

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DESYREL® safely and effectively. See full prescribing information for DESYREL.

DESYREL® (trazodone hydrochloride) tablets, for oral use
Initial U.S. Approval: 1981

WARNING: SUICIDAL THOUGHTS and BEHAVIORS *See full prescribing information for complete boxed warning.*

- Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients (5.1)
- Closely monitor for clinical worsening and emergence of suicidal thoughts and behaviors (5.1)
- DESYREL is not approved for use in pediatric patients (8.4)

-----INDICATIONS AND USAGE-----

DESYREL is a selective serotonin reuptake inhibitor indicated for the treatment of major depressive disorder (MDD) (1).

-----DOSAGE AND ADMINISTRATION-----

- Starting dose: 150 mg in divided doses daily. May be increased by 50 mg per day every three to four days. Maximum dose: 400 mg per day in divided doses (2).
- DESYREL should be taken shortly after a meal or light snack (2).
- Tablets should be swallowed whole or broken in half along the score line, and should not be chewed or crushed (2).
- When discontinued, gradual dose reduction is recommended (2).

-----DOSAGE FORMS AND STRENGTHS-----

- Scored tablets: 50 mg, 100 mg, 150 mg and 300 mg (3).

-----CONTRAINDICATIONS-----

- Concomitant use of monoamine oxidase inhibitors (MAOIs), or use within 14 days of stopping MAOIs (4).

-----WARNINGS AND PRECAUTIONS-----

- Serotonin Syndrome: Increased risk when co-administered with other serotonergic agents (e.g., SSRI, SNRI, triptans), but also when taken alone. If it occurs, discontinue DESYREL and initiate supportive treatment (5.2).
- Cardiac Arrhythmias: Increases the QT interval. Avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval (5.3)

- Orthostatic Hypotension and Syncope: Warn patients of risk and symptoms of hypotension (5.4).
- Increased Risk of Bleeding: Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), other antiplatelet drugs, warfarin, and other anticoagulants may increase this risk (5.5).
- Priapism: Cases of painful and prolonged penile erections and priapism have been reported. Immediate medical attention should be sought if signs and symptoms of prolonged penile erections or priapism are observed (5.6).
- Activation of Mania or Hypomania: Screen for bipolar disorder and monitor for mania or hypomania (5.7).
- Potential for Cognitive and Motor Impairment: Has potential to impair judgment, thinking, and motor skills. Advise patients to use caution when operating machinery (5.9).
- Angle-Closure Glaucoma: Avoid use of antidepressants, including DESYREL, in patients with untreated anatomically narrow angles. (5.10).

-----ADVERSE REACTIONS-----

Most common adverse reactions (incidence \geq 5% and twice that of placebo) are: edema, blurred vision, syncope, drowsiness, fatigue, diarrhea, nasal congestion, weight loss (6).

To report SUSPECTED ADVERSE REACTIONS, contact Pragma Pharmaceuticals, LLC at 414-434-6604 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- CNS Depressants: DESYREL may enhance effects of alcohol, barbiturates, or other CNS depressants (7).
- CYP3A4 Inhibitors: Consider DESYREL dose reduction based on tolerability (2.5, 7).
- CYP3A4 Inducers: Increase in DESYREL dosage may be necessary (2.5, 7).
- Digoxin or Phenytoin: Monitor for increased digoxin or phenytoin serum levels (7).
- Warfarin: Monitor for increased or decreased prothrombin time (7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS and BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors [see *Warnings and Precautions (5.1)*]. DESYREL is not approved for use in pediatric patients [see *Use in Specific Populations (8.4)*].

1 INDICATIONS AND USAGE

DESYREL® is indicated for the treatment of major depressive disorder (MDD) in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Dose Selection

An initial dose of 150 mg/day in divided doses is suggested. The dosage should be initiated at a low-dose 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.

The dose may be increased by 50 mg/day every 3 to 4 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.

Once an adequate response has been achieved, dosage may be gradually reduced, with subsequent adjustment depending on therapeutic response.

2.2 Important Administration Instructions

DESYREL® can be swallowed whole or administered as a half tablet by breaking the tablet along the score line.

DESYREL should be taken shortly after a meal or light snack.

2.3 Screen for Bipolar Disorder Prior to Starting DESYREL

Prior to initiating treatment with DESYREL or another antidepressant, screen patients for a personal or family history of bipolar disorder, mania, or hypomania [see *Warnings and Precautions (5.7)*].

