UZEDY (risperidone) extended-release injectable suspension, for subcutaneous use

1 INDICATIONS AND USAGE

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

2 DOSAGE 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)

3 DOSAGE AND ADMINISTRATION

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 100 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td>3 mg of oral risperidone per day</td>
<td>75 mg 150 mg</td>
<td>75 mg</td>
</tr>
<tr>
<td>4 mg of oral risperidone per day</td>
<td>100 mg 200 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>5 mg of oral risperidone per day</td>
<td>125 mg 250 mg</td>
<td>125 mg</td>
</tr>
</tbody>
</table>

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

4 ADVERSE REACTIONS

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

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)

5 WARNINGS AND PRECAUTIONS

- 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)

6 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 hyposecretion, constipation, dry mouth, increased appetite, increased weight, fatigue, rash, nasal congestion, upper respiratory tract infection, nasopharyngitis, and pharyngolaryngeal pain. (6.1)

7 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)

8 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.
1 INDICATIONS AND USAGE
UZEDY™ (risperidone) extended-release injectable suspension 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.

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.

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 Prefilled Syringe
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 Safety Needle
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.
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.
Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that may occur 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 unknown. In two of four placebo-controlled trials in elderly patients with dementia-related psychosis, 4.3% of 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 Boxed Warning and Warnings and Precautions (5.2)].

In longer-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).

Table 2: Change in Random Glucose 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>Placebo</th>
<th>Oral Risperidone</th>
<th>Mean change from baseline (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=555</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=748</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=164</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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>Placebo</th>
<th>Oral Risperidone</th>
<th>Mean change from baseline (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=559</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=742</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=156</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Proportion of Patients with Shifts between -1 mg to 8 mg per day >8 mg to 16 mg per day

<table>
<thead>
<tr>
<th>Serum Glucose</th>
<th>Proportion of Patients with Shifts</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3/525)</td>
<td>0.6%</td>
</tr>
<tr>
<td>(3/702)</td>
<td>0%</td>
</tr>
<tr>
<td>(0/158)</td>
<td></td>
</tr>
</tbody>
</table>

In longer-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 atypical antipsychotics, obtain a fasting lipid profile at baseline and monitor periodically during treatment.

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>
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<td></td>
</tr>
<tr>
<td>N=156</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5: Proportion of Patients with Shifts between -1 mg to 8 mg per day >8 mg to 16 mg per day

<table>
<thead>
<tr>
<th>Triglycerides</th>
<th>Proportion of Patients with Shifts</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0.6%)</td>
<td>2.7%</td>
</tr>
<tr>
<td>(2.5%)</td>
<td>1.8%</td>
</tr>
<tr>
<td>(3.3%)</td>
<td>4.3%</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).
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% (6/3,067) 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 judgement, thinking, and motor skills. Somnolence was a commonly reported adverse reaction associated with oral risperidone treatment, especially when ascertainment 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.

Table 5. Mean Change in Body Weight (kg) and the Proportion of Subjects with ≥7% Gain in Body Weight From 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>Change from baseline</th>
<th>≥7% increase from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Oral Risperidone</td>
<td>2.9%</td>
<td>8.7%</td>
</tr>
</tbody>
</table>

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)]
- Priapism [see Warnings and Precautions (5.12)]
- 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, 2,667 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, patients 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 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 122 patients exposed to once monthly and 199 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, dyskinesia, tremor, sedation, dizziness, anxiety, blunted 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% 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>Adverse Reaction</th>
<th>Oral Risperidone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></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><strong>Gastrointestinal Disorders</strong></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>Dyspepsa</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><strong>General Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
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<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood creatine phosphokinase increased</td>
<td>1</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Heart rate increased</td>
<td>&lt;1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinsonism*</td>
<td>14</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Akathisia*</td>
<td>10</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Sedation</td>
<td>10</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Dystonia*</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Tremor*</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness postural</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>32</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>Anxiety</td>
<td>16</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>4</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>&lt;1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Dry skin</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*Parkinsonism includes extrapyramidal disorder, musculoskeletal stiffness, parkinsonism, cogwheel rigidity, akinesia, bradykinesia, hypokinesia, masked facies, muscle rigidity, and Parkinson's disease. Akathisia includes akathisia and restlessness. Dystonia includes dystonia, muscle spasms, and muscular contractions involuntary, muscle contraction, oculeogryration, tongue paralysis. Tremor includes tremor and parkinsonian rest tremor.

