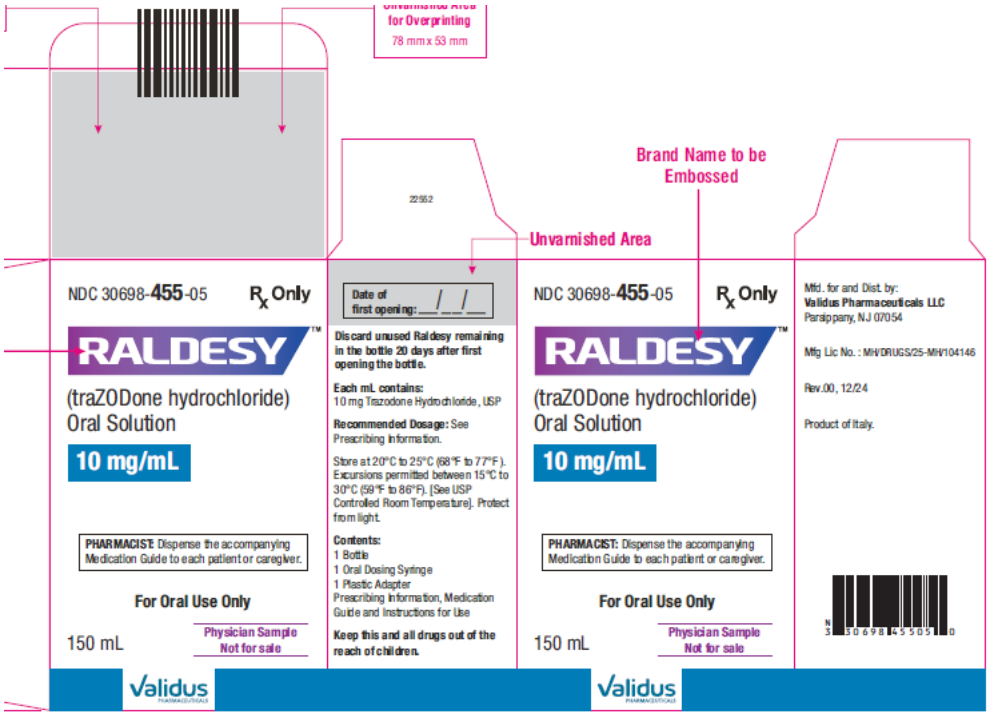
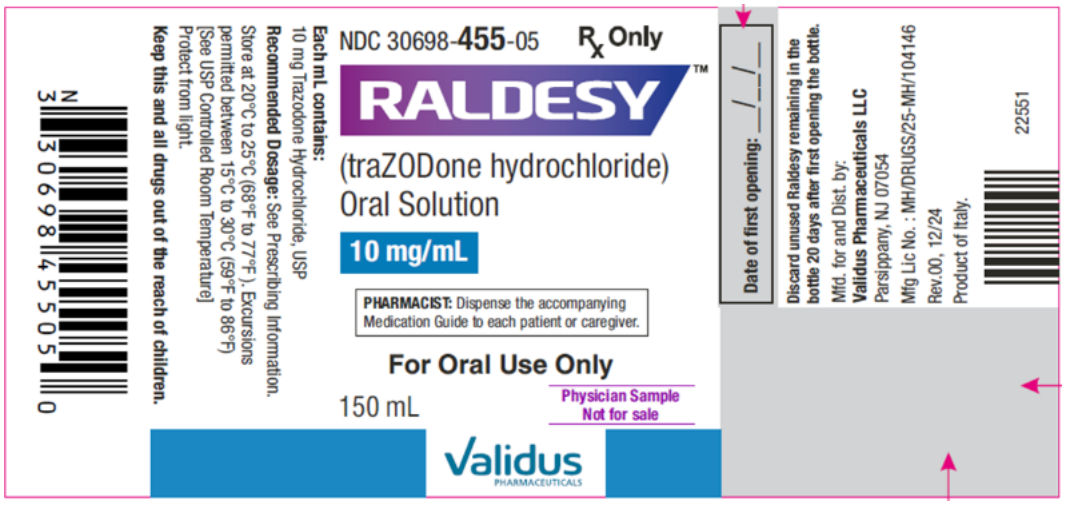

