WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. UZEDY is not approved for use in patients with dementia-related psychosis. (5.1)

INDICATIONS AND USAGE

UZEDY is an atypical antipsychotic indicated for the treatment of schizophrenia in adults. (1)

DOSAGE AND ADMINISTRATION

• Establish tolerability with oral risperidone prior to initiating UZEDY. (2.1)
• Administer UZEDY by subcutaneous injection in the abdomen or upper arm by a healthcare professional. Do not administer by any other route. (2.1)
• Initiate UZEDY at the clinically appropriate dose using the following table. (2.1)

<table>
<thead>
<tr>
<th>Prior Oral Risperidone Therapy</th>
<th>UZEDY Dosage Once Monthly</th>
<th>UZEDY Dosage Once Every 2 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg of oral risperidone per day</td>
<td>50 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>3 mg of oral risperidone per day</td>
<td>75 mg</td>
<td>150 mg</td>
</tr>
<tr>
<td>4 mg of oral risperidone per day</td>
<td>100 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>5 mg of oral risperidone per day</td>
<td>125 mg</td>
<td>250 mg</td>
</tr>
</tbody>
</table>

• See Full Prescribing Information for important preparation and administration information. (2.4)

DOSEAGE FORMS AND STRENGTHS

Extended-release injectable suspension: 50 mg/0.14 mL, 75 mg/0.21 mL, 100 mg/0.28 mL, 125 mg/0.35 mL, 150 mg/0.42 mL, 200 mg/0.56 mL, and 250 mg/0.7 mL single-dose prefilled syringes. (3)

CONTRAINdications

Known hypersensitivity to risperidone, paliperidone, or any of the components in UZEDY. (4)

WARNINGS AND PRECAUTIONS

• Cerebrovascular Adverse Reactions, in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular reactions (e.g., stroke, transient ischemia attack). (5.2)
• Neuroleptic Malignant Malignant Syndrome (NMS): Manage with immediate discontinuation and close monitoring. (5.3)
• Tardive Dyskinesia: Discontinue treatment if clinically appropriate. (5.4)

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

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1 INDICATIONS AND USAGE

UZEDY® is indicated for the treatment of schizophrenia in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

For patients who have never taken risperidone, establish tolerability with oral risperidone prior to initiating UZEDY.

UZEDY must be administered by a healthcare professional as an abdominal or upper arm subcutaneous injection. Do not administer UZEDY by any other route.

For detailed preparation and administration instructions, see Dosage and Administration (2.4).

2.2 Dosage Modifications in Patients with Renal Impairment or Hepatic Impairment

Prior to initiating UZEDY in patients with renal or hepatic impairment, titrate with oral risperidone to at least 2 mg once daily. Following oral titration, and based on clinical response and tolerability, the recommended dosage of UZEDY is 50 mg once monthly (50 mg, 75 mg, 100 mg, or 125 mg) or once every 2 months (100 mg, 150 mg, 200 mg, or 250 mg) given via abdominal or upper arm subcutaneous injection. Neither a loading dose nor supplemental oral risperidone doses are recommended when switching.

Table 1: Dosage Recommendations for Switching from Daily Oral Risperidone to UZEDY

<table>
<thead>
<tr>
<th>Prior Therapy</th>
<th>UZEDY Dosage Once Monthly</th>
<th>UZEDY Dosage Once Every 2 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg of oral risperidone per day</td>
<td>50 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>4 mg of oral risperidone per day</td>
<td>75 mg</td>
<td>150 mg</td>
</tr>
<tr>
<td>3 mg of oral risperidone per day</td>
<td>100 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>2 mg of oral risperidone per day</td>
<td>125 mg</td>
<td>250 mg</td>
</tr>
</tbody>
</table>

Patients can switch between doses of UZEDY once monthly and once every 2 months by administering the first dose of the new dosing regimen on the next scheduled date of administration in the original dosing regimen. Revise the dose administration schedule to reflect the change. When a dose of UZEDY is missed, administer the next UZEDY injection as soon as possible. Do not administer more frequently than recommended.

2.3 Dosage Modifications for Concomitant Use with Strong CYP2D6 Inhibitors and Strong CYP3A4 Inducers

Concomitant Use with Strong CYP2D6 Inhibitors

When initiation of fluoxetine or paroxetine is considered, place patients on a lower dose of UZEDY prior to the planned start of fluoxetine or paroxetine therapy to adjust for the expected increase in plasma concentrations of risperidone.

When fluoxetine or paroxetine is initiated in patients receiving the recommended dose of 50 mg once monthly or 100 mg once every 2 months of UZEDY, continue treatment with these doses unless clinical judgment necessitates interruption of UZEDY (see Drug Interactions (7.1)).

Concomitant Use with Strong CYP3A4 Inducers

At the initiation of therapy with strong CYP3A4 inducers (such as carbamazepine), patients should be closely monitored during the first 4 to 8 weeks since the dose of UZEDY may need to be adjusted. A dose increase, or additional oral risperidone, may be considered.

On discontinuation of a strong CYP3A4 inducer, re-evaluate the dosage of UZEDY or any additional oral risperidone therapy and, if necessary, decrease to adjust for the expected increase in plasma concentration of risperidone.

2.4 Preparation and Administration Instructions

• Read the instructions for preparation and administration below before administering UZEDY.

• For subcutaneous injection only. Do not inject by any other route.

• To be administered by a healthcare professional only.

• Allow UZEDY to come to room temperature for at least 30 minutes prior to administration.

• As a universal precaution, always wear gloves.

STEP 1

Check to make sure UZEDY kit contains:

• One sterile single-dose, prefilled glass syringe

• One sterile 21G x 5/8” needle

Do not substitute any components of the kit for administration.

STEP 2

Remove the kit from refrigerated storage and allow the package to sit at room temperature (20°C to 25°C [68°F to 77°F]) for at least 30 minutes.

Note: UZEDY is a solid at refrigerated temperatures and must reach room temperature prior to administration. Do not warm any other way and keep protected from light.

STEP 3

Check that the drug in the syringe is white to off-white, opaque in color, and free from non-white particulate matter. Check that the pouch label states the needle size is 21G x 5/8”.

Do not use if any component of the kit is damaged or if the expiration date has passed.

STEP 4

Expose the safety needle hub by peeling back the paper tab of the needle pouch. Set aside for use in Step 7.

STEP 5

IMPORTANT: This step must be performed to ensure complete dosing. UZEDY is viscous and forceful downward flicks are required to move the bubble to the cap of the syringe. Failure to move the bubble to the cap of the syringe could result in incomplete dosage.