2.4 Switching to or from Monoamine Oxidase Inhibitor Antidepressant

At least 14 days must elapse between discontinuation of a monoamine oxidase inhibitor (MAOI) antidepressant and initiation of DESYREL. In addition, at least 14 days must elapse after stopping DESYREL before starting an MAOI antidepressant [see *Contraindications (4)*, *Warnings and Precautions (5.2)*].

2.5 Dosage Recommendations for Concomitant Use with Strong CYP3A4 Inhibitors or Inducers

Coadministration with Strong CYP3A4 Inhibitors

Consider reducing DESYREL dose based on tolerability when DESYREL is coadministered with a strong CYP3A4 inhibitor [see *Drug Interactions (7.1)*].

Coadministration with Strong CYP3A4 Inducers

Consider increasing DESYREL dose based on therapeutic response when DESYREL is coadministered with a strong CYP3A4 inducer [see *Drug Interactions (7.1)*].

2.6 Discontinuation of Treatment with DESYREL

Adverse reactions may occur upon discontinuation of DESYREL [See *Warnings and Precautions (5.8)*]. Gradually reduce the dosage rather than stopping DESYREL abruptly whenever possible.

3 DOSAGE FORMS AND STRENGTHS

- 50 mg: White, round, scored, film-coated tablet; bisected with “50” and “P 005” debossed on one side and plain on the other side.
- 100 mg: White, round, scored, film-coated tablet; bisected with “100” and “P 006” debossed on one side and plain on the other side.
- 150 mg: White, rectangular, scored tablet; trisected on both sides, debossed with “P” and “007” on one side and “50”, “50”, “50” on the other side, with a bisect on each edge.
- 300 mg: White, rectangular, scored tablet; trisected on one side debossed with “100”, “100”, “100” and bisected on the other side debossed with “P” and “008”.

4 CONTRAINDICATIONS

DESYREL is contraindicated in:

- Patients taking, or within 14 days of stopping, monoamine oxidase inhibitors (MAOIs), including MAOIs such as linezolid or intravenous methylene blue, because of an increased risk of serotonin syndrome [see *Warnings and Precautions (5.2)*, *Drug Interactions (7.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and over 4,400 pediatric patients, the incidence of suicidal thoughts and behaviors in pediatric and young adult patients was greater in antidepressant-treated patients than in placebo-treated patients. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about antidepressant drug effect on suicide.

Table 1: Risk Differences of the Number of Cases of Suicidal Thoughts or Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Patients

Age Range (years)	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional patients
18-24	5 additional patients
	Decreases Compared to Placebo
25-64	1 fewer patient
≥65	6 fewer patients

It is unknown whether the risk of suicidal thoughts and behaviors in pediatric and young adult patients extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants delay the recurrence of depression.

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing DESYREL, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

5.2 Serotonin Syndrome

Serotonin-norepinephrine reuptake inhibitors (SNRIs) and SSRIs, including DESYREL, can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is **increased with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John’s Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs [see Contraindications (4), Drug Interactions (7.1)]**. Serotonin syndrome can also occur when these drugs are used alone.

Serotonin syndrome signs and symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms

(e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of DESYREL with MAOIs is contraindicated. In addition, do not initiate DESYREL in a patient being treated with MAOIs such as linezolid or intravenous methylene blue. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection). If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking DESYREL, discontinue DESYREL before initiating treatment with the MAOI [see *Contraindications (4), Drug Interactions (7.1)*].

Monitor all patients taking DESYREL for the emergence of serotonin syndrome. Discontinue treatment with DESYREL and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of DESYREL with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms.

5.3 Cardiac Arrhythmias

Clinical studies indicate that trazodone hydrochloride may be arrhythmogenic in patients with preexisting cardiac disease. Arrhythmias identified include isolated PVCs, ventricular couplets, tachycardia with syncope, and torsade de pointes. Postmarketing events, including torsade de pointes have been reported at doses of 100 mg or less with the immediate-release form of DESYREL. DESYREL should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval. DESYREL 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) may cause cardiac arrhythmias [see *Adverse Reactions (6.2)*].

DESYREL prolongs the QT/QT_c interval. The use of DESYREL should be avoided in patients with known QT prolongation or in combination with other drugs that are inhibitors of CYP3A4 (e.g., itraconazole, clarithromycin, voriconazole), or known to prolong QT interval including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), certain antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and certain antibiotics (e.g., gatifloxacin). Concomitant administration of drugs may increase the risk of cardiac arrhythmia [see *Drug Interactions (7.1)*].

