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

UZEDY (risperidone) extended-release injectable suspension, for subcutaneous use
Initial U.S. Approval: 1993

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning.
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. UZEDY is not approved for use in patients with dementia-related psychosis. (5.1)

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

Prior Oral Risperidone Therapy	UZEDY Dosage Once Monthly	UZEDY Dosage Once Every 2 Months
2 mg of oral risperidone per day	50 mg	100 mg
3 mg of oral risperidone per day	75 mg	150 mg
4 mg of oral risperidone per day	100 mg	200 mg
5 mg of oral risperidone per day	125 mg	250 mg

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

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)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Cerebrovascular Adverse Reactions, in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular reactions (e.g., stroke, transient ischemia attack). (5.2)
- Neuroleptic Malignant Syndrome (NMS): Manage with immediate discontinuation and close monitoring. (5.3)
- Tardive Dyskinesia: Discontinue treatment if clinically appropriate. (5.4)
- 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, 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. (6.1)

The most common injection site reactions with UZEDY (≥5% and greater than placebo) were 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: 4/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
2.2 Dosage Modifications in Patients with Renal Impairment or Hepatic Impairment
2.3 Dosage Modifications for Concomitant Use with Strong CYP2D6 Inhibitors and Strong CYP3A4 Inducers
2.4 Preparation and Administration Instructions
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
5.2 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis
5.3 Neuroleptic Malignant Syndrome
5.4 Tardive Dyskinesia
5.5 Metabolic Changes
5.6 Hyperprolactinemia
5.7 Orthostatic Hypotension and Syncope
5.8 Falls
5.9 Leukopenia, Neutropenia, and Agranulocytosis
5.10 Potential for Cognitive and Motor Impairment
5.11 Seizures
5.12 Dysphagia
5.13 Priapism
5.14 Body Temperature Regulation
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Drugs Having Clinically Important Interactions with UZEDY

Reference ID: 5166001

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.

Reference ID: 5166001

FULL PRESCRIBING INFORMATION

WARNING: 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. UZEDY is not approved for the treatment of patients with dementia-related psychosis and has not been studied in this patient population *[see Warnings and Precautions (5.1)].*

1 INDICATIONS AND USAGE

UZEDY is indicated for the treatment of schizophrenia in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

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

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

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

To start UZEDY, switch from oral daily risperidone. Initiate UZEDY, as either a once monthly injection or a once every 2 month injection, 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

Prior Therapy	UZEDY Dosage Once Monthly	UZEDY Dosage Once Every 2 Months
2 mg of oral risperidone per day	50 mg	100 mg
3 mg of oral risperidone per day	75 mg	150 mg
4 mg of oral risperidone per day	100 mg	200 mg
5 mg of oral risperidone per day	125 mg	250 mg

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

Reference ID: 5166001

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, re-evaluated 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.

On discontinuation of a strong CYP3A4 inducer in a patient treated with UZEDY 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

- 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.

Reference ID: 5166001

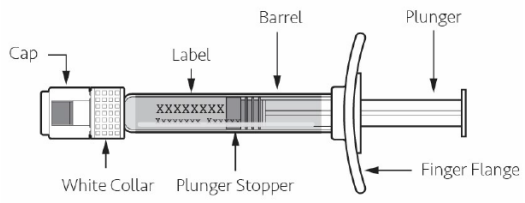
- As a universal precaution, always wear gloves.

STEP 1

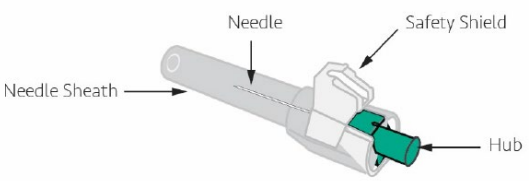
Check to make sure UZEDY kit contains:

- One sterile single-dose, prefilled glass syringe
- One sterile 21G x 5/8” needle

Do not substitute any components of the kit for administration.