Firmly hold the syringe by the white collar.

Flick Syringe Forcefully Three Times to Move the Bubble to the Cap

• Flick with a forceful downward whipping motion of your full arm to move the bubble to the cap of the syringe.

• Repeat this action 3 times to ensure that the bubble is at the cap of the syringe.
**STEP 6**

Hold the syringe vertically by the white collar. Bend and snap off the cap. Do not touch the syringe tip to avoid contamination.

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**STEP 7**

*Attach the Needle to the Syringe*

- Hold the syringe vertically with the white collar at the top.
- Push the green hub of safety needle inside the white collar of syringe and rotate the safety needle while holding the white collar until secure and tight.

Inspect the needle connection to check that the hub is not damaged.

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**STEP 8**

*Select Injection Site from the Following Areas:*

- Stomach area (abdomen) around the belly button
- Back and outer area of the upper arms

Do not inject UZEDY anywhere except in the areas specified above.
Do not inject UZEDY into an area that is tender, red, bruised, callused, tattooed, hard, or has scars or stretch marks.

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**STEP 9**

Clean the Injection Site with an alcohol wipe.

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**STEP 10**

Remove the needle sheath by pulling the needle sheath away from the green hub to expose the needle. Do not expel any visible air bubble.

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**STEP 11**

Pinch at least 1 inch of the area of cleaned skin with your free hand.

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**STEP 12**

Insert the needle into subcutaneous tissue (actual angle of injection will depend on the amount of subcutaneous tissue). Do not apply pressure to the plunger.

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**STEP 13**

Release the pinched skin once the needle is in the subcutaneous tissue.

---

**STEP 14**

*Inject the Medication*

- Push on the plunger using a slow, firm, and steady push until the entire dose is delivered.
- Inject the entire dose at one time, without interruption.
- Check that the plunger stopper is at the White Collar.

**IMPORTANT:** UZEDY is viscous. Resistance will be experienced during dose delivery. Do not use excessive force in an attempt to deliver UZEDY faster.

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**STEP 15**

Wait 2-3 seconds after the entire dose is delivered before removing the needle. Slowly pull the needle out from the injection site at the same angle as insertion.
There will be an audible click when the needle safety shield is locked. Dispose of all syringe components in a suitable sharps container.

3 DOSAGE FORMS AND STRENGTHS

Extended-release injectable suspension: sterile, white to off-white opaque viscous suspension available in the following strengths: 50 mg/0.14 mL, 75 mg/0.21 mL, 100 mg/0.28 mL, 125 mg/0.35 mL, 150 mg/0.42 mL, 200 mg/0.56 mL, and 250 mg/0.7 mL.

Each strength is provided as a kit, which includes: one single-dose prefilled syringe and one 21 gauge, 5/8-inch needle.

4 CONTRAINDICATIONS

UZEDY is contraindicated in patients with a known hypersensitivity to risperidone, its metabolite, paliperidone, or to any of its components. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported in patients treated with risperidone or paliperidone.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6- to 1.7-times the risk of death in placebo-treated patients. Over the course of a typical 10-week double-blind controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

In two of four placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus oral risperidone when compared to patients treated with oral risperidone alone or with placebo plus furosemide. No pathophysiologic mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed.

UZEDY is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning and Warnings and Precautions (5.2)].

5.2 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

Cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73 to 97 years) in trials of oral risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse reactions in patients treated with oral risperidone compared to patients treated with placebo. UZEDY is not approved for the treatment of patients with dementia-related psychosis [see Warnings and Precautions (5.3)].

5.3 Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status including delirium, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If NMS is suspected, immediately discontinue UZEDY and provide supportive treatment and monitoring.

5.4 Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict, which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the cumulative dose. The syndrome can develop, after relatively brief treatment periods, even at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Table 2: Change in Random Glucose from Seven Placebo-Controlled, 3- to 8-Week, Fixed- or Flex-Dose Studies in Adults with Schizophrenia or Another Indication with Oral Risperidone

<table>
<thead>
<tr>
<th>Placebo</th>
<th>1 mg to 8 mg per day</th>
<th>Oral Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change from baseline (mg/dL)</td>
<td>N=555</td>
<td>1.4</td>
</tr>
<tr>
<td>Proportion of Patients with Shifts</td>
<td>N=164</td>
<td>0.6</td>
</tr>
</tbody>
</table>

In long-term, controlled and uncontrolled studies, oral risperidone was associated with a mean change in glucose of +2.8 mg/dL at Week 24 (N=151) and +4.1 mg/dL at Week 48 (N=50).

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Before or soon after initiation of antipsychotic medications, obtain a fasting lipid profile at baseline and monitor periodically during treatment.

Table 3: Change in Random Lipids from Seven Placebo-Controlled, 3- to 8-Week, Fixed- or Flex-Dose Studies in Adults with Schizophrenia or Another Indication with Oral Risperidone

<table>
<thead>
<tr>
<th>Placebo</th>
<th>1 mg to 8 mg per day</th>
<th>Oral Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change from baseline (mg/dL)</td>
<td>N=559</td>
<td>0.6</td>
</tr>
<tr>
<td>Proportion of Patients with Shifts</td>
<td>N=156</td>
<td>3.3</td>
</tr>
</tbody>
</table>

In long-term, controlled and uncontrolled studies, oral risperidone was associated with a mean change in cholesterol of +2.7% at Week 24 (N=231) and +5.5 mg/dL at Week 48 (N=86); and (b) non-fasting triglycerides of +19.9 mg/dL at Week 24 (N=52).
UZEDY® (risperidone) extended-release injectable suspension

Weight Gain
Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended. Data on mean changes in body weight and the proportion of subjects meeting a weight gain criterion of ≥7% or greater of body weight from 7 placebo-controlled, 3- to 8-week, fixed- or flexible-dose studies in adults with schizophrenia or another indication with oral risperidone are presented in Table 4.

<table>
<thead>
<tr>
<th>Weight Gain</th>
<th>Change from baseline</th>
<th>0.3</th>
<th>0.7</th>
<th>2.2</th>
</tr>
</thead>
</table>

Table 4: Mean Change in Body Weight (kg) and the Proportion of Subjects with ≥7% Gain in Body Weight From Seven Placebo-Controlled, 3- to 8-Week, Fixed- or Flexible-Dose Studies in Adults With Schizophrenia or Another Indication With Oral Risperidone

In longer-term, controlled and uncontrolled studies, oral risperidone was associated with a mean change in weight of +4.3 kg at Week 24 (n=395) and +5.3 kg at Week 48 (n=203).