for Overprinting
78 mm x 53 mm
Brand Name to be Embossed
Unvarnished Area
NDC 30698-455-05
Rx Only
RALDESY
(traZODone hydrochloride)
Oral Solution
10 mg/mL
PHARMACIST: Dispense the accompanying Medication Guide to each patient or caregiver.
For Oral Use Only
150 mL
Physician Sample
Not for sale
Date of first opening: __/__/__
Discard unused Raldesy remaining in the bottle 20 days after first opening the bottle.
Each mL contains:
10 mg Trazodone Hydrochloride, USP
Recommended Dosage: See Prescribing Information.
Store at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]. Protect from light.
Contents:
1 Bottle
1 Oral Dosing Syringe
1 Plastic Adapter
Prescribing Information, Medication Guide and Instructions for Use
Keep this and all drugs out of the reach of children.
Mfd. for and Dist. by:
Validus Pharmaceuticals LLC
Parsippany, NJ 07054
Mfg Lic No. : MH/DRUGS/25-MH/104146
Rev.00, 12/24
Product of Italy.
Validus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Protect from light.
Keep this and all drugs out of the reach of children.
Date of first opening: __/__/__
Discard unused Raldesy remaining in the bottle 20 days after first opening the bottle.
Mfd. for and Dist. by:
Validus Pharmaceuticals LLC
Parsippany, NJ 07054
Mfg Lic No. : MH/DRUGS/25-MH/104146
Rev.00, 12/24
Product of Italy.
22551

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RALDESY™ safely and effectively. See full prescribing information for RALDESY™.

RALDESY™ (trazodone hydrochloride) oral solution
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. Closely monitor for clinical worsening and emergence of suicidal thoughts and behaviors (5.1).**
- **RALDESY is not approved for use in pediatric patients (8.4).**

----------INDICATIONS AND USAGE----------
RALDESY is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of major depressive disorder (MDD) in adults (1).

----------DOSAGE AND ADMINISTRATION----------
- Starting dosage: 150 mg orally in divided doses daily. May be increased by 50 mg per day every three to four days. Maximum dosage: 400 mg per day in divided doses (2.1).
- Administer RALDESY shortly after a meal or light snack (2.1).
- When discontinuing RALDESY, gradually reduce dose (2.5).

----------DOSAGE FORMS AND STRENGTHS----------
- Oral solution: 10 mg/mL

----------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 RALDESY 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 RALDESY, in patients with untreated anatomically narrow angles (5.10).

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥ 5% and twice that of placebo) are: edema, blurred vision, syncope, drowsiness, fatigue, diarrhea, nasal congestion, weight loss (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Validus Pharmaceuticals LLC at 1-866-982-5438 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- CNS Depressants: RALDESY may enhance effects of alcohol, barbiturates, or other CNS depressants (7).
- CYP3A4 Inhibitors: Consider RALDESY dose reduction based on tolerability (2.5, 7).
- CYP3A4 Inducers: Increase in RALDESY 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.

Revised: 08/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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)]*. RALDESY is not approved for use in pediatric patients *[see Use in Specific Populations (8.4)]*.

1 INDICATIONS AND USAGE

RALDESY™ is indicated for the treatment of major depressive disorder (MDD) in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The initial dosage of RALDESY for the treatment of MDD in adults is 150 mg daily, taken orally, in divided doses. The dosage should be initiated at a low-dose and increased gradually, depending on clinical response and an tolerance. Occurrence of drowsiness may require the administration of a major portion of the daily dose at bedtime or a reduction of dosage *[see Dosage and Administration (2.5)]*.

The dose may be increased by 50 mg daily every 3 to 4 days. The maximum recommended dosage for outpatients usually should not exceed 400 mg daily in divided doses. Inpatients (i.e., more severely depressed patients) may be given up to, but not in excess, of 600 mg daily in divided doses.

Administer RALDESY orally after a meal or light snack *[see Clinical Pharmacology (12.3)]*.

2.2 Screen for Bipolar Disorder Prior to Starting RALDESY

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

2.3 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 RALDESY. In addition, at least 14 days must elapse after stopping RALDESY before starting an MAOI antidepressant *[see Contraindications (4), Warnings and Precautions (5.2)]*.

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

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

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

2.5 Discontinuation of Treatment with RALDESY

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

3 DOSAGE FORMS AND STRENGTHS

RALDESY (10 mg/mL) Oral Solution: Clear, colorless solution

4 CONTRAINDICATIONS

RALDESY 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 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1,000 patients treated are provided in Table 1.

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 1,000 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 and that depression itself is a risk factor for suicidal thoughts and behaviors.

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 RALDESY, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

5.2 Serotonin Syndrome

SSRIs, including RALDESY, 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 RALDESY with MAOIs is contraindicated. In addition, do not initiate RALDESY 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 RALDESY, discontinue RALDESY before initiating treatment with the MAOI *[see Contraindications (4), Drug*

Interactions (7.1)].

Monitor all patients taking RALDESY for the emergence of serotonin syndrome. Discontinue treatment with RALDESY and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of RALDESY 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 reports, including torsade de pointes have been reported at doses of 100 mg or less with the immediate-release trazodone hydrochloride tablets. RALDESY 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. RALDESY is not recommended for use during the initial recovery phase of myocardial infarction. Caution should be used when administering RALDESY to patients with cardiac disease and such patients should be closely monitored, since antidepressant drugs (including RALDESY) may cause cardiac arrhythmias *[see Adverse Reactions (6.2)]*.