Prefilled Syringe



Safety Needle

STEP 2

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

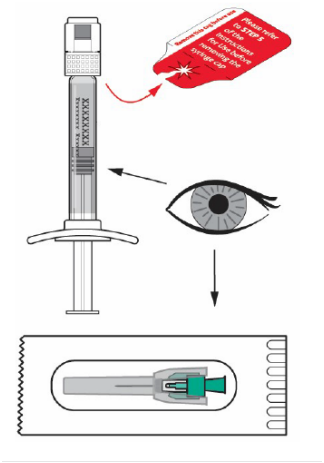
Note: UZEDY is a solid at refrigerated temperatures and must reach room temperature prior to administration. Do not warm any other way and keep protected from light.

STEP 3

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

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

Reference ID: 5166001



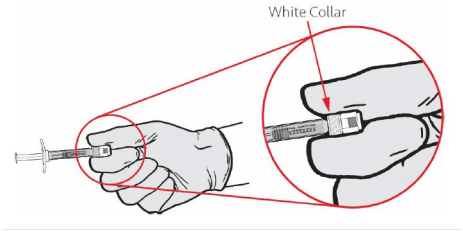
STEP 4

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

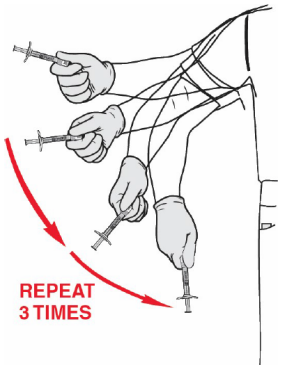
- Flick with a forceful downward whipping motion of your full arm to move the bubble to the cap of the syringe.
- Repeat this action 3 times to ensure that the bubble is at the cap of the syringe.

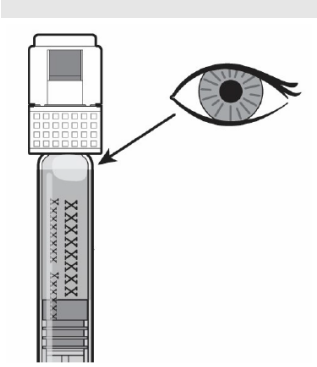
Note: Standing while you do this may help achieve required force.

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.

Reference ID: 5166001



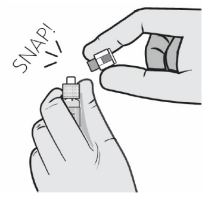


Flick downwards forcefully with your full arm

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.

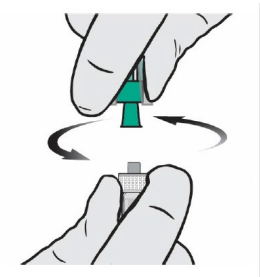


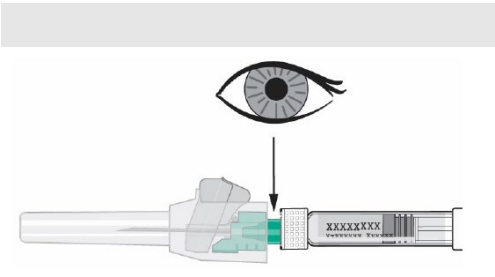
STEP 7

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

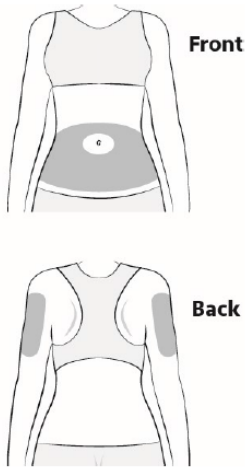
Select Injection Site from the Following Areas:

- 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.

Reference ID: 5166001

Do not inject UZEDY into an area that is tender, red, bruised, callused, tattooed, hard, or has scars or stretch marks.



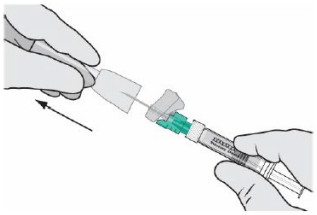
STEP 9

Clean the Injection Site with an alcohol wipe.

STEP 10

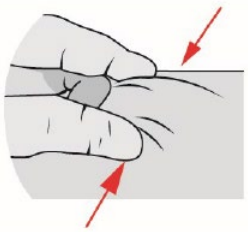
Remove the needle sheath by pulling the needle sheath away from the green hub to expose the needle.