5.6 Hyperprolactinemia
As with other drugs that antagonize dopamine D2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This in turn may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia may lead to decreased bone density in both female and male patients. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. An increase in pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats [see Nonclinical Toxicology (13.1)]. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

5.7 Orthostatic Hypotension and Syncope
UZEDY may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2007) of patients treated with oral risperidone in Phase 2 and 3 studies in adults with schizophrenia. UZEDY should be used with particular caution in (1) patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia and (2) in the elderly and patients with renal or hepatic impairment. Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs. Clinically significant hypotension has been observed with concomitant use of oral risperidone and antihypertensive medication.

5.8 Falls
Antipsychotics, including UZEDY, may cause somnolence, postural hypotension, motor and sensory instability which may lead to falls and, consequently, fractures or other fall-related injuries. Somnolence, postural hypotension, motor and sensory instability have been reported with the use of risperidone. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.9 Leukopenia, Neutropenia, and Agranulocytosis
In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including risperidone. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and a history of drug-induced leukopenia/neutropenia. In patients with a pre-existing history of a clinically significant low WBC or ANC or a history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of UZEDY at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Discontinue UZEDY in patients with absolute neutrophil count <1000/mm^3 and follow their WBC followed until recovery.

5.10 Potential for Cognitive and Motor Impairment
UZEDY, like other antipsychotics, may cause somnolence and has the potential to impair judgement, thinking, and motor skills. Somnolence was a commonly reported adverse reaction associated with oral risperidone treatment, especially when ascertained by direct questioning of patients. This adverse reaction is dose-related, and in a study utilizing a checklist to detect adverse reactions, 41% of the high-dose patients (oral risperidone 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse reactions than spontaneous reporting, by which 8% of oral risperidone 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse reaction.

UZEDY® (risperidone) extended-release injectable suspension

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that treatment with UZEDY does not affect them adversely.

5.11 Seizures
During premarketing studies of oral risperidone in adult patients with schizophrenia, seizures occurred in 0.3% of patients (9 out of 2,607 patients), two in association with hyponatremia. Use UZEDY cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

5.12 Dysphagia
Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer’s dementia. Antipsychotic drugs, including UZEDY, should be used cautiously in patients at risk for aspiration.

5.13 Priapism
Priapism has been reported during postmarketing surveillance for other risperidone products. A case of priapism was reported in premarketing studies of UZEDY. Severe priapism may require surgical intervention.

5.14 Body Temperature Regulation
Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral risperidone use. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use UZEDY with caution in patients who may experience these conditions.

6 ADVERSE REACTIONS
The following are discussed in more detail in other sections of the labeling:
- Increased mortality in elderly patients with dementia-related psychosis [see Boxed Warning and Warnings and Precautions (5.1)]
- Cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis [see Warnings and Precautions (5.2)]
- Neuroleptic malignant syndrome [see Warnings and Precautions (5.3)]
- Tardive dyskinesia [see Warnings and Precautions (5.4)]
- Metabolic changes [see Warnings and Precautions (5.5)]
- Hyperprolactinemia [see Warnings and Precautions (5.6)]
- Orthostatic hypotension and syncope [see Warnings and Precautions (5.7)]
- Falls [see Warnings and Precautions (5.8)]
- Leukopenia, neutropenia and agranulocytosis [see Warnings and Precautions (5.9)]
- Potential for cognitive and motor impairment [see Warnings and Precautions (5.10)]
- Seizures [see Warnings and Precautions (5.11)]
- Dysphagia [see Warnings and Precautions (5.12)]
- Priapism [see Warnings and Precautions (5.13)]
- Body temperature regulation [see Warnings and Precautions (5.14)]

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 clinical practice. The safety of UZEDY for the treatment of schizophrenia in adults is based on adequate and well-controlled studies of oral risperidone in studies of patients with schizophrenia and other indications. The results of those adequate and well-controlled studies are presented below.

The data described in this section are derived from a clinical trial database consisting of 9,803 patients exposed to one or more doses of oral risperidone for the treatment of schizophrenia and other psychiatric disorders. Of these 9,803 patients, 2,687 were patients who received oral risperidone in double-blind, placebo-controlled trials. The conditions and duration of treatment with oral risperidone varied greatly and included (in overlapping categories) double-blind, fixed- and flexible-dose, placebo- or active-controlled studies and open-label phases of studies, inpatients and outpatients, and short-term (up to 12 weeks) and longer-term (up to 3 years) exposures. Safety was assessed by collecting adverse reactions and performing physical examinations, vital signs, body weights, laboratory analyses, and ECGs.

Injection site reactions for UZEDY presented in this section (see “Injection Site Reactions with UZEDY” below) are based on a randomized withdrawal study in patients with schizophrenia consisting of a 12-week open-label oral risperidone (2 mg to 5 mg) stabilization phase, followed by a placebo-controlled phase in which patients were randomized to UZEDY (once monthly or once every 2 months) or placebo for a variable time until impending relapse or study completion [see Clinical Studies (14)].

The safety of UZEDY was evaluated in a total of 740 adult patients with schizophrenia who received at least 1 dose of UZEDY during the clinical development program. A total of 361 patients were exposed to UZEDY for at least 6 months, of which 221 patients were exposed to UZEDY for at least 12 months, which included 127 patients exposed to once monthly and 194 patients to once every 2 months dosing regimens. In addition, 32 patients were exposed to UZEDY for at least 24 months.

Adverse Reactions in Studies with Oral Risperidone
The most common adverse reactions in clinical trials of oral risperidone (>5% and twice placebo) were parkinsonism, akathisia, dystonia, tremor, sedation, dizziness, anxiety, blurred vision, nausea, vomiting, upper abdominal pain, stomach discomfort, dyspepsia, diarrhea, salivary hypersecretion, constipation, dry mouth, increased appetite, increased weight, fatigue, rash, nasal congestion, upper respiratory tract infection, nasopharyngitis, and pharyngolaryngitis.

