug trials is conducted under a different set of conditions.

	Treatment-Emergent Symptom Incidence			
	Inpts.		**Outpts.**	
	D	**P**	**D**	**P**
Number of Patients	142	95	157	158
% of Patients Reporting				
Allergic				
Skin Condition/ Edema	2.8	1.1	7.0	1.3
Autonomic				
Blurred Vision	6.3	4.2	14.7	3.8
Constipation	7.0	4.2	7.6	5.7
Dry Mouth	14.8	8.4	33.8	20.3
Cardiovascular				
Hypertension	2.1	1.1	1.3	*
Hypotension	7.0	1.1	3.8	0.0
Shortness of Breath	*	1.1	1.3	0.0
Syncope	2.8	2.1	4.5	1.3
Tachycardia/ Palpitations	0.0	0.0	7.0	7.0
CNS				
Anger/Hostility	3.5	6.3	1.3	2.5
Confusion	4.9	0.0	5.7	7.6
Decreased Concentration	2.8	2.1	1.3	0.0
Disorientation	2.1	0.0	*	0.0
Dizziness/Light-headedness	19.7	5.3	28.0	15.2
Drowsiness	23.9	6.3	40.8	19.6
Excitement	1.4	1.1	5.1	5.7
Fatigue	11.3	4.2	5.7	2.5
Headache	9.9	5.3	19.8	15.8
Insomnia	9.9	10.5	6.4	12.0
Impaired Memory	1.4	0.0	*	*
Nervousness	14.8	10.5	6.4	8.2
Gastrointestinal				
Abdominal/ Gastric Disorder	3.5	4.2	5.7	4.4
Bad Taste in Mouth	1.4	0.0	0.0	0.0
Diarrhea	0.0	1.1	4.5	1.9
Nausea/Vomiting	9.9	1.1	12.7	9.5
Musculoskeletal				
Musculoskeletal Aches/Pains	5.6	3.2	5.1	2.5
Neurological				
Incoordination	4.9	0.0	1.9	0.0
Paresthesia	1.4	0.0	0.0	*
Tremors	2.8	1.1	5.1	3.8
Sexual Function				
Decreased Libido	*	1.1	1.3	*
Other				
Decreased Appetite	3.5	5.3	0.0	*
Eyes Red/ Tired/Itching	2.8	0.0	0.0	0.0
Head Full-Heavy	2.8	0.0	0.0	0.0
Malaise	2.8	0.0	0.0	0.0
Nasal/Sinus Congestion	2.8	0.0	5.7	3.2
Nightmares/ Vivid Dreams	*	1.1	5.1	5.7
Sweating/Clamminess	1.4	1.1	*	*
Tinnitus	1.4	0.0	0.0	*
Weight Gain	1.4	0.0	4.5	1.9
Weight Loss	*	3.2	5.7	2.5

* Incidence less than 1%.

D = DESYREL P = Placebo

Occasional sinus bradycardia has occurred in long-term studies.

In addition to the relatively common (i.e., greater than 1%) untoward events enumerated above, the following adverse events have been reported to occur in association with the use of DESYREL® (trazodone hydrochloride) in the controlled clinical studies: akathisia, allergic reaction, anemia, chest pain, delayed urine flow, early menses, flatulence, hallucinations/delusions, hematuria, hypersalivation, hypomania, impaired speech, impotence, increased appetite, increased libido, increased urinary frequency, missed periods, muscle twitches, numbness, and retrograde ejaculation.

Postintroduction Reports

Although the following adverse reactions have been reported in DESYREL users, the causal association has neither been confirmed nor refuted.

Voluntary reports received since market introduction include the following: abnormal dreams, agitation, alopecia, anxiety, aphasia, apnea, ataxia, breast enlargement or engorgement, cardiospasm, cerebrovascular accident, chills, cholestatis, clitorism, congestive heart failure, diplopia, edema, extrapyramidal symptoms, grand mal seizures, hallucinations, hemolytic anemia, hirsutism, hyperbilirubinemia, increased amylase, increased salivation, insomnia, leukocytosis, leukonychia, jaundice, lactation, liver enzyme alterations, methemoglobinemia, nausea/vomiting (most frequently), paresthesia, paranoid reaction, priapism (See **WARNINGS** and **PRECAUTIONS, Information for Patients**; some patients have required surgical intervention), pruritis, psoriasis, psychosis, rash, stupor, inappropriate ADH syndrome, tardive dyskinesia, unexplained death, urinary incontinence, urinary retention, urticaria, vasodilation, vertigo and weakness.

Cardiovascular system effects which have been reported include the following: conduction block, orthostatic hypotension and syncope, palpitations, bradycardia,

atrial fibrillation, myocardial infarction, cardiac arrest, arrhythmia, and ventricular ectopic activity, including ventricular tachycardia (see **WARNINGS**).