Do not expel any visible air bubble.



STEP 11

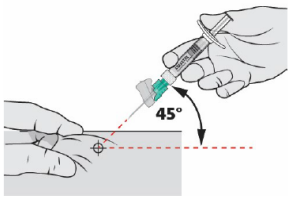
Pinch at least 1 inch of the area of cleaned skin with your free hand.



STEP 12

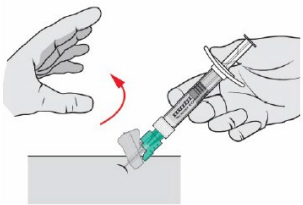
Insert the needle into subcutaneous tissue (actual angle of injection will depend on the amount of subcutaneous tissue). Do not apply pressure to the plunger.

Reference ID: 5166001



STEP 13

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

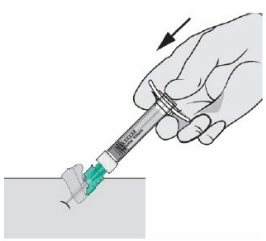


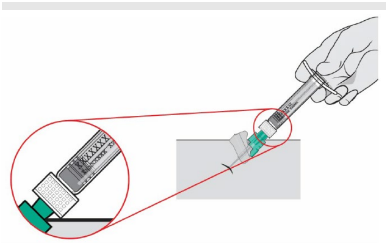
STEP 14

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.

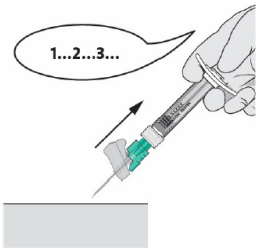
IMPORTANT: UZEDY is viscous. Resistance will be experienced during dose delivery. Do not use excessive force in an attempt to deliver UZEDY faster.





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.

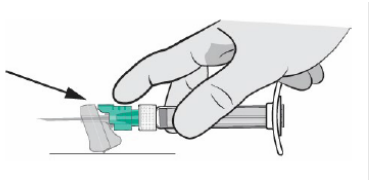


STEP 16

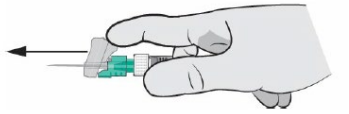
Reference ID: 5166001

Activate (lock) the safety needle shield using one of the following methods:

- **Surface Activation:** Place the needle shield on a flat surface and pull the syringe backward until the needle shield covers the needle tip.



- **Finger/Thumb Activation:** Press either your thumb or finger on the needle shield and push it forward until the needle shield covers the needle tip.



There will be an audible click when the needle safety shield is locked.

Dispose of all syringe components in a suitable sharps container.

3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6- to 1.7-times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%,

Reference ID: 5166001

compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

In two of four placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus oral risperidone when compared to patients treated with oral risperidone alone or with placebo plus furosemide. No 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)]*.

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

Cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73 to 97 years) in trials of oral risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse reactions in patients treated with oral risperidone compared to patients treated with placebo. UZEDY is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)].*

5.3 Neuroleptic Malignant Syndrome

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

If NMS is suspected, immediately discontinue UZEDY and provide symptomatic treatment and monitoring.

5.4 Tardive Dyskinesia

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

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

Reference ID: 5166001

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

Given these considerations, UZEDY should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response. Periodically reassess the need for continued treatment.

If signs and symptoms of tardive dyskinesia appear in a patient treated with UZEDY, drug discontinuation should be considered. However, some patients may require treatment with UZEDY despite the presence of the syndrome.

5.5 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

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,

Reference ID: 5166001

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 2*.

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

		Oral Risperidone	
	Placebo	**1 mg to 8 mg per day**	**>8 mg to 16mg per day**
		Mean change from baseline (mg/dL)	
	N=555	**N=748**	**N=164**
Serum Glucose	-1.4	0.8	0.6
		Proportion of Patients with Shifts	
Serum Glucose (<140 mg/dL to ≥200 mg/dL)	0.6% (3/525)	0.4% (3/702)	0% (0/158)

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.

Pooled data 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 3*.