Commonly Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials - Adult Patients with Schizophrenia Treated with Oral Risperidone

Table 5 lists the adverse reactions reported in 2% or more of oral risperidone-treated adult patients with schizophrenia in three 4- to 8-week, double-blind, placebo-controlled trials.
UZEDY® (risperidone) extended-release injectable suspension

Table 5: Adverse Reactions in ≥2% of Oral Risperidone-Treated Adult Patients (and greater than placebo) with Schizophrenia in Double-Blind, Placebo-Controlled Trials

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Percentage of Patients Reporting Reaction</th>
<th>Oral Risperidone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 mg to 8 mg per day (N=366)</td>
<td>8 mg to 16 mg per day (N=198)</td>
<td>Placebo (N=225)</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision blurred</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>8</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Dysepsia</td>
<td>8</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Salivary hypersecretion</td>
<td>2</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
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<td>Fatigue</td>
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<td>1</td>
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<td>&lt;1</td>
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<td>Infections and Infestations</td>
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<td>Sinusitis</td>
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<td>Urinary tract infection</td>
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<td>Pain in extremity</td>
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<td>Nervous System Disorders</td>
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<td>0</td>
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<tr>
<td>Anxiety</td>
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<td>Respiratory, Thoracic and Mediastinal Disorders</td>
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<td>Dyspnea</td>
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<td>2</td>
<td>0</td>
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<tr>
<td>Epistaxis</td>
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<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
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</tr>
<tr>
<td>Rash</td>
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<td>4</td>
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</tr>
<tr>
<td>Dry skin</td>
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<td>3</td>
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<tr>
<td>Vascular Disorders</td>
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</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>2</td>
<td>1</td>
<td>0</td>
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</tbody>
</table>

*Dose Groups Placebo Oral Risperidone Oral Risperidone Oral Risperidone Oral Risperidone Oral Risperidone

UZEDY® (risperidone) extended-release injectable suspension

Table 6: Adverse Reactions Associated with Discontinuation in ≥2% of Oral Risperidone-Treated Adult Patients in Schizophrenia Trials

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Oral Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>1.4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.8%</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>0.8%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0.8%</td>
</tr>
<tr>
<td>Dystonia</td>
<td>0.5%</td>
</tr>
<tr>
<td>Agitation</td>
<td>0.5%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.5%</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>0.3%</td>
</tr>
<tr>
<td>Akathisia</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Discontinuation for extrapyramidal symptoms (including Parkinsonism, akathisia, dystonia, and tardive dyskinesia) was 1% in placebo-treated patients, and 3.4% in active control-treated patients in a double-blind, placebo- and active-controlled trial.

Dose Dependency of Adverse Reactions in Clinical Trials of Oral Risperidone

Extrapyramidal Symptoms

Data from two fixed-dose trials in adults with schizophrenia provided evidence of dose-relatedness for extrapyramidal symptoms associated with oral risperidone treatment. Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of oral risperidone (2, 6, 10, and 16 mg/day), including (1) a Parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS:

Table 7: Extrapyramidal Symptoms Associated with Oral Risperidone-Treated Adult Patients in an 8-Week Fixed Dose Schizophrenia Trial

| Dose Groups Placebo Oral Risperidone 2 mg Oral Risperidone 6 mg Oral Risperidone 10 mg Oral Risperidone 16 mg |
|---------------------------------------------------------------|--|--|--|--|
| Parkinsonism                                                  | 12 | 4.5 | 9 | 23 | 26 |
| EPS incidence                                                 | 13% | 17% | 21% | 23% | 35% |

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of oral risperidone (1, 4, 8, 12, and 16 mg/day):
###extrapyramidal symptoms associated with oral risperidone-treated adult patients in an 8-week fixed dose schizophrenia trial

<table>
<thead>
<tr>
<th>Dose Groups</th>
<th>Oral Risperidone 1 mg</th>
<th>Oral Risperidone 4 mg</th>
<th>Oral Risperidone 8 mg</th>
<th>Oral Risperidone 12 mg</th>
<th>Oral Risperidone 16 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinsonism</td>
<td>0.6</td>
<td>1.7</td>
<td>2.4</td>
<td>2.9</td>
<td>4.1</td>
</tr>
<tr>
<td>EPS Incidence</td>
<td>7%</td>
<td>12%</td>
<td>17%</td>
<td>18%</td>
<td>20%</td>
</tr>
</tbody>
</table>

###changes in body weight

Weight gain was observed in short-term, controlled trials and longer-term uncontrolled studies in adults [see Warnings and Precautions (6.2) and Adverse Reactions (6)].

###dystonia

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

###other adverse reactions

Adverse reaction data elicited by a checklist for side effects from a large study comparing 5 fixed doses of oral risperidone (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend (p < 0.05) for the following adverse reactions: somnolence, vision abnormal, dizziness, palpitations, weight increase, erectile dysfunction, ejaculation disorder, sexual function abnormal, fatigue, and skin discoloration.

###changes in lab values

Between-group comparisons for pooled placebo-controlled trials of oral risperidone in adults revealed no statistically significant differences between oral risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTC, and PR intervals, and heart rate. When all oral risperidone doses were pooled from randomized controlled trials in several indications, there was a mean change in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of oral risperidone were associated with a higher mean increase in heart rate compared to placebo (4 to 6 beats per minute).

###injection site reactions with uzedy

Local tolerability assessments were administered to patients who reported injection site adverse reactions in a randomized withdrawal study with UZEDY in adult patients with schizophrenia. The injection site was assessed by appropriately trained personnel throughout the clinical development program.

All injection site reactions (nodule, pruritus, erythema, mass, and swelling) were mild to moderate in severity with the exception of 1 case of severe pruritus which resolved after 6 days. Injection site reactions were more frequent in 22 patients (13%) in the placebo group, 30 patients (21%) in the UZEDY once monthly group, and 37 patients (21%) in the UZEDY once every 2 months group. The most common injection site reactions were: nodule (7% in each UZEDY-treated group and 3% in the placebo group) and pruritus (5% and 3% in the UZEDY-treated once monthly and once every 2 months groups, respectively, and 2% in the placebo group).

###2.2 postmarketing experience

The following adverse reactions have been identified during post-approval use of oral risperidone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are listed by body system and include all reports.

####cardiovascular system

Adverse events associated with cardiovascular system included: orthostatic hypotension, syncope, palpitations, and tachycardia.

####gastrointestinal system

Adverse events associated with gastrointestinal system included: constipation, diarrhea, nausea, anaphylactic reaction, angioedema, anemia, abdominal pain, diarrhea, constipation, abdominal distention, melena, ileus, acute pancreatitis, enteritis, duodenal ulcer, dyspepsia, dysphagia, gastritis, and colitis.

####hematopoietic system

Adverse events associated with hematopoietic system included: decreased hemoglobin, decreased hematocrit, leukopenia, neutropenia, anemia, and agranulocytosis.

####neurological system

Adverse events associated with neurological system included: extrapyramidal symptoms, akathisia, tremor, hypokinesia, dystonia, hyperkinesia, chorea, paresthesia, hypotonia, tics, and movement disorders.