5.4 Orthostatic Hypotension and Syncope

Hypotension, including orthostatic hypotension and syncope has been reported in patients receiving trazodone hydrochloride. Concomitant use with an antihypertensive may require a reduction in the dose of the antihypertensive drug.

5.5 Increased Risk of Bleeding

Drugs that interfere with serotonin reuptake inhibition, including DESYREL, increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), other antiplatelet drugs, warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to drugs that interfere with serotonin reuptake have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages.

Inform patients about the risk of bleeding associated with the concomitant use of DESYREL and antiplatelet agents or anticoagulants. For patients taking warfarin, carefully monitor coagulation indices when initiating, titrating, or discontinuing DESYREL.

5.6 Priapism

Cases of priapism (painful erections greater than 6 hours in duration) have been reported in men receiving DESYREL. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Men who have an erection lasting greater than 4 hours, whether painful or not, should immediately discontinue the drug and seek emergency medical attention [see *Adverse Reactions (6.2), Overdosage (10)*].

DESYREL should be used with caution in men who have conditions that might predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia), or in men with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease).

5.7 Activation of Mania or Hypomania

In patients with bipolar disorder, treating a depressive episode with DESYREL or another antidepressant may precipitate a mixed/manic episode. Activation of mania/hypomania has been reported in a small proportion of patients with major affective disorder who were treated with antidepressants. Prior to initiating treatment with DESYREL, screen patients for any personal or family history of bipolar disorder, mania, or hypomania [see *Dosage and Administration (2.3)*].

5.8 Discontinuation Syndrome

Adverse reactions after discontinuation of serotonergic antidepressants, particularly after abrupt discontinuation, include: nausea, sweating, dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations),

tremor, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. A gradual reduction in dosage rather than abrupt cessation is recommended whenever possible [See *Dosage and Administration* (2.6)].

5.9 Potential for Cognitive and Motor Impairment

DESYREL® may cause somnolence or sedation and may impair the mental and/or physical ability required for the performance of potentially hazardous tasks. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

5.10 Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including DESYREL may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy. Avoid use of antidepressants, including DESYREL, in patients with untreated anatomically narrow angles.

5.11 Hyponatremia

Hyponatremia may occur as a result of treatment with SNRIs and SSRIs, including DESYREL. Cases with serum sodium lower than 110 mmol/L have been reported. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

In patients with symptomatic hyponatremia, discontinue DESYREL and institute appropriate medical intervention. Elderly patients, patients taking diuretics, and those who are volume-depleted may be at greater risk of developing hyponatremia with SSRIs and SNRIs [see *Use in Specific Populations* (8.5)].

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Suicidal Thoughts and Behavior in Children, Adolescents and Young Adults [see *Boxed Warning and Warnings and Precautions* (5.1)]
- Serotonin Syndrome [see *Warnings and Precautions* (5.2)]
- Cardiac Arrhythmias (see *Warnings and Precautions* (5.3))
- Orthostatic Hypotension and Syncope [see *Warnings and Precautions* (5.4)]
- Increased Risk of Bleeding [see *Warnings and Precautions* (5.5)]
- Priapism [see *Warnings and Precautions* (5.6)]
- Activation of Mania or Hypomania [see *Warnings and Precautions* (5.7)]
- Discontinuation Syndrome [see *Warnings and Precautions* (5.8)]
- Potential for Cognitive and Motor Impairment [see *Warnings and Precautions* (5.9)]
- Angle-Closure Glaucoma [see *Warnings and Precautions* (5.10)]
- Hyponatremia [see *Warnings and Precautions* (5.11)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Table 2: Common Adverse Reactions Occurring in ≥ 2% of DESYREL-treated Patients and Greater than the Rate of Placebo-Treated Patients as Observed in Controlled Clinical Studies

	Inpatients		Outpatients	
	Desyrel®N =142	Placebo N=95	Desyrel®N =157	Placebo N=158
Allergic				
Skin Condition/Edema	3%	1%	7%	1%
Autonomic				
Blurred Vision	6%	4%	15%	4%
Constipation	7%	4%	8%	6%
Dry Mouth	15%	8%	34%	20%
Cardiovascular				
Hypertension	20%	1%	1%	*
Hypotension	7%	1%	4%	0
Syncope	3%	2%	5%	1%
CNS				
Confusion	5%	0	6%	8%
Decreased Concentration	3%	2%	1%	0