Reference ID: 5166001

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

		Oral Risperidone	
	Placebo	**1 mg to 8 mg per day**	**>8 mg to 16mg per day**
		Mean change from baseline (mg/dL)	
Cholesterol Change from baseline	**N=559** 0.6	**N=742** 6.9	**N=156** 1.8
Triglycerides Change from baseline	**N=183** -17.4	**N=307** -4.9	**N=123** -8.3
		Proportion of Patients with Shifts	
Cholesterol (<200 mg/dL to ≥240 mg/dL)	2.7% (10/368)	4.3% (22/156)	6.3% (6/96)
Triglycerides (<500 mg/dL to ≥500 mg/dL)	1.1% (2/180)	2.7% (8/301)	2.5% (3/121)

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

		Oral Risperidone	
	Placebo (n=597)	**1 mg to 8 mg per day (n=769)**	**>8 mg to 16mg per day (n=158)**
Weight (kg) Change from baseline	-0.3	0.7	2.2
Weight Gain ≥7% increase from baseline	2.9%	8.7%	20.9%

Reference ID: 5166001

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 D_2 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% (6/2607) 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.

Reference ID: 5166001

5.9 Leukopenia, Neutropenia, and Agranulocytosis

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

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

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

5.10 Potential for Cognitive and Motor Impairment

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

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

5.11 Seizures

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

5.12 Dysphagia

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

5.13 Priapism

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

Reference ID: 5166001

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

Reference ID: 5166001

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 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 112 patients exposed to once monthly and 109 patients to once every 2 months dosing regimens. In addition, 32 patients were exposed to UZEDY for at least 24 months.

Adverse Reactions in Studies with Oral Risperidone

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

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

	Percentage of Patients Reporting Reaction		
	Oral Risperidone		
System/Organ Class Adverse Reaction	**2 mg to 8 mg per day (N=366)**	**>8 mg to 16 mg per day (N=198)**	**Placebo (N=225)**
Cardiac Disorders			
Tachycardia	1	3	0
Eye Disorders			
Vision blurred	3	1	1

Reference ID: 5166001

Gastrointestinal Disorders			
Nausea	9	4	4
Constipation	8	9	6
Dyspepsia	8	6	5
Dry mouth	4	0	1
Abdominal discomfort	3	1	1
Salivary hypersecretion	2	1	<1
Diarrhea	2	1	1
General Disorders			
Fatigue	3	1	0
Chest pain	2	2	1
Asthenia	2	1	<1
Infections and Infestations			
Nasopharyngitis	3	4	3
Upper respiratory tract infection	2	3	1
Sinusitis	1	2	1
Urinary tract infection	1	3	0
Investigations			
Blood creatine phosphokinase increased	1	2	<1
Heart rate increased	<1	2	0
Musculoskeletal and Connective Tissue Disorders			
Back pain	4	1	1
Arthralgia	2	3	<1
Pain in extremity	2	1	1
Nervous System Disorders			
Parkinsonism*	14	17	8
Akathisia*	10	10	3
Sedation	10	5	2
Dizziness	7	4	2
Dystonia*	3	4	2
Tremor*	2	3	1
Dizziness postural	2	0	0
Psychiatric Disorders			
Insomnia	32	25	27

Reference ID: 5166001

Anxiety	16	11	11
Respiratory, Thoracic and Mediastinal Disorders			
Nasal congestion	4	6	2
Dyspnea	1	2	0
Epistaxis	<1	2	0
Skin and Subcutaneous Tissue Disorders			
Rash	1	4	1
Dry skin	1	3	0
Vascular Disorders			
Orthostatic hypotension	2	1	0

* 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, muscle contractions involuntary, muscle contracture, oculogyration, 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

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, aptyalism

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, onychomycosis, acarodermatitis, bronchopneumonia, respiratory tract infection, tracheobronchitis, otitis media chronic

Reference ID: 5166001

***Investigations**:* body temperature increased, blood prolactin 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, transaminases 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, gynecomastia, 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

<u>Discontinuations Due to Adverse Drug Reactions with Oral Risperidone</u>

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:

Reference ID: 5166001

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

Adverse Reaction	Oral Risperidone		
	2 mg to 8 mg per day (N=366)	>8 mg to 16 mg per day (N=198)	Placebo (N=225)
Dizziness	1.4%	1%	0%
Nausea	1.4%	0%	0%
Vomiting	0.8%	0%	0%
Parkinsonism	0.8%	0%	0%
Somnolence	0.8%	0%	0%
Dystonia	0.5%	0%	0%
Agitation	0.5%	0%	0%
Abdominal pain	0.5%	0%	0%
Orthostatic hypotension	0.3%	0.5%	0%
Akathisia	0.3%	2%	0%

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

Dose Dependency of Adverse Reactions in Clinical Trials of Oral Risperidone

Extrapyramidal Symptoms

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

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

Dose Groups	Placebo	Oral Risperidone 2 mg	Oral Risperidone 6 mg	Oral Risperidone 10 mg	Oral Risperidone 16 mg
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	17%	21%	21%	35%

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

Reference ID: 5166001

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

Dose Groups	Oral Risperidone 1 mg	Oral Risperidone 4 mg	Oral Risperidone 8 mg	Oral Risperidone 12 mg	Oral Risperidone 16 mg
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	17%	18%	20%

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

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

Changes in ECG

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

Injection Site Reactions with UZEDY

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

Reference ID: 5166001

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 reported in 22 patients (13%) in the placebo group, 36 patients (20%) in the UZEDY once monthly group, and 37 patients (21%) in the UZEDY once every 2 months group. The most common injection site reactions were: nodule (7% in each UZEDY-treated group and 3% in the placebo group) and pruritus (5% and 3% in the UZEDY-treated once monthly and once every 2 months groups, respectively, and 2% in the placebo group).

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: alopecia, 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

Strong CYP2D6 Inhibitors	
Clinical Impact:	Concomitant use of UZEDY with strong CYP2D6 inhibitors may increase the plasma exposure of risperidone and lower the plasma exposure of a major active metabolite, 9-hydroxyrisperidone *[see Clinical Pharmacology (12.3)]*.
Intervention:	When initiation of strong CYP2D6 inhibitors is considered, patients may be placed on the lowest dose (50 mg once monthly or 100 mg once every 2 months) of UZEDY prior to the planned start of strong CYP2D6 inhibitors to adjust for the expected increase in plasma concentrations of risperidone. When strong CYP2D6 inhibitors are initiated in patients receiving UZEDY 50 mg once monthly or 100 mg once every 2 months, it is recommended to continue treatment with the same dose unless clinical judgment necessitates interruption of UZEDY treatment. The effects of discontinuation of strong CYP2D6 inhibitors on the

Reference ID: 5166001

	pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied *[see Clinical Pharmacology (12.3)]*.
Strong CYP3A4 Inducers	
Clinical Impact:	Concomitant use of UZEDY and a strong CYP3A4 inducer may cause decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone which could lead to decreased efficacy of UZEDY *[see Clinical Pharmacology (12.3)]*.
Intervention:	Changes in efficacy and safety should be carefully monitored with any dose adjustment of UZEDY. At the initiation of therapy with a strong CYP3A4 inducer, patients should be closely monitored during the first 4 to 8 weeks. In patients receiving UZEDY at a specific dose, consider increasing the dose to the next highest dose. In patients receiving UZEDY 125 mg once monthly or 250 mg once every 2 months, additional oral risperidone therapy may need to be considered. On discontinuation of a strong CYP3A4 inducer, the dosage of UZEDY or any additional oral risperidone therapy should be reevaluated and, if necessary, decreased to adjust for the expected increase in plasma concentration of risperidone and 9-hydroxyrisperidone. For patients treated with UZEDY 50 mg once monthly or UZEDY 100 mg once every 2 months discontinuing from a strong CYP3A4 inducer, it is recommended to continue treatment with the same dose unless clinical judgment necessitates interruption of UZEDY treatment *[see Dosage and Administration (2.3)]*.
Centrally-Acting Drugs and Alcohol	
Clinical Impact:	Due to additive pharmacologic effects, the concomitant use of centrally-acting drugs, including alcohol, may increase nervous system disorders.
Intervention:	Caution should be used when UZEDY is administered in combination with other centrally-acting drugs or alcohol.
Hypotensive Agents	
Clinical Impact:	Because of its potential for inducing hypotension, UZEDY may enhance the hypotensive effects of other therapeutic agents with this potential.
Intervention:	Caution should be used when UZEDY is administered with other therapeutic effects of other therapeutic agents with this potential.
Dopamine Agonists	
Clinical Impact:	Agents with central antidopaminergic activity such as UZEDY may antagonize the pharmacologic effects of dopamine agonists.
Intervention:	Caution should be used when UZEDY is administered in combination with levodopa and dopamine agonists.
Methylphenidate	
Clinical Impact:	Concomitant use with methylphenidate, when there is change in dosage of either medication, may increase the risk of extrapyramidal symptoms (EPS) *[see Adverse Reactions (6.2)]*.
Intervention:	Monitor for symptoms of EPS with concomitant use of UZEDY and methylphenidate.