Trazodone hydrochloride prolongs the QT/QT_c interval. The use of RALDESY 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 RALDESY, 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 RALDESY and antiplatelet agents or anticoagulants. For patients taking warfarin, carefully monitor coagulation indices when initiating, titrating, or discontinuing RALDESY .

5.6 Priapism

Cases of priapism (painful erections greater than 6 hours in duration) have been reported in males receiving trazodone hydrochloride tablets. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Males 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)].*

RALDESY should be used with caution in males 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 RALDESY 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 RALDESY, 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

RALDESY™ 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 RALDESY 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 RALDESY, in patients with untreated anatomically narrow angles.

5.11 Hyponatremia

Hyponatremia may occur as a result of treatment with SNRIs and SSRIs, including RALDESY. 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 RALDESY 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 Behaviors inPediatric and Young Adult Patients *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.2)]*
- Cardiac Arrythmias (*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.

The safety of RALDESY for the treatment of MDD in adults is based on studies of trazodone hydrochloride tablets. Below is a display of adverse reactions of trazodone hydrochloride tablets from those studies.

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

	Inpatients		Outpatients	
	Trazodone hydrochloride N=142	Placebo N=95	**Trazodone hydrochloride** 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 trazodone hydrochloride tablets. 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

Table 3 displays clinically significant drug interactions with RALDESY.

Table 3: Clinically Significant Drug Interactions with RALDESY

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	The concomitant use of MAOIs and serotonergic drugs including RALDESY increases the risk of serotonin syndrome.
Intervention:	RALDESY is contraindicated in patients taking MAOIs, including MAOIs such as linezolid or intravenous methylene blue *[see Contraindications (4), Dosage and Administration (2.3, 2.4), and Warnings and Precautions (5.2)].*
Other Serotonergic Drugs	
Clinical Impact:	The concomitant use of serotonergic drugs, including RALDESY and other serotonergic drugs increases the risk of serotonin syndrome.
Intervention:	Monitor patients for signs and symptoms of serotonin syndrome, particularly during RALDESY initiation. If serotonin syndrome occurs, consider discontinuation of RALDESY and/or concomitant serotonergic drugs *[see Warnings and Precautions (5.2)].*
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 RALDESY may potentiate the risk of bleeding.
Intervention:	Inform patients of the increased risk of bleeding with the concomitant use of RALDESY and antiplatelet agents and anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio (INR) when initiating or discontinuing RALDESY *[see Warnings and Precautions (5.5)].*
Strong CYP3A4 Inhibitors	
Clinical Impact:	The concomitant use of RALDESY and strong CYP3A4 inhibitors increased the exposure of trazodone compared to the use of RALDESY alone.
Intervention:	If RALDESY is used with a potent CYP3A4 inhibitor, the risk of adverse reactions, including cardiac arrhythmias, may be increased and a lower dose of RALDESY should be considered *[see Dosage and Administration (2.5), Warnings and Precautions (5.3)].*
Strong CYP3A4 Inducers	
Clinical Impact:	The concomitant use of RALDESY and strong CYP3A4 inducers decreased the exposure of trazodone compared to the use of RALDESY alone.
Intervention:	Patients should be closely monitored to see if there is a need for an increased dose of RALDESY when taking CYP3A4 inducers *[see Dosage and Administration (2.5)].*
Digoxin and Phenytoin	
Clinical Impact:	Digoxin and phenytoin are narrow therapeutic index drugs. Concomitant use of RALDESY can increase digoxin or phenytoin concentrations.
Intervention:	Measure serum digoxin or phenytoin concentrations before initiating concomitant use of RALDESY. Continue monitoring and reduce digoxin or phenytoin dose as necessary.
Central Nervous System (CNS) Depressants	
Clinical Impact:	RALDESY may enhance the response CNS depressants.
Intervention:	Patients should be counseled that RALDESY may enhance the response to alcohol, barbiturates, and other CNS depressants.
QT Interval Prolongation	

Clinical Impact:	Concomitant use of drugs that prolong the QT interval may add to the QT effects of RALDESY and increase the risk of cardiac arrhythmia.
Intervention:	Avoid the use of RALDESY in combination with other drugs known to prolong QTc *[see Warnings and Precautions (5.3)]*.

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 should encourage patients to enroll by calling the National Pregnancy Registry for Antidepressants at 1-866-961-2388 or visiting online at https://womensmentalhealth.org/ research/pregnancyregistry/antidepressants/.