Disorientation	2%	0	*	0
Dizziness/Light-Headedness	20%	5%	28%	15%
Drowsiness	24%	6%	41%	20%
Fatigue	11%	4%	6%	3%
Headache	10%	5%	20%	16%
Nervousness	15%	11%	6%	8%
Gastrointestinal				
Abdominal/Gastric Disorder	4%	4%	6%	4%
Diarrhea	0	1%	5%	1%
Nausea/Vomiting	10%	1%	13%	10%
Musculoskeletal				
Aches/Pains	6%	3%	5%	3%
Neurological				
Incoordination	5%	0	2%	*
Tremors	3%	1%	5%	4%
Other				
Eyes Red/Tired/Itching	3%	0	0	0
Head Full-Heavy	3%	0	0	0
Malaise	3%	0	0	0
Nasal/Sinus Congestion	3%	0	6%	3%
Weight Gain	1%	0	5%	2%
Weight Loss	*	3%	6%	3%

Other adverse reactions occurring at an incidence of <2% with the use of 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 memory, impaired speech, impotence, increased appetite, increased libido, increased urinary frequency, missed periods, muscle twitches, numbness, paresthesia, retrograde ejaculation, shortness of breath, and tachycardia/palpitations. Occasional sinus bradycardia has occurred in long-term studies.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of DESYREL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure:

Blood and lymphatic system disorders: hemolytic anemia, leukocytosis

Cardiac disorders: cardiospasm, congestive heart failure, conduction block, orthostatic hypotension and syncope, palpitations, bradycardia, atrial fibrillation, myocardial infarction, cardiac arrest, arrhythmia, ventricular ectopic activity, including ventricular tachycardia and QT prolongation. Prolonged QT interval, torsade de pointes, and ventricular tachycardia have been reported at doses of 100 mg per day or less [see *Warnings and Precautions* (5.3)].

Endocrine disorders: inappropriate ADH syndrome

Eye disorders: diplopia

Gastrointestinal disorders: increased salivation, nausea/vomiting

General disorders and administration site conditions: chills, edema, unexplained death, weakness

Hepatobiliary disorders: cholestasis, jaundice, hyperbilirubinemia, liver enzyme alterations

Investigations: increased amylase

Metabolism and nutrition disorders: methemoglobinemia

Nervous system disorders: aphasia, ataxia, cerebrovascular accident, extrapyramidal symptoms, grand mal seizures, paresthesia, tardive dyskinesia, vertigo

Psychiatric disorders: abnormal dreams, agitation, anxiety, hallucinations, insomnia, paranoid reaction, psychosis, stupor

Renal and urinary disorders: urinary incontinence, urinary retention

Reproductive system and breast disorders: breast enlargement or engorgement, clitorism, lactation, priapism [see *Warnings and Precautions* (5.6)]

Respiratory, thoracic and mediastinal disorders: apnea

Skin and subcutaneous tissue disorders: alopecia, hirsutism, leukonychia, pruritus, psoriasis, rash, urticaria

Vascular disorders: vasodilation

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions With DESYREL

Table 3: Clinically Important Drug Interactions with DESYREL

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	The concomitant use of MAOIs and serotonergic drugs including DESYREL increases the risk of

