IMPORTANT SAFETY 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. RALDESY is not approved for use in pediatric patients.

INDICATIONS AND USAGE

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

ADMINISTRATION

Administer RALDESY orally after a meal or light snack.

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.

WARINGS AND PRECAUTIONS

Suicidal Thoughts and Behaviors in Pediatric and Young Adult 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.

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.

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. Serotonin syndrome can also occur when these drugs are used alone.

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. 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.

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.

Cardiac Arrhythmias

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.

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.

Increased Risk of Bleeding

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.

Priapism

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).

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.

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.

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.

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.

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 Full Prescribing Information for warnings and precautions of RALDESY.

ADVERSE REACTIONS

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

- Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients
- Serotonin Syndrome
- Cardiac Arrythmias
- Orthostatic Hypotension and Syncope
- Increased Risk of Bleeding
- Priapism
- Activation of Mania or Hypomania
- Discontinuation Syndrome
- Potential for Cognitive and Motor Impairment
- Angle-Closure Glaucoma
- Hyponatremia

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.

See Full Prescribing Information for additional adverse reactions associated with RALDESY.

DRUG INTERACTIONS

Monoamine Oxidase Inhibitors (MAOIs)
RALDESY is contraindicated in patients taking MAOIs, including MAOIs such as linezolid or intravenous methylene blue.

Other Serotonergic Drugs
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.

Antiplatelet Agents and Anticoagulants
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.

Strong CYP3A4 Inhibitors
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.

Strong CYP3A4 Inducers
Patients should be closely monitored to see if there is a need for an increased dose of RALDESY when taking CYP3A4 inducers.

Digoxin and Phenytoin
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
Patients **should** be counseled that RALDESY may enhance the response to alcohol, barbiturates, and other CNS depressants.

QT Interval Prolongation
Avoid the use of RALDESY in combination with other drugs known to prolong QTc.

See Full Prescribing Information for Potential Drug Interactions.

USE IN SPECIFIC POPULATIONS

Pregnancy

There are risks associated with untreated depression in pregnancy. 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.

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/.

Lactation

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.

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.

Geriatric Use

Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse reaction.

Renal Impairment

RALDESY should be used with caution in this population.

Hepatic Impairment

RALDESY should be used with caution in this population.

DOSAGE FORMS AND STRENGTHS

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

RALDESY is available only by prescription.

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.

Please see Full Prescribing Information for www.raldesy.com.

Manufactured for and distributed by:
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