Risk Summary

Published prospective cohort studies, case series, and case reports over several decades with trazodone hydrochloride tablets use in pregnant women have not identified any drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes *(see Data).* There are risks associated with untreated depression in pregnancy *(see Clinical Considerations).*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/m^2 basis. There was also an increase in congenital anomalies in the rabbit at approximately 7.3 to 22 times the MRHD on a mg/m^2 basis *(see Data).*

The 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
Women who discontinue antidepressants during pregnancy are more likely to experience a relapse of major depression than women who continue antidepressants. This finding is from a prospective, longitudinal study of 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. 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/m^2 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/m^2 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 RALDESY and any potential adverse effects on the breastfed child from RALDESY or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of RALDESY in the pediatric patients 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 geriatric and younger patients. However, as experience with trazodone hydrochloride in geriatric patients is limited, RALDESY should be used with caution in these 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. RALDESY should be used with caution in this population.

8.7 Hepatic Impairment

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

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Trazodone hydrochloride 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.

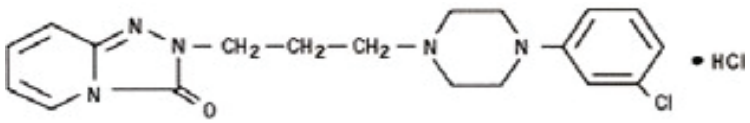
10 OVERDOSAGE

Death from overdose has occurred in patients ingesting trazodone 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 trazodone 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. Consider contacting the Poison Help line 1-888-222-1222 or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION



RALDESY contains trazodone hydrochloride, a selective serotonin reuptake inhibitor and 5HT2 receptor antagonist. 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(2*H*)-one hydrochloride. It is a white odorless crystalline powder which is freely soluble in water. The structural formula is represented as follows:

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

RALDESY Oral Solution: Each mL contains 10 mg of Trazodone Hydrochloride, USP equivalent to 9.1 mg of trazodone base. The following inactive ingredients: disodium edetate, glycerin, ortho phosphoric acid, propyl gallate, propylene glycol, purified water, sodium benzoate, sorbitol, and sucralose. The pH of the oral solution is 3.8 to 4.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of trazodone's antidepressant action is unclear, 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 (Ki = 367 nM) and acts as an antagonist at 5-HT-2A (Ki = 35.6 nM) serotonin receptors. Trazodone is also an antagonist at several other monoaminergic receptors including 5-HT2B (Ki = 78.4 nM), 5-HT2C (Ki = 224 nM), α1A (Ki = 153 nM), α2C (Ki = 155 nM) receptors and it is a partial agonist at 5-HT1A (Ki = 118 nM) receptor.

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

12.3 Pharmacokinetics

No clinically significant difference in pharmacokinetics of trazodone was observed between RALDESY and immediate-release trazodone hydrochloride tablet administered under fed conditions.

Absorption
Peak plasma levels occur approximately one hour after administration under fed conditions.

Effect of Food
Ingestion of a high-fat meal with RALDESY lowers mean Cmax of trazodone by 31% and increases mean AUC by 8%. Median Tmax was similar between fed and fasted conditions.

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

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
The average terminal elimination half-life of RALDESY under fed state is 18 hours.

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/m^2 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/m^2 basis.

14 CLINICAL STUDIES

The efficacy of RALDESY for the treatment of MDD in adults is based on studies of trazodone hydrochloride tablets.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

RALDESY™ contains 10 mg/mL of trazodone hydrochloride. It is a clear, colorless solution and is supplied as:

150 mL amber glass bottle

- NDC 30698-455-03 with child-resistant cap along with a 10 mL calibrated oral dosing syringe and bottle adapter.

150 mL white, opaque, high-density polyethylene (HDPE) bottle

- NDC 30698-455-02 with child-resistant cap along with a 10 mL calibrated oral dosing syringe and bottle adapter.

300 mL amber glass bottle

- NDC 30698-455-04 with child-resistant cap along with a 10 mL calibrated oral dosing syringe and bottle adapter.

300 mL white, opaque, HDPE bottle

- NDC 30698-455-01 with child-resistant cap along with a 10 mL calibrated oral dosing syringe and bottle adapter.

The bottle, bottle adapter and the dosing syringe are placed in a carton.

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15ºC to 30ºC (59°F to 86ºF) [see USP Controlled Room Temperature]. Protect from light. Discard any unused RALDESY remaining in the bottle 30 days after first opening the bottle.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

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 RALDESY 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 RALDESY 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)]*.

Increased Risk of Bleeding

Inform patients about the concomitant use of RALDESY 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)]*.

Activation of Mania or 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)]*.

Discontinuation Syndrome

Advise patients not to abruptly discontinue RALDESY and to discuss any tapering regimen with their healthcare provider. Adverse reactions can occur when RALDESY 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 RALDESY. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to RALDESY during pregnancy *[see Use in Special Populations (8.1)].*

Manufactured for and distributed by:
Validus Pharmaceuticals LLC
Parsippany, NJ 07054

Mohan Sapru

Digitally signed by Mohan Sapru
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