	serotonin syndrome.
Intervention:	DESYREL is contraindicated in patients taking MAOIs, including MAOIs such as linezolid or intravenous methylene blue [see <i>Contraindications (4), Dosage and Administration (2.3, 2.4), and Warnings and Precautions (5.2)</i>].
Examples:	isocarboxazid, moclobemide, phenelzine, selegiline, tranylcypromine
Other Serotonergic Drugs	
Clinical Impact:	The concomitant use of serotonergic drugs including DESYREL and other serotonergic drugs increases the risk of serotonin syndrome.
Intervention:	Monitor patients for signs and symptoms of serotonin syndrome, particularly during DESYREL initiation. If serotonin syndrome occurs, consider discontinuation of DESYREL and/or concomitant serotonergic drugs [see <i>Warnings and Precautions (5.2)</i>].
Examples:	triptans, antidepressants (tricyclic and serotonin uptake inhibitors), fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort
Antiplatelet Agents and Anticoagulants	
Clinical Impact:	Serotonin release by platelets plays an important role in hemostasis. The concurrent use of an antiplatelet agent or anticoagulant with DESYREL may potentiate the risk of bleeding.
Intervention:	Inform patients of the increased risk of bleeding with the concomitant use of DESYREL and antiplatelet agents and anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio (INR) when initiating or discontinuing DESYREL [see <i>Warnings and Precautions (5.5)</i>].
Examples:	warfarin, rivaroxaban, dabigatran, clopidogrel
Strong CYP3A4 Inhibitors	
Clinical Impact:	The concomitant use of DESYREL and strong CYP3A4 inhibitors increased the exposure of trazodone compared to the use of DESYREL alone.
Intervention:	If DESYREL is used with a potent CYP3A4 inhibitor, the risk of adverse reactions, including cardiac arrhythmias, may be increased and a lower dose of DESYREL should be considered [see <i>Dosage and Administration (2.5), Warnings and Precautions (5.3)</i>].
Examples:	itraconazole, ketoconazole, clarithromycin, indinavir
Strong CYP3A4 Inducers	
Clinical Impact:	The concomitant use of DESYREL and strong CYP3A4 inducers decreased the exposure of trazodone compared to the use of DESYREL alone.
Intervention:	Patients should be closely monitored to see if there is a need for an increased dose of DESYREL when taking CYP3A4 inducers [see <i>Dosage and Administration (2.5)</i>].
Examples:	rifampin, carbamazepine, phenytoin, St. John's wort
Digoxin and Phenytoin	
Clinical Impact:	Digoxin and phenytoin are narrow therapeutic index drugs. Concomitant use of DESYREL can increase digoxin or phenytoin concentrations.
Intervention:	Measure serum digoxin or phenytoin concentrations before initiating concomitant use of DESYREL. Continue monitoring and reduce digoxin or phenytoin dose as necessary.
Examples:	digoxin, phenytoin
Central Nervous System (CNS) Depressants	
Clinical Impact:	Desyrel may enhance the response CNS depressants.
Intervention:	Patients should be counseled that DESYREL may enhance the response to alcohol, barbiturates, and other CNS depressants.
Examples:	alcohol, barbiturates
QT Interval Prolongation	
Clinical Impact:	Concomitant use of drugs that prolong the QT interval may add to the QT effects of DESYREL and increase the risk of cardiac arrhythmia.
Intervention:	Avoid the use of DESYREL in combination with other drugs known to prolong QTc [see <i>Warnings and Precautions (5.3)</i>].
Examples:	Class 1A antiarrhythmics: quinidine, procainamide, disopyramide; Class 3 antiarrhythmics: amiodarone, sotalol; Antipsychotics: ziprasidone, chlorpromazine, thioridazine; Antibiotics: gatifloxacin

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/>

Risk Summary

Published prospective cohort studies, case series, and case reports over several decades with DESYREL use in pregnant women have not identified any drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes (*see Data*). Trazodone hydrochloride has been shown to cause increased fetal resorption and other adverse effects on the fetus in the rat when given at dose levels approximately 7.3 to 11 times the maximum recommended human dose (MRHD) of 400 mg/day in adults on a mg/m² basis. There was also an increase in congenital anomalies in the rabbit at approximately 7.3 to 22 times the MRHD on a mg/m² basis (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

A prospective, longitudinal study followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. The women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

Data

Human Data

While available studies cannot definitively establish the absence of risk, published data from prospective cohort studies, case series, and case reports over several decades have not identified an association with trazodone use during pregnancy and major birth defects, miscarriage, or other adverse maternal or fetal outcomes. All available studies have methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

No teratogenic effects were observed when trazodone was given to pregnant rats and rabbits during the period of organogenesis at oral doses up to 450 mg/kg/day. This dose is 11 and 22 times, in rats and rabbits, respectively, the maximum recommended human dose (MRHD) of 400 mg/day in adults on a mg/m² basis. Increased fetal resorption and other adverse effects on the fetus in rats at 7.3 to 11 times the MRHD and increase in congenital anomalies in rabbits at 7.3 to 22 times the MRHD on a mg/m² basis were observed. No further details on these studies are available.

8.2 Lactation

Risk Summary

Data from published literature report the transfer of trazodone into human milk. There are no data on the effect of trazodone on milk production. Limited data from postmarketing reports have not identified an association of adverse effects on the breastfed child. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DESYREL and any potential adverse effects on the breastfed child from DESYREL or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established. Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients [see *Boxed Warning, Warnings and Precautions (5.1)*].

8.5 Geriatric Use

Reported clinical literature and experience with trazodone has not identified differences in responses between elderly and younger patients. However, as experience in the elderly with trazodone hydrochloride is limited, it should be used with caution in geriatric patients.

Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse reaction [see *Warnings and Precautions (5.11)*].

8.6 Renal Impairment

Trazodone has not been studied in patients with renal impairment. Trazodone should be used with caution in this population.