OVERDOSE

Animal Oral LD_{50}

The oral LD_{50} of the drug is 610 mg/kg in mice, 486 mg/kg in rats, and 560 mg/kg in rabbits.

Signs and Symptoms

Death from overdose has occurred in patients ingesting DESYREL (trazodone hydrochloride) and other drugs concurrently (namely, alcohol; alcohol + chloral hydrate + diazepam; amobarbital; chlordiazepoxide; or meprobamate).

The most severe reactions reported to have occurred with overdose of DESYREL alone have been priapism, respiratory arrest, seizures, and EKG changes. The reactions reported most frequently have been drowsiness and vomiting. Overdosage may cause an increase in incidence or severity of any of the reported adverse reactions (see **ADVERSE REACTIONS**).

Treatment

There is no specific antidote for DESYREL. Treatment should be symptomatic and supportive in the case of hypotension or excessive sedation. Any patient suspected of having taken an overdose should have the stomach emptied by gastric lavage. Forced diuresis may be useful in facilitating elimination of the drug.

DOSAGE AND ADMINISTRATION

The dosage should be initiated at a low level and increased gradually, noting the clinical response and any evidence of intolerance. Occurrence of drowsiness may require the administration of a major portion of the daily dose at bedtime or a reduction of dosage. DESYREL should be taken shortly after a meal or light snack. Symptomatic relief may be seen during the first week, with optimal antidepressant effects typically evident within two weeks. Twenty-five percent of those who respond to DESYREL require more than two weeks (up to four weeks) of drug administration.

Usual Adult Dosage

An initial dose of 150 mg/day in divided doses is suggested. The dose may be increased by 50 mg/day every three to four days. The maximum dose for outpatients usually should not exceed 400 mg/day in divided doses. Inpatients (i.e., more severely depressed patients) may be given up to but not in excess of 600 mg/day in divided doses.

Maintenance

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

Although there has been no systematic evaluation of the efficacy of DESYREL beyond six weeks, it is generally recommended that a course of antidepressant drug treatment should be continued for several months.

HOW SUPPLIED

DESYREL® (trazodone hydrochloride)

Tablets, **50 mg**—round, orange/scored, film-sealed (debossed with **DESYREL** and **MJ 775**)

NDC 0087-0775-41	Bottles of 100
NDC 0087-0775-43	Bottles of 1000
NDC 0087-0775-42	Cartons of 100 Unit Doses

Tablets, **100 mg**—round, white/scored, film-sealed (debossed with **DESYREL** and **MJ 776**)

NDC 0087-0776-41	Bottles of 100
NDC 0087-0776-43	Bottles of 1000
NDC 0087-0776-42	Cartons of 100 Unit Doses

Tablets, **150 mg**—orange, in the Dividose® tablet design (debossed with **MJ** and **778** on front; **"50," "50," "50"** on reverse)

NDC 0087-0778-43	Bottles of 100
NDC 0087-0778-44	Bottles of 500

Tablets, **300 mg**—yellow, in the Dividose® tablet design (debossed with **MJ** and **796** on front; **"100," "100," "100"** on reverse)

NDC 0087-0796-41	Bottles of 100

U.S. Patent Nos. 4,215,104
4,258,027

Storage

Store at room temperature. Protect from temperatures above 104°F (40°C).

Dispense in tight, light-resistant container (USP).

REFERENCES

a. Williams JBW, Ed: Diagnostic and Statistical Manual of Mental Disorders-III, American Psychiatric Association May, 1980.
b. Lue TF, Physiology of erection and pathophysiology of impotence. In: Wash PC, Retik AB, Stamey TA, Vaughan ED, eds. Campbell's Urology. Sixth edition. Philadelphia: W.B. Saunders; 1992: 722-725.
c. Goldstein I, Krane RJ, Diagnosis and therapy of erectile dysfunction. In: Wash PC, Retik AB, Stamey TA, Vaughan ED, eds. Campbell's Urology. Sixth edition. Philadelphia: W.B. Saunders; 1992: 3071-3072.
d. Yealy DM, Hogya PT: Priapism. *Emerg Med Clin North Am.* 1988; 6:509-520.
e. Banos JE, Bosch F, Farre M, Drug-induced priapism. Its aetiology, incidence and treatment. *Med Toxicol Adverse Drug Exp.* 1989; 4:46-58.
f. O'Brien WM, O'Connor KP, Lynch JH. Priapism: current concepts. *Ann Emerg Med.* 1989; 980-983.
g. Bardin ED, Krieger JN. Pharmacological priapism: comparison of trazodone- and papaverine-associated cases. *Int Urol Nephrol.* 1990; 22:147-152.

CAUTION: Federal law prohibits dispensing without prescription.

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