####other body systems

Adverse events associated with other body systems included: rash, urticaria, angioedema, pruritus, cough, and upper respiratory tract infection.

####blood disorders

Adverse events associated with blood disorders included: lymphopenia and increased white blood cell counts.

####endocrine system

Adverse events associated with endocrine system included: glucose intolerance, diabetes mellitus, and galactorrhea.

####respiratory system

Adverse events associated with respiratory system included: bronchitis, pharyngitis, and pneumonia.

####vision, ear, and hearing

Adverse events associated with vision, ear, and hearing included: increased intraocular pressure, visual disturbances, and otitis media.

####other

Adverse events associated with other included: death, and “other.”

###7.2 drugs having no clinically important interactions with uzedy

Based on pharmacokinetic studies with oral risperidone, no dosage adjustment of UZEDY is required when administered concomitantly with amitriptyline, cimetidine, ranitidine, clozapine, topiramate, and moderate CYP3A4 inhibitors (erythromycin). Additionally, no dosage adjustment is necessary for lithium, valproate, topiramate, digoxin, and CYP2D6 substrates (donepezil and galantamine) when co-administered with UZEDY [see Clinical Pharmacology (12.3)].

###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 antipsychotics, including UZEDY, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or online at http://womensmentalhealth.org/clinicaland-research-programs/pregnancyregistry/.

###risk summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery [see Clinical Considerations]. Overall, available data from published epidemiologic studies of pregnant women exposed to risperidone have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes [see Data]. There is a risk to the mother associated with untreated schizophrenia and with exposure to antipsychotics, including UZEDY, during pregnancy [see Clinical Considerations].

Oral administration of risperidone to pregnant mice caused cleft palate at doses 3- to 4-times the oral MRHD based on mg/m² body surface area. Risperidone was not teratogenic in rats or rabbits at doses up to 6-times the oral MRHD based on mg/m² body surface area. Increased stillbirths and decreased birth weight occurred after oral risperidone administration to pregnant rats at 1.5-times the oral MRHD based on mg/m² body surface area. Learning was impaired in offspring of rats when the dams were dosed at 0.6-times the oral MRHD and offspring mortality increased at doses 0.1- to 3-times the oral MRHD based on mg/m² body surface area. The background risk of major birth defects is unknown in the general population. 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.

Dose-associated maternal and/or embryo/fetal risk

There is a risk to the mother from untreated schizophrenia, including increased risk of relapse, hospitalization, and suicide. Schizophrenia is associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.
Fetal/Neonatal Adverse Reactions
Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including risperidone, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

Data
Human Data
Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A prospective observational study including 6 women treated with risperidone demonstrated placental passage of risperidone. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects. There was a small increase in the risk of major birth defects (RR = 1.26, 95% CI = 1.02 to 1.56) observed in oral treatment with risperidone during organogenesis (RR = 1.26, 95% CI = 0.88 to 1.81) in a subgroup of 1566 women exposed to risperidone during the first trimester of pregnancy; however, there is no mechanism of action to explain the difference in malformation rates.

Animal data
No developmental toxicity studies were conducted with subcutaneous risperidone suspension.

Oral administration of risperidone to pregnant mice during organogenesis caused cleft palate at 10 mg/kg/day which is 3-times the oral MRHD of 16 mg/day based on mg/m² body surface area; maternal toxicity occurred at 4-times the oral MRHD. Risperidone was not teratogenic when administered orally to rats at 0.1, 0.5, and 5 mg/kg/day and rabbits at 0.3 to 5 mg/kg/day, which are up to 6-times the oral MRHD of 16 mg/day risperidone based on mg/m² body surface area. Learning was impaired in offspring of rats dosed orally throughout pregnancy at 1 mg/kg/day which is 0.6-times the oral MRHD and neuronal cell death increased in fetal brains of offspring of rats dosed during pregnancy at 1 and 2 mg/kg/day which are 0.6- and 1.2-times the oral MRHD based on mg/m² body surface area; postnatal development and the growth of the offspring were also delayed. Rat offspring mortality increased during the first 4 days of lactation when pregnant rats were dosed through day 15 post-coitum at 0.1 to 5 mg/kg/day. A post-natal delay of 3-times the oral MRHD of 16 mg/day based on mg/m² body surface area is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams; a no-effect dose could not be determined. The rate of stillbirths was increased at 2.5 mg/kg or 1.5-times the oral MRHD based on mg/m² body surface area. In a rat cross-fostering study the number of live offspring was decreased, the number of stillbirths increased, and the birth weight was decreased in offspring of drug-treated pregnant rats. In addition, the number of deaths increased by Day 1 among offspring of drug-treated pregnant rats, regardless of whether or not the offspring were cross-fostered. Risperidone also appeared to impair maternal behavior in that offspring body weight gain and survival (from Day 1 to 4 of lactation) was reduced in offspring born to control rats or reared by drug-treated dams. All of these effects occurred at 5 mg/kg which is 3-times the oral MRHD based on mg/m² and the only dose tested in the study.

8.2 Lactation
Risk Summary
Limited data from published literature reports the presence of risperidone and its metabolite, 9-hydroxyrisperidone, in human breast milk at relative infant dose ranging between 2.3 and 4.7% of the maternal weight-adjusted dosage. There are reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to risperidone. Clinical Considerations: There is no information on the effects of risperidone on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for UZEDY and any potential adverse effects on the breastfed child from UZEDY or from the mother’s underlying condition.

Clinical Considerations
Infants exposed to UZEDY through breastmilk should be monitored for excess sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements).

8.3 Females and Males of Reproductive Potential
Infertility
Females
Based on the pharmacologic action of risperidone, (D₂ receptor antagonism), treatment with UZEDY may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential [see Warnings and Precautions (5.6)].

8.4 Pediatric Use
The safety and effectiveness of UZEDY have not been established in pediatric patients.

Juvenile Animal Toxicity Data
No juvenile animal studies were conducted with subcutaneous risperidone suspension.

Juvenile rats were dosed with oral risperidone from weeks 10 to 50 of age (equivalent to the period of childhood through adolescence in humans), at doses of 0.3, 1.25, or 5 mg/kg/day. Brain length and density were decreased with a no-effect dose of 0.3 mg/kg/day; this dose produced plasma AUC of risperidone plus its active metabolite paliperidone (9-hydroxyrisperidone) that were similar to those in children and adolescents receiving the oral MRHD of 6 mg/day. In addition, sexual maturation was delayed at all doses in both males and females. The above effects should be considered in females after a 12-week drug-withdrawal period.