8.7 Hepatic Impairment

Trazodone has not been studied in patients with hepatic impairment. Trazodone should be used with caution in this population.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

DESYREL® is not a controlled substance.

9.2 Abuse

Although trazodone hydrochloride has not been systematically studied in preclinical or clinical studies for its potential for abuse, no indication of drug-seeking behavior was seen in the clinical studies with trazodone hydrochloride.

10 OVERDOSAGE

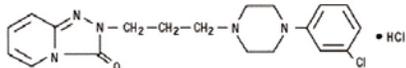
Death from overdose has occurred in patients ingesting DESYREL and other CNS depressant drugs concurrently (alcohol; alcohol and chloral hydrate and diazepam; amobarbital; chlordiazepoxide; or meprobamate).

The most severe reactions reported to have occurred with overdose of DESYREL alone have been priapism, respiratory arrest, seizures, and ECG changes, including QT prolongation. 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.

There is no specific antidote for trazodone hydrochloride overdose. In managing overdosage, consider the possibility of multiple drug involvement. For current information on the management of poisoning or overdose, contact a poison control center (1-800-222-1222 or www.poisson.org).

11 DESCRIPTION

DESYREL (trazodone hydrochloride) tablets for oral administration contain trazodone hydrochloride, a selective serotonin reuptake inhibitor and 5HT₂ receptor antagonist. DESYREL 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. The structural formula is represented as follows:



Molecular Formula: C₁₉H₂₂ClN₅O • HCl

Molecular Weight: 408.33

Each tablet, for oral administration, contains 50 mg, 100 mg, 150 mg or 300 mg of trazodone hydrochloride, USP. In addition, each tablet contains the following inactive ingredients:

50 mg and 100 mg: Corn starch, dibasic calcium phosphate, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium starch glycolate, and triacetin

150 mg: magnesium stearate, microcrystalline cellulose, pregelatinized starch, and stearic acid

300 mg: magnesium stearate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, and stearic acid

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of trazodone's antidepressant action is not fully understood, but is thought to be related to its enhancement of serotonergic activity in the CNS. Trazodone is both a selective serotonin reuptake inhibitor (SSRI) and a 5HT₂ receptor antagonist and the net result of this action on serotonergic transmission and its role in trazodone's antidepressant effect is unknown.

12.2 Pharmacodynamics

Preclinical studies have shown that trazodone selectively inhibits neuronal reuptake of serotonin (K_i = 367 nM) and acts as an antagonist at 5-HT_{2A} (K_i = 35.6 nM) serotonin receptors. Trazodone is also an antagonist at several other monoaminergic receptors including 5-HT_{2B} (K_i = 78.4 nM), 5-HT_{2C} (K_i = 224 nM), α_{1A} (K_i = 153 nM), α_{2C} (K_i = 155 nM) receptors and it is a partial agonist at 5-HT_{1A} (K_i = 118 nM) receptor.

Trazodone antagonizes alpha 1-adrenergic receptors, a property which may be associated with postural hypotension.

12.3 Pharmacokinetics

Absorption

In humans, trazodone hydrochloride is absorbed after oral administration without selective localization in any tissue. When trazodone hydrochloride 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 trazodone hydrochloride is taken on an empty stomach or 2 hours after dosing when taken with food.

Metabolism

In vitro studies in human liver microsomes show that trazodone is metabolized, via oxidative cleavage, to an active metabolite, m-chlorophenylpiperazine (mCPP) by CYP3A4. Other metabolic pathways that may be involved in the metabolism of trazodone have not been well characterized. Trazodone is extensively metabolized; less than 1% of an oral dose is excreted unchanged in the urine.

Elimination

In some patients trazodone may accumulate in the plasma.

Protein Binding

Trazodone is 89 to 95% protein bound *in vitro* at concentrations attained with therapeutic doses in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No drug- or dose-related occurrence of carcinogenesis was evident in rats receiving trazodone in daily oral doses up to 7.3 times the maximum recommended human dose (MRHD) of 400 mg/day in adults on a mg/m² basis.

Mutagenesis

No genotoxicity studies were conducted with trazodone.

Impairment of Fertility

Trazodone has no effect on fertility in rats at doses up to 7.3 times the MRHD in adults on a mg/m² basis.

14 CLINICAL STUDIES

The efficacy and safety of trazodone hydrochloride were established from inpatient and outpatient trials of the trazodone immediate release formulation in the treatment of major depressive disorder.

