UZEDY™ (risperidone) extended-release injectable suspension

- Metabolic Changes: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. (5.5)
- Hyperprolactinemia: Prolactin elevations occur and persist during chronic administration. Long- standing hyperprolactinemia, when associated with hypogonadism, can lead to decreased bone density in females and males. (5.6)
- Orthostatic Hypotension and Syncope: Monitor heart rate and blood pressure and warn patients with known cardiovascular disease or cerebrovascular disease, and risk of dehydration or syncope. (5.7)
- Leukopenia, Neutropenia, and Agranulocytosis: Perform complete blood counts (CBC) in patients with a history of clinically significant low white blood cell count (WBC) or history of leukopenia or neutropenia. Consider discontinuing UZEDY if a clinically significant decline in WBC occurs in the absence of other causative factors. (5.9)
- Potential for Cognitive and Motor Impairment: Use caution when operating machinery. (5.10)
- Seizures: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. (5.11)
- Priapism: Priapism has been reported. Severe priapism may require surgical intervention. (5.13)

ADVERSE REACTIONS

The most common adverse reactions with risperidone (≥5% and greater than placebo) were parkinsonism, akathisia, dyskinesia, 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 pharyngolaryngeal pain. (6.1)

The most common injection site reactions with UZEDY (≥5% and greater than placebo) were injection site reactions, including redness, pain, bruising, pruritus, and nodule. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP2D6 inhibitors (e.g., fluoxetine, paroxetine): Increase risperidone plasma concentration. (2.3, 7.1)
- Strong CYP3A4 inducers (e.g., carbamazepine): Decrease plasma concentrations of risperidone. (2.3, 7.1)

USE IN SPECIFIC POPULATIONS

Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)

See 17 for PATIENT COUNSELING INFORMATION Revised: 5/2023

7 DRUG INTERACTIONS
7.1 Drugs Having Clinically Important Interactions with UZEDY
7.2 Drugs Having No Clinically Important Interactions with UZEDY

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
8.8 Patients with Parkinson’s Disease or Dementia with Lewy Bodies

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
**UZEDY™ (risperidone) extended-release injectable suspension**

**FULL PRESCRIBING INFORMATION**

**INDICATIONS AND USAGE**

UZEDY is indicated for the treatment of schizophrenia in adults.

**DOSAGE AND ADMINISTRATION**

**2.1 Recommended Dosage**

To start UZEDY, switch from oral daily risperidone. Initiate UZEDY, as either a once monthly injection or a once every 2 month injection, keeping in mind that the day after the last dose of oral therapy. See Table 1 to determine how to switch from oral risperidone to UZEDY 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>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>

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.

**2.2 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 [see Use in Specific Populations (8.6, 8.7) and Clinical Pharmacology (12.3)]

**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 or when the UZEDY is not used for the last 2 weeks, decrease the dose to 50 mg once monthly or 100 mg once every 2 months, continue treatment with these doses unless clinical judgment necessitates interruption of UZEDY [see Drug Interactions (7.1)].

**2.4 Preparation and Administration Instructions**

- Do not substitute any components of the kit for administration.
- Do not administer more frequently than recommended.
- Do not administer more frequently than recommended.
- Do not administer more frequently than recommended.
- Do not administer more frequently than recommended.
- Do not administer more frequently than recommended.
- Do not administer more frequently than recommended.
UZEDY™ (risperidone) extended-release injectable suspension

Note: Standing while you do this may help achieve required force.

Check that the Bubble is at the Cap of the Syringe
- The bubble will appear partially opaque.
- Holding the syringe up to light or against a dark backdrop may improve visibility.
- If the bubble is not at the cap, repeat Step 5 until it is.

Flick downwards forcefully with your full arm

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.

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.

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.

STEP 9
Clean the Injection Site with an alcohol wipe.

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.

STEP 11
Pinch at least 1 inch of the area of cleaned skin with your free hand.

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.

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.

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

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 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical placebo-controlled trial, the rate of death in drug-treated patients was about 4 to 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 other characteristics 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 pathological 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)).

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 longer-term, controlled and uncontrolled studies in adults, 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). In longer-term, controlled and uncontrolled studies in adults, 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. Published data from 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 2.