Juvenile rats, treated with oral risperidone from days 12 to 50 of age (equivalent to the period of infancy through adolescence in humans) showed impaired learning and memory performance (reversible only in females), with a no-effect dose of 0.63 mg/kg/day which is 0.5 times the oral MRHD of 6 mg/day for children, based on mg/m² body surface area. This dose produced plasma AUC of risperidone plus paliperidone about half the exposure observed in humans at the oral MRHD. No other consistent effects on neurobehavioral or reproductive development were seen up to the highest tested dose of 1.25 mg/kg/day which is 1 time the oral MRHD and produced plasma AUC of risperidone plus paliperidone that were about two thirds of those observed in humans at the oral MRHD of 6 mg/day for children.

8.5 Geriatric Use
Clinical studies of UZEDY in the treatment of schizophrenia did not include patients older than 65 years to determine whether or not they respond differently from younger patients. In general, dose selection for geriatric patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

UZEDY is substantially excreted by the kidneys, and the risk of reactions may be greater in patients with impaired renal function. Because geriatric patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see Warnings and Precautions (5.7) and Clinical Pharmacology (12.3)].

Elderly patients with dementia-related psychosis treated with UZEDY are at an increased risk of death compared to placebo. UZEDY is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning and Warnings and Precautions (5.1, 5.2)].

8.6 Renal Impairment
In patients with renal impairment, titrate with oral risperidone (up to at least 2 mg daily) before initiating treatment with UZEDY [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]. UZEDY was not studied in patients with renal impairment.

8.7 Hepatic Impairment
In patients with hepatic impairment, titrate with oral risperidone (up to at least 2 mg daily) before initiating treatment with UZEDY [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]. UZEDY has not been studied in patients with hepatic impairment; however, such effect has been investigated with oral risperidone.

8.8 Patients with Parkinson’s Disease or Dementia with Lewy Bodies
Patients with Parkinson’s disease or dementia with Lewy bodies can experience increased sensitivity to UZEDY. Manifestations can include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with neuroleptic malignant syndrome.

10. OVERDOSAGE

10.1 Human Experience
No cases of overdose were reported in premarketing studies with UZEDY.

In premarketing experience with oral risperidone, there were eight reports of acute risperidone overdose with estimated doses ranging from 20 to 300 mg and no fatalities. In general, deaths were attributed to an overdose with extrapyramidal symptoms, and clinical features consistent with neuroleptic malignant syndrome.

Management of Overdose
There is no specific antidote to risperidone. Provide supportive care including close medical supervision and monitoring. Treatment should consist of general measures employed in the management of overdose with any drug. Consider the possibility of multiple drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Consider contacting the Poison Help Line (1-800-222-1222) or medical toxicologist for additional overdose management recommendations.

11. DESCRIPTION

UZEDY contains risperidone, an atypical antipsychotic. Risperidone belongs to the chemical class of benzisoxazole derivatives. The chemical designation 3-[2-(4-(6-fluoro-1,2-benzoxazol-3-yl) piperidin-1-yl)-ethy1]-2-methyl-6,7,8,9-tetrahydroprydin-1(2H)-one. Its molecular formula is C₁₈H₁₈F₂NO₂ and its molecular weight is 410.3 g/mol.

The structural formula is:

![Risperidone Structural Formula]

Risperidone is a white to off-white powder. It is practically insoluble in water and soluble in methanol and 0.1 N HCl. It has the following pKa values: 8.28 (piperidine moiety) and 3.12 (pyrimidine moiety). UZEDY is a sterile, white to off-white opaque viscous extended-release injectable suspension, intended for subcutaneous administration in the following strengths of risperidone (and deliverable volumes from a single-dose prefilled syringe): 50 mg (0.14 mL), 75 mg (0.21 mL), 100 mg (0.28 mL), 125 mg (0.35 mL), 150 mg (0.42 mL), 200 mg (0.56 mL), and 250 mg (0.7 mL). The inactive ingredients include dimethyl sulfoxide (45% w/w), methoxy-poly(ethylene glycol)-co-poly(lactide) (15% w/w), and poly(DL-lactide)-co-poly(ethylene glycol)-co-poly(lactide) (10% w/w).

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
The mechanism of action of risperidone, in schizophrenia, is unclear. The drug’s therapeutic activity in schizophrenia could be mediated through a combination of dopamine Type 2 (D₂) and serotonin Type 2 (5HT₂) receptor antagonism. The clinical effect from risperidone results from the combined concentrations of risperidone and its major metabolite, 9-hydroxyrisperidone (paliperidone) [see Clinical Pharmacology (12.2)]. Antagonism at receptors other than D₂ and 5HT₂ may explain some of the other effects of risperidone.
The average exposure values (Cavg, ss) over the dosing period are comparable for UZEDY administered once monthly and once every 2 months at corresponding doses. Following both once monthly (50 mg to 125 mg) and once every 2 months dosing (100 mg to 250 mg), the mean exposure of risperidone and 9-hydroxyrisperidone combined (AUCC,ss) of UZEDY corresponds to that of oral risperidone (5 to 5 mg/day) administered over an equivalent dosing period (see Table I). Absorption

UZEDY contains risperidone in a liquid delivery system. Following subcutaneous injection, a depot forms which provides a sustained plasma levels of risperidone and 9-hydroxyrisperidone combined over one month or two months. All UZEDY doses, administered once monthly or once every 2 months, showed two absorption peaks for risperidone in plasma. After subcutaneous administration, median tmax, for the risperidone and 9-hydroxyrisperidone combined ranges from 8 to 14 days. Therapeutic concentrations in plasma are within 6 to 24 hours following the first subcutaneous injection. UZEDY administered in the abdomen and upper arm results in similar pharmacokinetic profiles for all UZEDY doses, permitting either injection site to be used interchangeably. Distribution

Once absorbed, risperidone is rapidly distributed. The volume of distribution is 1 to 2 L/kg. Risperidone is bound to albumin and \( \alpha \)-acid glycoprotein. The plasma protein binding of risperidone is approximately 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displace each other from plasma binding sites. Elimination

The combined clearance of the risperidone and 9-hydroxyrisperidone following UZEDY administration is 14.3 L/h at steady state. The mean apparent half-life (t1/2) of UZEDY ranges between 14 to 22 days for risperidone, 9-hydroxyrisperidone, and risperidone and 9-hydroxyrisperidone combined. Metabolism