16 HOW SUPPLIED/STORAGE AND HANDLING

- 50 mg: White, round, scored, film-coated tablet; bisected with “50” and “P 005” debossed on one side and plain on the other side.
Bottles of 100 NDC 58463-005-01
- 100 mg: White, round, scored, film-coated tablet; bisected with “100” and “P 006” debossed on one side and plain on the other side.
Bottles of 100 NDC 58463-006-01
- 150 mg: White, rectangular, scored tablet; trisected on both sides, debossed with “P” and “007” on one side and “50”, “50”, “50” on the other side, with a bisect on each edge.
Bottles of 100 NDC 58463-007-01
- 300 mg: White, rectangular, scored tablet; trisected on one side debossed with “100”, “100”, “100” and bisected on the other side debossed with “P” and “008”.
Bottles of 100 NDC 58463-008-01

Store at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C and 30°C (59°F to 86°F) [see *USP Controlled Room Temperature*].

Dispense in a tight, light-resistant container as defined in the USP.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Suicidal Thoughts and Behaviors

Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dosage is adjusted up or down and instruct them to report such symptoms to the healthcare provider [see *Box Warning and Warnings and Precautions (5.1)*].

Dosage and Administration

Advise patients that DESYREL should be taken shortly after a meal or light snack. Advise patients regarding the importance of following dosage titration instructions [see *Dosage and Administration (2)*].

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of DESYREL with other serotonergic drugs including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort, and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid). Patients should contact their health care provider or report to the emergency room if they experience signs or symptoms of serotonin syndrome [see *Warnings and Precautions (5.2) and Drug Interactions (7)*].

Activation of Mania/Hypomania

Advise patients and their caregivers to observe for signs of activation of mania/hypomania and instruct them to report such symptoms to the healthcare provider [see *Warnings and Precautions (5.7)*].

Increased Risk of Bleeding

Inform patients about the concomitant use of DESYREL with aspirin, NSAIDs, other antiplatelet drugs, warfarin, or other anticoagulants because the combined use of drugs that interfere with serotonin reuptake and these medications has been associated with an

increased risk of bleeding. Advise them to inform their health care providers if they are taking or planning to take any prescription or over-the-counter medications that increase the risk of bleeding [see *Warnings and Precautions (5.5)*].

Discontinuation Syndrome

Advise patients not to abruptly discontinue DESYREL and to discuss any tapering regimen with their healthcare provider. Adverse reactions can occur when DESYREL is discontinued [see *Warnings and Precautions (5.8)*].

Concomitant Medications

Advise patients to inform their health care providers if they are taking, or plan to take any prescription or over-the-counter medications since there is a potential for interactions [see *Drug Interactions (7.1)*].

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy with DESYREL. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DESYREL during pregnancy [see *Use in Special Populations (8.1)*].

Manufactured in Canada for:
Pragma Pharmaceuticals, LLC.
Distributed by: Fera
Pharmaceuticals, LLC.
Locust Valley, N.Y. 11560

PPI-005

Revised 10/18

MEDICATIONGUIDE
DESYREL[®] (DEZ ur el)
(trazodone hydrochloride)
tablets, for oral use

What is the most important information I should know about DESYREL?

Antidepressant medicines, depression or other serious mental illnesses, and suicidal thoughts or actions: Talk to your healthcare provider about:

- All risks and benefits of treatment with antidepressant medicines
- All treatment choices for depression or other serious mental illnesses
- 1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
- 2. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions.**
Some people may have a higher risk of having suicidal thoughts or actions. These include people who have or have a family history of bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
- 3. How can I watch for and try to prevent suicidal thoughts and actions?**
 - Pay close attention to any changes, especially sudden changes in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
 - Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts or feelings.
 - Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Call a healthcare provider right away if you have any of the following symptoms, especially if they are new, worse, or worry you:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Trouble sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking (mania)
- Other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. You should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to your healthcare provider about the side effects of your medicines.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you take. Keep a list of all medicines to show your healthcare provider. Do not start new medicines without first checking with your healthcare provider.

It is not known if DESYREL is safe and effective in children.

What is DESYREL?

DESYREL is a prescription medicine used in adults to treat major depressive disorder (MDD). DESYREL belongs to a class of medicines known as SSRIs (or selective serotonin reuptake inhibitors).

Do not take DESYREL:

- If you take a monoamine oxidase inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid, and intravenous methylene blue.
- Do not take an MAOI within 2 weeks of stopping DESYREL unless directed to do so by your healthcare provider.