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

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Placebo</th>
<th>Oral Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Cholesterol</td>
<td>N=555</td>
<td>Mean change from baseline (mg/dL)</td>
</tr>
<tr>
<td>Change from baseline (mg/dL)</td>
<td>-1.4</td>
<td>-1.8</td>
</tr>
<tr>
<td>Serum Triglycerides</td>
<td>N=748</td>
<td>Proportion of Patients with Shifts</td>
</tr>
<tr>
<td>Change from baseline (mg/dL)</td>
<td>0.6%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Serum HDL-C</td>
<td>N=164</td>
<td>Change from baseline (mg/dL)</td>
</tr>
<tr>
<td>Mean change from baseline (mg/dL)</td>
<td>0%</td>
<td>-0.8</td>
</tr>
<tr>
<td>Serum LDL-C</td>
<td>(0/158)</td>
<td>Proportion of Patients with Shifts</td>
</tr>
<tr>
<td>Mean change from baseline (mg/dL)</td>
<td>-8.3</td>
<td>-1.8</td>
</tr>
<tr>
<td>Serum TG</td>
<td>(0/158)</td>
<td>Proportion of Patients with Shifts</td>
</tr>
<tr>
<td>Mean change from baseline (mg/dL)</td>
<td>-8.3</td>
<td>-1.8</td>
</tr>
</tbody>
</table>

In longer-term, controlled and uncontrolled studies in adults, 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).

Hyperglycemia

Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics including risperidone. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics, including UZEDY, should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes who are starting treatment with atypical antipsychotics, including UZEDY, should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics, including UZEDY, should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics, including UZEDY, should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic, including risperidone, was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of risperidone.

Pooled data from three double-blind, placebo-controlled schizophrenia studies and four double-blind, placebo-controlled studies in another indication with oral risperidone are presented in Table 3.

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

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Placebo</th>
<th>Oral Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Cholesterol</td>
<td>N=559</td>
<td>Mean change from baseline (mg/dL)</td>
</tr>
<tr>
<td>Change from baseline (mg/dL)</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>N=742</td>
<td>Mean change from baseline (mg/dL)</td>
</tr>
<tr>
<td>Mean change from baseline (mg/dL)</td>
<td>4.3%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>N=156</td>
<td>Proportion of Patients with Shifts</td>
</tr>
<tr>
<td>Mean change from baseline (mg/dL)</td>
<td>6.3%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>(2/180)</td>
<td>Change from baseline (mg/dL)</td>
</tr>
<tr>
<td>Mean change from baseline (mg/dL)</td>
<td>2.5%</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

In longer-term, controlled and uncontrolled studies, oral risperidone was associated with a mean change in (a) non-fasting cholesterol of +4.4 mg/dL 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).
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 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

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Placebo (n=597)</th>
<th>1 mg to 8 mg per day (n=769)</th>
<th>&gt;8 mg to 16 mg per day (n=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Gain</td>
<td>Change from baseline</td>
<td>0.7</td>
<td>2.2</td>
</tr>
<tr>
<td>≥7% increase from baseline</td>
<td>2.9%</td>
<td>8.7%</td>
<td>20.9%</td>
</tr>
</tbody>
</table>

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 antagonist properties. Syncope was reported in 0.2% (6/2607) 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 treat promptly if such symptoms or signs occur. Discontinue **UZEDY** in patients with absolute neutrophil count <1000/mm3 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 judgment, 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.

### 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 premarket 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 while participating 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 untillimping 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 351 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 72 patients exposed to one or more 2 months dosing regimens. In addition, 32 patients were exposed to **UZEDY** for at least 24 months.

### 6.1.1 Adverse Reactions in Patients with Schizophrenia

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 pharyngolaryngeal pain.