**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:

**Blood and Lymphatic System Disorders:** anemia, granulocytopenia, neutropenia

**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

**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,onychomykosis, acarodermatitis, bronchopneumonia, respiratory tract infection, tracheobronchitis, otitis media chronic

**Investigations:** body temperature increased, blood prolactin increased, alamine 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, rhabdomyolysis

**Nervous System Disorders:** balance disorder, disturbance in attention, dysarthria, 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, neuroleptic 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, gynecomastra, galactorrhea, vaginal discharge, menstrual disorder, erectile dysfunction, retrograde ejaculation, ejaculation disorder, sexual dysfunction, breast enlargement

**Respiratory, Thoracic, and Mediastinal Disorders:** wheezing, pneumonia aspiration, 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:** hypotension, flushing

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

Approximately 7% (39/564) 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>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 Dependence 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 2 mg</th>
<th>Oral Risperidone 6 mg</th>
<th>Oral Risperidone 10 mg</th>
<th>Oral Risperidone 16 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinsonism</td>
<td>12</td>
<td>0.9</td>
<td>2.4</td>
<td>2.8</td>
<td>2.6</td>
</tr>
<tr>
<td>EPS incidence</td>
<td>13%</td>
<td>17%</td>
<td>21%</td>
<td>23%</td>
<td>35%</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):
Table 9: Clinically Important Drug Interactions with UZEDY

7.1 Drugs Having Clinically Important Interactions with UZEDY

Interaction data provided in this section is based on studies with oral risperidone. The interactions of UZEDY with co-administration of other drugs have not been studied. The drug-drug interaction data from the oral form of risperidone may not be applicable to the UZEDY formulation.

Other Adverse Reactions

Adverse reactions 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 Body Weight

Weight gain was observed in short-term, controlled trials and longer-term uncontrolled studies in adults (see Warnings and Precautions (5.5) 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

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UZEDY™ (risperidone) extended-release injectable suspension

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 antipsychotics during pregnancy, 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 = 1.2, 95% CI: 0.83-1.78) 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 0.8 to 10 mg/kg/day and rats to 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. Leaning was impaired in offspring of rats treated 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 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 growth of the offspring were also delayed.

Rat offspring mortality increased during the first 4 days of lactation when pregnant rats were dosed through gestation at 0.31 to 5 mg/kg/day which is 0.1- to 3-times the oral MRHD of 16 mg/day based on mg/m² body surface area. It 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) were reduced in offspring born to control 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 during lactation (see 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 breast milk 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 decrease 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 dogs were treated with oral risperidone from weeks 10 to 50 of age (equivalent to the period of childhood through adolescence in humans), at doses of 0.31, 1.25, or 5 mg/kg/day. Bone 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 recovery 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 above 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

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, most frequently reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, 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

UZEDY contains risperidone, an atypical antipsychotic. Risperidone belongs to the chemical class of benzisoxazol derivatives. The chemical designation 3-[2-(4-(6-flouro-1-benzazocol-3-yl)-piperidin-1-yl)-ethyl]-2-methyl-6,8,9-tetrahydropropidol(1,2-a) pyrimidin-4-one. Its molecular formula is C23H27FN4O2 and its molecular weight is 410.5 g/mol. The structural formula is:
The average exposure values (Cavg, ss) over the dosing period are comparable for UZEDY administered subcutaneous injection with oral UZEDY. The effect of hepatic impairment on the pharmacokinetics of oral risperidone has been evaluated with young healthy subjects.[see Use in Specific Populations (8.6)]. The effect of hepatic impairment on the pharmacokinetics of UZEDY has not been studied.