- Do not start DESYREL if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your healthcare provider.

Before you take DESYREL tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems, including QT prolongation or a family history of it
- have ever had a heart attack
- have bipolar disorder
- have liver or kidney problems
- have other serious medical conditions
- are pregnant or plan to become pregnant. It is not known if DESYREL will harm your unborn baby. Talk to your healthcare provider about the risk to your unborn baby if you take DESYREL.
 - If you become pregnant during treatment with DESYREL, talk to your healthcare provider about registering with the National Pregnancy Registry for Antidepressants. You can register by calling 1-844-405-6185.
- are breastfeeding or plan to breastfeed. DESYREL passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take DESYREL.
- have taken a Monoamine Oxidase Inhibitor (MAOI) or if you have stopped taking an MAOI in the last 2 weeks.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Using DESYREL with certain other medicines can affect each other causing serious side effects.

Especially tell your healthcare provider if you take:

- triptans used to treat migraine headache
- medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, SSRIs, SNRIs, buspirone, or antipsychotics
- tramadol
- over-the-counter supplements such as tryptophan or St. John's Wort
- nonsteroidal anti-inflammatory drugs (NSAIDS)
- aspirin
- warfarin (Coumadin, Jantoven)
- phenytoin (Mesantoin)
- diuretics

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take DESYREL?

- Take DESYREL exactly as your healthcare provider tells you.
- DESYREL should be taken shortly after a meal or light snack.
- If you feel drowsy after taking DESYREL, talk to your healthcare provider. Your healthcare provider may change your dose or the time of day you take your DESYREL.
- Do not stop taking DESYREL without talking to your healthcare provider.
- DESYREL should be swallowed whole or broken in half along the score line. Do not chew or crush DESYREL. Tell your healthcare provider if you cannot swallow trazodone either whole or as a half tablet.
- If you take too much DESYREL, call your healthcare provider, your Poison Control Center at 1-800-222-1222, or go to the nearest emergency room right away.

What should I avoid while taking DESYREL?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how DESYREL affects you. DESYREL can slow your thinking and motor skills.
- Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking DESYREL until you talk with your healthcare provider. DESYREL may make your sleepiness or dizziness worse if you take it with alcohol or other medicines that cause sleepiness or dizziness.

What are the possible side effects of DESYREL?**DESYREL can cause serious side effects or death, including:**

- See “What is the most important information I should know about DESYREL?”
- **Serotonin syndrome.** Symptoms of serotonin syndrome include: agitation, hallucinations, problems with coordination, fast heartbeat, tight muscles, trouble walking, sweating, fever, nausea, vomiting, and diarrhea.
- **Irregular or fast heartbeat or faint (QT prolongation)**
- **Low blood pressure.** You feel dizzy or faint when you change positions (go from sitting to standing)
- **Unusual bruising or bleeding**
- **Erection lasting for more than 6 hours (priapism)**
- **Feeling high or in a very good mood, then becoming irritable, or having too much energy, feeling like you have to keep talking or do not sleep (mania).**
- **Withdrawal symptoms.** Symptoms of withdrawal can include anxiety, agitation, and sleep problems. Do not stop taking DESYREL without talking to your healthcare provider.
- **Visual problems.**
 - eye pain
 - changes in vision
 - swelling or redness in or around the eye

Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.

- **Low sodium in your blood (hyponatremia).** Symptoms of hyponatremia include: headache, feeling weak, feeling confused, trouble concentrating, memory problems and feeling unsteady when you walk.

Get medical help right away, if you have any of the symptoms listed above.

The most common side effects of DESYREL include:

- swelling
- blurred vision
- dizziness
- sleepiness
- tiredness
- diarrhea
- stuffy nose
- weight loss

These are not all the possible side effects of DESYREL. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store DESYREL?

- Store DESYREL at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep in tight container
- Keep out of the light
- Safely throw away medicine that is out of date or no longer needed.

Keep DESYREL and all medicines out of the reach of children.**General information about the safe and effective use of DESYREL.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use DESYREL for a condition for which it was not prescribed. Do not give DESYREL to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about DESYREL that is written for health professionals.

What are the ingredients in DESYREL?

Active ingredient: trazodone hydrochloride, USP

Inactive ingredients: 50 mg and 100 mg: Corn starch, dibasic calcium phosphate, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium starch glycolate, and triacetin 150 mg: magnesium stearate, microcrystalline cellulose, pregelatinized starch, and stearic acid 300 mg: magnesium stearate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, and stearic acid

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