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% 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>Adverse Reaction</th>
<th>Percentage of Patients Reporting Reaction</th>
<th>Oral Risperidone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
<td></td>
<td>2 mg to 8 mg per day (N=366)</td>
<td>2 to 8 mg per day (N=198)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td></td>
<td></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td></td>
<td></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Vision blurred</td>
<td></td>
<td></td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Sinusitis</td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td></td>
<td></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Back pain</td>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
<td></td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td></td>
<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Parkinsonism*</td>
<td></td>
<td></td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Akathisia*</td>
<td></td>
<td></td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Sedation</td>
<td></td>
<td></td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Dystonia*</td>
<td></td>
<td></td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Tremor*</td>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness postural</td>
<td></td>
<td></td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td><strong>Musculoskeletal, Connective Tissue, and Bone Disorders</strong></td>
<td></td>
<td></td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sinusitis</td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td></td>
<td></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Back pain</td>
<td></td>
<td></td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td></td>
<td></td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*PARKinsonism includes extrapyramidal disorder, musculoskeletal stiffness, parkinsonism, cogwheel rigidity, akathisia, bradykinesia, hypokinesia, masked facies, muscle rigidity, and Parkinson’s disease. Akathisia includes akathisia and restlessness. Dystonia includes dystonia, muscle spasms, muscle contractions involuntary, muscle contracture, occlusalgyria, tongue paralysis. Tremor includes tremor and parkinsonian rest tremor.

For All Other Adverse Reactions Observed During the Clinical Trial Evaluations of Oral Risperidone

The following is a list of additional adverse drug reactions that have been reported during the clinical trial evaluation of oral risperidone:

**Cardiac Disorders:** sinus bradycardia, sinus tachycardia, atrioventricular block first degree, bundle branch block left, bundle branch block right, atrioventricular block

**Ear and Labyrinth Disorders:** ear pain, tinnitus

**Endocrine Disorders:** hyperprolactinemia

### UZEDY™ (risperidone) extended-release injectable suspension

**Eye Disorders:** ocular hyperemia, eye discharge, conjunctivitis, eye rolling, eyelid edema, eye swelling, eyelid margin crusting, dry eye, lacrimation increased, photophobia, glaucoma, visual acuity reduced

**Gastrointestinal Disorders:** dysphagia, fecaloma, fecal incontinence, gastritis, lip swelling, cheilitis, aphthosis

**General Disorders:** edema peripheral, thirst, gait disturbance, chest discomfort, chest pain, influenza-like illness, pitting edema, edema, chills, sluggishness, malaise, face edema, discomfort, generalized edema, drug withdrawal syndrome, peripheral coldness, feeling abnormal

**Immune System Disorders:** drug hypersensitivity

**Infections and Infestations:** pneumonia, influenza, ear infection, viral infection, pharyngitis, tonsillitis, bronchitis, eye infection, localized infection, cystitis, cellulitis, otitis media, orrhyhomyoschitis, aacodermatitis, bronchopneumonia, respiratory tract infection, tracheobronchitis, otitis media chronic

**Investigations:** body temperature increased, blood protein increased, alanine aminotransferase increased, electrocardiogram abnormal, eosinophil count increased, white blood cell count decreased, blood glucose increased, hemoglobin decreased, hematocrit decreased, body temperature decreased, blood pressure decreased, transaminase increased

**Metabolism and Nutrition Disorders:** decreased appetite, polydipsia, anorexia

**Musculoskeletal, Connective Tissue, and Bone Disorders:** joint swelling, joint stiffness, musculoskeletal chest pain, posture abnormal, myalgia, neck pain, muscular weakness, muscle rigidity, rhodobomyolysis

**Nervous System Disorders:** balance disorder, disturbance in attention, dysartria, unresponsive to stimuli, depressed level of consciousness, movement disorder, transient ischemic attack, coordination abnormal, cerebrovascular accident, speech disorder, syncope, loss of consciousness, hypoesthesia, tardive dyskinesia, cerebral ischemia, cerebrovascular disorder, neuropsychiatric malignant syndrome, diabetic coma, head titubation

**Psychiatric Disorders:** agitation, blunted affect, confusional state, middle insomnia, nervousness, sleep disorder, listlessness, libido decreased, anorgasmia

**Renal and Urinary Disorders:** enuresis, dysuria, pollakiuria, urinary incontinence

**Reproductive System and Breast Disorders:** menstruation irregular, amenorrhea, gynecomastia, galactorrhea, vaginal discharge, menstrual disorder, erectile dysfunction, retrograde ejaculation, ejaculation disorder, sexual dysfunction, breast enlargement