12.2 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 schizoaffective disorder after single doses (12.5 to 225 mg, n = 195) and 3 repeated monthly doses (75 mg and 150 mg, n = 24).

For all doses, steady-state levels of risperidone and 9-hydroxyrisperidone were approached within 2 months of UZEDY initiation. Steady-state plasma exposure values of risperidone, 9-hydroxyrisperidone, and risperidone and 9-hydroxyrisperidone combined following once monthly administration of UZEDY are approximately 2- to 2.5-fold higher than single dose exposure, while the values for UZEDY administered once every 2 months are about 15-fold higher than the respective single dose exposure. After administration of UZEDY, plasma levels of risperidone, 9-hydroxyrisperidone, and risperidone and 9-hydroxyrisperidone combined (AUC(0-τ), Cτ) increase in a dose-proportional manner.

The average exposure values (Cτ) 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 (AUC(0-τ)) of UZEDY corresponds to that of oral risperidone (up 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 form 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 α1-acid glycoprotein. The plasma protein binding of risperidone is 90% to 95%, 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, antihistaminics, and other drugs. CYP2D6 is subject to genetic polymorphism (about 6 to 8% of Caucasian Americans, 1% to 2% of Japanese and Chinese, and 6% to 17% of Japanese, and 9% to 27% of African and African American individuals are poor or ultrarapid metabolizers of CYP2D6). The enzyme metabolic activity can be estimated by the debrisoquine or dextromethorphan hydroxylation test in vivo. The relative activity of CYP2D6 isoenzymes is determined by the ratio of urinary debrisoquine or dextromethorphan metabolites to the respective parent drug. In vivo, CYP2D6 metabolizer status is a major determinant of the clearance of risperidone and its active metabolite, 9-hydroxyrisperidone.

CYP2D6 is expressed in the liver and the intestines. The primary metabolite is 9-hydroxyrisperidone, with a small fraction of the dose metabolized as N-demethylated compounds, 1-acid glycoprotein. The clearance of risperidone is 10 to 20% lower in females compared to males and in elderly compared to young healthy subjects.[see Use in Specific Populations (8.5)].

CYP2D6 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.

12.3 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies were conducted with subcutaneous risperidone suspension. Carcinogenicity studies were conducted with oral risperidone in mice and rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 8 mg/kg for 18-months to mice and for 25-months to rats. These doses are equivalent to approximately 0.2-, 0.75-, and 3-times (mice) and 0.4-, 1.5-, and 6-times (rats) the oral MRHD of 16 mg/day, based on a mg/m² body surface area. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The table below summarizes the multiples of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

<table>
<thead>
<tr>
<th>Dosage (mg/kg)</th>
<th>mg/m² Body Surface Area</th>
<th>Multiples of Human Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>0.02</td>
<td>1</td>
</tr>
<tr>
<td>0.75</td>
<td>0.75</td>
<td>3.75</td>
</tr>
<tr>
<td>3</td>
<td>3.0</td>
<td>18.75</td>
</tr>
</tbody>
</table>
UZEDY™ (risperidone) extended-release injectable suspension

No evidence of mutagenic or clastogenic potential for risperidone was found in the in vitro tests of Ames gene mutation, the mouse lymphoma assay, rat hepatocyte DNA-repair assay, the chromosomal aberration test in human lymphocytes, Chinese hamster ovary cells, or in the in vivo 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(ether glycol)-co-poly(ether glycol)-co-poly(lysine) dissolved in dimethyl sulfoxide.

Mutagenesis

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 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.

The primary efficacy endpoint was time to impending relapse. Relapse was defined as one 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 psychiatric 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.

Figure 1: Kaplan-Meier Curve of Cumulative Proportion of UZEDY-Treated Patients with Relapse Over Time

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 57519-305-10)
- 75 mg/0.21 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 57519-520-10)
- 100 mg/0.35 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 57519-630-10)
- 150 mg/0.42 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 57519-740-10)
- 200 mg/0.56 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 57519-850-10)
- 250 mg/0.7 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 57519-960-10)

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 (5.4)].

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
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