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme cytochrome CYP2D6 with minor contribution by CYP3A4. A minor metabolic pathway is through N-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug results from the combined concentrations of risperidone plus 9-hydroxyrisperidone). CYP2D6 is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiaarrhythmics, and other drugs. CYP2D6 is subject to genetic polymorphism (about 6 to 8% of Caucasians, and a very low percentage of Asians, have little or no activity and are “poor metabolizers”) and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone; whereas, poor CYP2D6 metabolizers convert it much more slowly. Population PK analysis demonstrates that plasma exposure to risperidone and 9-hydroxyrisperidone combined was similar in CYP2D6 extensive, intermediate, poor and non-poor metabolizers following subcutaneous injection with UZEDY. Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of “C-risperidone administered as a solution to three healthy male volunteers, total recovery of radioactivity at 1-week was 84%, including 70% in the urine and 14% in the feces. Specific Populations

Based on population pharmacokinetic analyses, age, sex, race and weight do not have a clinically meaningful effect on the pharmacokinetics of UZEDY. Patients with Renal Impairment

UZEDY was not studied in patients with renal impairment; however, such effect has been investigated with oral risperidone. In patients with moderate to severe renal disease treated with oral risperidone, the apparent clearance (CL/F) of risperidone and 9-hydroxyrisperidone combined was decreased by 60% in patients with moderate to severe renal disease compared with young healthy subjects [see Use in Specific Populations (8.6)]. Patients with Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of UZEDY has not been studied. The effect of hepatic impairment on the pharmacokinetics of oral risperidone was evaluated in a phase I study. While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished clearance of both albumin and \( \alpha \)-acid glycoprotein [see Use in Specific Populations (8.7)]. Drug Interaction Studies

No specific drug interaction studies have been performed with UZEDY. The drug interaction data presented in this section include studies with oral risperidone. Effects of other drugs on the exposures of risperidone, 9-hydroxyrisperidone, and risperidone and 9-hydroxyrisperidone combined as well as the effects of risperidone on the exposures of other drugs is summarized below. Effects of Other Drugs on Risperidone, 9-Hydroxyrisperidone, and Risperidone and 9-Hydroxyrisperidone Combined Pharmacokinetics

Strong CYP3A4 Inhibitors (Fluoxetine and Paroxetine)

Fluoxetine (20 mg once daily) and paroxetine (20 mg once daily), potent CYP2D6 inhibitors, have been shown to increase the plasma concentration of risperidone by 2.5- to 2.8-fold and 3- to 9-fold, respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10%. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied. Moderate CYP3A4 Inhibitor (Erythromycin)

There were no significant interactions between oral risperidone and erythromycin, a moderate CYP3A4 inhibitor. Strong CYP3A4 Inducer (Carbamazepine)

Carbamazepine co-administration with oral risperidone decreased the steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known CYP3A4 enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of UZEDY treatment. Amantadine, Cimetidine, Ranitidine, Clozapine

Clinically meaningful pharmacokinetic interaction between UZEDY and other drugs, such as amantadine, cimetidine, ranitidine, and clozapine, is not expected. Other CYP2D6 Substrates

• Amantadine did not affect the pharmacokinetics of risperidone or of risperidone and 9-hydroxyrisperidone combined following concomitant administration with oral risperidone.
• Cimetidine and ranitidine increased the bioavailability of oral risperidone by 64% and 26%, respectively. However, cimetidine did not affect the AUC of risperidone and 9-hydroxyrisperidone combined, whereas ranitidine increased the AUC of risperidone and 9-hydroxyrisperidone combined by 20%.
• Chronic administration of citalopram with oral risperidone have shown to affect the clearance of risperidone; however, clinical relevance is unknown.
• There was no clinically relevant effect of oral risperidone (1 to 6 mg/day) on the pharmacokinetics of topiramate 400 mg/day.

Effects of Oral Risperidone on Pharmacokinetics of Other Drugs

Lithium

Repeated doses of oral risperidone (3 mg twice daily) did not affect the exposure (AUC) or peak plasma concentrations (Cmax) of lithium (n = 13).

Valproate

Repeated doses of oral risperidone (4 mg once daily) did not affect the predose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n = 21). However, there was a 20% increase in valproate peak plasma concentration (Cmax) after concomitant administration of oral risperidone.

Topiramate

Oral risperidone administered at doses from 1 to 6 mg/day concomitantly with topiramate 400 mg/day resulted in a 23% decrease in risperidone Cmax and a 33% decrease in risperidone AUC0-24 hour at steady state. Minimal reductions in the exposure to risperidone and 9-hydroxyrisperidone combined, and no change for 9-hydroxyrisperidone were observed. This interaction is unlikely to be of clinical significance. There was no clinically relevant effect of oral risperidone on the pharmacokinetics of topiramate.

Digoxin

Oral risperidone (0.25 mg twice daily) did not show a clinically relevant effect on the pharmacokinetics of digoxin.

CYP2D6 Substrates

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP2D6. Therefore, UZEDY is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, oral risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP2D6.
Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5- to 6-fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unclear [see Warnings and Precautions (5.6)].

Mammary gland adenocarcinomas
- Rat: Female, 0.2 (2.4), none
- Rat: Male, 0.4 (2.4), none
- Male, 6.0 (37.5), 1.5 (9.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5- to 6-fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unclear [see Warnings and Precautions (5.6)].

Mammary gland adenocarcinomas
- Rat: Female, 0.2 (2.4), none
- Rat: Male, 0.4 (2.4), none
- Male, 6.0 (37.5), 1.5 (9.4)

Impairment of Fertility

No mating and fertility studies were conducted with subcutaneous risperidone suspension. Oral risperidone (0.16 to 5 mg/kg) impaired mating, but not fertility, in rat reproductive studies at doses 0.1- to 3-times the oral MRHD of 16 mg/day based on mg/m² body surface area. The effect appeared to be in females, since impaired mating behavior was not noted in the male fertility study. In a subchronic study in Beagle dogs in which risperidone was administered orally at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 6- to 10-times the oral MRHD based on mg/m² body surface area. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. A no-effect dose could not be determined in either rat or dog.

14 CLINICAL STUDIES

The efficacy of UZEDY for the treatment of schizophrenia in adults is based, in part, on the established effectiveness of oral risperidone as well as in a randomized withdrawal study (Study 1: NCT03503318) with UZEDY in adults who met the DSM-5 criteria for schizophrenia. The results from Study 1 are presented below.