**Respiratory, Thoracic, and Mediastinal Disorders:** wheezing, pneumonia aspcention, sinus congestion, dysphonia, productive cough, pulmonary congestion, respiratory tract congestion, rales, respiratory disorder, hyperventilation, nasal edema

**Skin and Subcutaneous Tissue Disorders:** erythema, skin discoloration, skin lesion, pruritus, skin disorder, rash erythematous, rash papular, acne, hyperkeratosis, seborrheic dermatitis, rash generalized, rash maculopapular

**Vascular Disorders:** hypertension, flushing

**Discontinuances Due to Adverse Drug Reactions with Oral Risperidone**

Approximately 7% (29/454) of oral risperidone-treated patients in double-blind, placebo-controlled trials discontinued treatment due to an adverse reaction, compared with 4% (10/225) who were receiving placebo. The adverse reactions associated with discontinuation in 2 or more oral risperidone-treated patients were:

### 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>Discontinuation</td>
<td>2 mg to 8 mg per day (N=366)</td>
</tr>
<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>Dizziness</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

<table>
<thead>
<tr>
<th>Dose Groups</th>
<th>Placebo</th>
<th>Oral Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral Risperidone 2 mg</td>
<td>Oral Risperidone 6 mg</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>1.2</td>
<td>0.8</td>
</tr>
<tr>
<td>EPS incidence</td>
<td>13%</td>
<td>17%</td>
</tr>
</tbody>
</table>

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):
The interactions of UZEDY with co-administration of other drugs have not been studied. The drug Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), sudden death, thrombocytopenia, puberty, pulmonary embolism, QT prolongation, sleep apnea syndrome, somnambulism, Stevens-secretion, intestinal obstruction, jaundice, mania, pancreatitis, pituitary adenoma, precocious metabolism, dysgeusia, hypoglycemia, hypothermia, ileus, inappropriate antidiuretic hormone cardiopulmonary arrest, catatonia, diabetic ketoacidosis in patients with impaired glucose These adverse reactions include: alopecia, anaphylactic reaction, angioedema, atrial fibrillation, changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rates. When all oral risperidone doses were pooled from randomized controlled trials in several indications, there was a mean increase in QTc at 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, 50 patients (26%) 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 group, respectively, and 2% in the placebo group).

6.2 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 include: agitation, anaphylactic reaction, angioedema, atrial fibrillation, cardiopulmonary arrest, catatonia, diabetic ketoacidosis in patients with impaired glucose metabolism, dysgeusia, hypoglycemia, hypothermia, ileus, inappropriate antidiuretic hormone secretion, intestinal obstruction, jaundice,mania, pancreatitis, pituitary adenoma, precocious puberty, pulmonary embolism, QT prolongation, sleep apnea syndrome, somnambulism, Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), sudden death, thrombocytopenia, thrombotic thrombocytopenic purpura, urinary retention, and water intoxication. Postmarketing cases of extrapyramidal symptoms (dystonia and dyskinesia) have been reported in patients concomitantly taking methylphenidate and risperidone when there was an increase or decrease in dosage, initiation, or discontinuation of either or both medications.

7 DRUG INTERACTIONS
The interactions of UZEDY with co-administration of other drugs have not been studied. The drug interaction data provided in this section is based on studies with oral risperidone.

7.1 Drugs Having Clinically Important Interactions with UZEDY
Table 9 includes clinically significant drug interactions with UZEDY.

Table 9: Clinically Important Drug Interactions with UZEDY

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 atypical antipsychotics, including UZEDY, during pregnancy. Healthcare providers are encouraged to register pregnant 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 are risks 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 maximum recommended human dose (MRHD) of 16 mg/day with maternal toxicity observed at 4-times MRHD based on mg/m2 body surface area. Risperidone was not teratogenic in rats 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 in the general 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
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.
UZEDY™ (risperidone) extended-release injectable suspension

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 dosage 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)].

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.

10.1 OVERDOSAGE 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 overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, risperidone adverse reactions were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hypotension, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

Postmarketing experience with oral risperidone included reports of acute overdose with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other postmarketing adverse reactions related to oral risperidone overdose include prolonged QT interval and convulsions. Torsade de pointes has been reported in association with combined overdose of oral risperidone and paroxetine.