Study 1 was a randomized withdrawal study in patients with schizophrenia consisting of a 12-week open-label oral risperidone (2 mg to 5 mg) stabilization phase, followed by a placebo-controlled phase in which patients were randomized to UZEDY (once monthly or every 2 months) or placebo for a variable time until impending relapse or study completion. UZEDY was administered once monthly or once every 2 months at doses of 50 mg to 250 mg compared with monthly placebo injections in adult patients meeting DSM-5 criteria for schizophrenia. Patients were required to have a Positive and Negative Syndrome Scale (PANSS) total score lower than 100 at the screening visit. Eligible screened patients were enrolled into an oral conversion and stabilization stage (12 weeks). Patients were administered oral risperidone (2 mg to 5 mg per day) to establish stability and tolerability. Eligible patients were randomized into the double-blind period of the study if they met the following randomization criteria for at least 4 consecutive weeks prior to the baseline visit: outpatient status, PANSS total ≤80, minimal presence of specific psychotic symptoms on the PANSS, as measured by a score of ≤4 on each of the following domains: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content (CGI-S score ≤4 [moderately ill]; CGI-SS score ≤2 [mildly suicidal]) on Part I and ≤5 [minimally worsened] on Part 2.

In the double-blind stage (variable in duration), patients were randomized to receive placebo, into the double-blind period of the study if they met the following randomization criteria for at least 4 consecutive weeks prior to the baseline visit: outpatient status, PANSS total ≤80, minimal presence of specific psychotic symptoms on the PANSS, as measured by a score of ≤4 on each of the following domains: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content (CGI-S score ≤4 [moderately ill]; CGI-SS score ≤2 [mildly suicidal]) on Part I and ≤5 [minimally worsened] on Part 2.

The primary efficacy endpoint was time to impending relapse. Relapse was defined as one or more of the following items:

- Clinical Global Impression–Improvement (CGI-I) of ≥5 (greater than or equal to minimally worse, i.e., minimally worse, much worse or very much worse), AND
- An increase of any of the following individual Positive and Negative Syndrome Scale (PANSS) items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score of >4 with an absolute increase of ≥2 on that specific item since randomization, OR
- An increase in any of the following 4 individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score of >4 and an absolute increase of ≥2 on the combined score of these 4 PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) since randomization
- Hospitalization due to worsening of psychotic symptoms (including partial hospitalization programs), excluding hospitalization for psychosocial reasons

15 PATIENT COUNSELING INFORMATION

Neuroleptic Malignant Syndrome (NMS)

Counsel patients about a potentially fatal adverse reaction, Neuroleptic Malignant Syndrome (NMS) that has been reported in association with administration of antipsychotic drugs. Advise patients, family members, or caregivers to contact the healthcare provider or report to the emergency room if they experience signs and symptoms of NMS [see Warnings and Precautions (5.3)].

Tardive Dyskinesia

Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their healthcare provider if these abnormal movements occur [see Warnings and Precautions (5.3)].

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

UZEDY (risperidone) extended-release injectable suspension, for subcutaneous use is a sterile, white to off-white opaque viscous suspension.

UZEDY is supplied in single-dose kits as follows:

- 50 mg/0.14 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 51759-505-10)
- 75 mg/0.21 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 51759-410-10)
- 100 mg/0.28 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 51759-520-10)
- 125 mg/0.35 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 51759-630-10)
- 150 mg/0.42 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 51759-740-10)
- 200 mg/0.56 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 51759-850-10)
- 250 mg/0.7 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 51759-960-10)

The prefilled syringe cap is not made with natural rubber latex.

Storage and Handling

Store in refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. UZEDY may be stored in unopened original packaging at room temperature, 20°C to 25°C (68°F to 77°F), for up to 90 days. If unopened, UZEDY may be returned to refrigerated storage within 90 days. Once the carton is opened, administer UZEDY or discard.

17 PATIENT COUNSELING INFORMATION

Neuroleptic Malignant Syndrome (NMS)

Counsel patients about a potentially fatal adverse reaction, Neuroleptic Malignant Syndrome (NMS) that has been reported in association with administration of antipsychotic drugs. Advise patients, family members, or caregivers to contact the healthcare provider or report to the emergency room if they experience signs and symptoms of NMS [see Warnings and Precautions (5.3)].

Tardive Dyskinesia

Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their healthcare provider if these abnormal movements occur [see Warnings and Precautions (5.3)].

Metabolic Changes

Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia and diabetes mellitus and the need for specific monitoring, including blood glucose, lipids, and weight [see Warnings and Precautions (5.5)].

Hyperprolactinemia

Counsel patients on signs and symptoms of hyperprolactinemia that may be associated with chronic use of UZEDY. Advise them to seek medical attention if they experience any of the following: amenorrhea or galactorrhea in females, erectile dysfunction, or gynecomastia in males [see Warnings and Precautions (5.6)].
Orthostatic Hypotension and Syncope
Educate patients about the risk of orthostatic hypotension and syncope, particularly at the time of initiating treatment, re-initiating treatment or increasing the dose [see Warnings and Precautions (5.7)].

Leukopenia/Neutropenia
Advise patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia that they should have their CBC monitored while being treated with UZEDY [see Warnings and Precautions (5.9)].

Potential for Cognitive and Motor Impairment
Inform patients that UZEDY has the potential to impair judgement, thinking, and motor skills. Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery, or operating a motor vehicle, until they are reasonably certain that UZEDY therapy does not affect them adversely [see Warnings and Precautions (5.10)].

Priapism
Advise patients of the possibility of painful or prolonged penile erections (priapism). Instruct the patient to seek immediate medical attention in the event of priapism [see Warnings and Precautions (5.13)].

Heat Exposure and Dehydration
Educate patients regarding appropriate care in avoiding overheating and dehydration [see Warnings and Precautions (5.14)].

Concomitant Medication
Advise patients to inform their healthcare providers if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interaction [see Drug Interactions (7)].

Alcohol
Advise patients to avoid alcohol during treatment with UZEDY [see Drug Interactions (7.1)].

Pregnancy
Advise patients to notify their healthcare professional if they become pregnant or intend to become pregnant during treatment with UZEDY. Advise patients that UZEDY may cause extrapyramidal and/or withdrawal symptoms (agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) in a neonate. Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to UZEDY during pregnancy [see Use in Specific Populations (8.1)].

Lactation
Advise breastfeeding women using UZEDY to monitor infants for somnolence, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) and to seek medical care if they notice these signs [see Use in Specific Populations (8.2)].

Infertility
Advise females of reproductive potential that UZEDY may impair fertility due to an increase in serum prolactin levels. The effects on fertility are reversible [see Use in Specific Populations (8.3)].

UZE-003
Manufactured for:
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