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 overdosage. 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
11.2 CLINICAL PHARMACOLOGY
11.2.1 Mechanism of Action
The mechanism of action of risperidone, in schizophrenia, is unclear. The drug's therapeutic function in schizophrenia could be due to 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 metabolic, 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.
12.2 Pharmacodynamics

Risperidone is a monogenic antagonist with high affinity (Ki of 0.12 to 2.3 nM) for the serotonin Type 2 (5HT2), dopamine Type 2 (D2), alpha1, and alpha2 adrenergic, and histaminergic receptors. Risperidone showed low to moderate affinity (Ki of 47 to 253 nM) for the serotonin 5HT3, 5HT4, and 5HT6 receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10 M) for cholinergic muscarinic or J1, and dopamine receptors.

12.3 Pharmacokinetics

The pharmacokinetics of the risperidone and 9-hydroxyrisperidone combined and the individual components (risperidone and 9-hydroxyrisperidone), following subcutaneous injection of UZEDY. were evaluated in both healthy subjects (n = 53) and in patients with clinically stable schizophrenia and schizophrenia. The combined clearance of the risperidone and 9-hydroxyrisperidone combined (AUC0-12h) of UZEDY corresponds to that of oral risperidone (2 mg to 5 mg/day) administered over an equivalent dosing period (see Table 1).

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 a decrease in absorption peak for risperidone in plasma. After subcutaneous administration, median t(m), 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.

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 minimal contribution by CYP3A4. A minor metabolic pathway is through N-dealkylation. The main metabolite, risperidone, 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, antiarhythmic, and other drugs. CYP2D6 is subject to genetic polymorphism (about 6 to 8% of Caucasian Americans, and 10% of African Americans, 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 has been 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 concentration of both albumin and alpha-acid glycoprotein [see Use in Specific Populations (8.7)].
No evidence of mutagenic or clastogenic potential for risperidone was found in the tumors in rodents is unclear prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine prolactin levels 5- to 6-fold in mice and rats at the same doses used in the carcinogenicity measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, Impairment of Fertility co-poly(D,L-lactide) and poly(D,L-lactide)-copolymer mixture of methoxy-poly(ethylene glycol)-

No evidence of mutagenic potential was found in the chromosomal aberration test in human lymphocytes, Chinese hamster ovary cells, or in the in vitro oral micronucleus test in mice and the sex-linked recessive lethal test in Drosophila. No evidence of mutagenic potential was found in the in vitro Ames reverse mutation test for the copolymer mixture of methoxy-poly(ethylene glycol)-co-poly(OL-lactide) and poly(OL-lactide)-co-poly(ethylene glycol)-co-poly(OL-lactide) dissolved in dimethyl sulfoxide. 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 administrated orally at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6- 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 once 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 items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content [CGI-S score ≤4 (moderately ill); CGI-SS score ≤2 (mildly suicidal)] on Part 1 and ≤5 (minimally worsened) on Part 2.

In the double-blind stage (variable in duration), patients were randomized to receive placebo, once monthly UZEDY, or once every 2 months UZEDY in doses based on the oral dose on which they were previously stabilized in the oral conversion and stabilization stage. 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 ≥4 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

The study met its prespecified primary endpoint for both the UZEDY once monthly and once every 2 months dosing regimens. Time to relapse was statistically significantly longer in the UZEDY-treated groups compared to the placebo group. The cumulative percentage of relapse over time was calculated using Kaplan-Meier product limit estimate of the time to relapse during the randomized withdrawal trial as shown in Figure 1. Subgroup analyses by gender, age, and race did not suggest any clear evidence of differential responsiveness to UZEDY.

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/0.34 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 51759-305-10)
- 75 mg/0.21 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 51759-300-10)
- 100 mg/0.16 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 51759-250-10)
- 150 mg/0.25 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 51759-400-10)
- 200 mg/0.56 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 51759-800-10)

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 (5.5)].

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 (5.5)].

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-002
Manufactured for:
Teva Neuroscience, Inc.
Parsippany, NJ 07054
©2023 Teva Neuroscience, Inc.