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

Reference ID: 5166001

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 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/m^2 body surface area. Risperidone was not teratogenic in rats or rabbits at doses up to 6-times the oral MRHD based on mg/m^2 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/m^2 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/m^2 body surface area.

The background risks of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

There is a risk to the mother from untreated schizophrenia, including increased risk of relapse, hospitalization, and suicide. Schizophrenia is associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

Fetal/Neonatal Adverse Reactions

Reference ID: 5166001

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including risperidone, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

Data

Human Data

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

Animal data

No developmental toxicity studies were conducted with subcutaneous risperidone suspension.

Oral administration of risperidone to pregnant mice during organogenesis caused cleft palate at 10 mg/kg/day which is 3-times the oral MRHD of 16 mg/day based on mg/m^2 body surface area; maternal toxicity occurred at 4-times the oral MRHD. Risperidone was not teratogenic when administered orally to rats at 0.6 to 10 mg/kg/day and rabbits at 0.3 to 5 mg/kg/day, which are up to 6-times the oral MRHD of 16 mg/day risperidone based on mg/m^2 body surface area. Learning was impaired in offspring of rats dosed orally throughout pregnancy at 1 mg/kg/day which is 0.6-times the oral MRHD and neuronal cell death increased in fetal brains of offspring of rats dosed during pregnancy at 1 and 2 mg/kg/day which are 0.6- and 1.2-times the oral MRHD based on mg/m^2 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 throughout gestation at 0.16 to 5 mg/kg/day which are 0.1- to 3-times the oral MRHD of 16 mg/day based on mg/m^2 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/m^2 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 but reared by drug-treated dams. All

Reference ID: 5166001

of these effects occurred at 5 mg/kg which is 3-times the oral MRHD based on mg/m^2 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 *(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 breastmilk should be monitored for excess sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements).

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the pharmacologic action of risperidone (D_2 receptor antagonism), treatment with UZEDY may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential *[see Warnings and Precautions (5.6)].*

8.4 Pediatric Use

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

Juvenile Animal Toxicity Data

No juvenile animal studies were conducted with subcutaneous risperidone suspension.

Juvenile 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 0.31 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 showed little or no reversibility in females after a 12 week drug-free 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

Reference ID: 5166001

MRHD of 6 mg/day for children, based on mg/m^2 body surface area. This dose produced plasma AUC of risperidone plus paliperidone about half the exposure observed in humans at the oral MRHD. No other consistent effects on neurobehavioral or reproductive development were seen up to the highest tested dose of 1.25 mg/kg/day which is 1 time the oral MRHD and produced plasma AUC of risperidone plus paliperidone that were about two thirds of those observed in humans at the oral MRHD of 6 mg/day for children.

8.5 Geriatric Use

Clinical studies of UZEDY in the treatment of schizophrenia did not include patients older than 65 years to determine whether or not they respond differently from younger patients.

In general, dose selection for geriatric patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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

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

8.6 Renal Impairment

In patients with renal impairment, titrate with oral risperidone (up to at least 2 mg daily) before initiating treatment with UZEDY *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

UZEDY was not studied in patients with renal impairment.

8.7 Hepatic Impairment

In patients with hepatic impairment, titrate with oral risperidone (up to at least 2 mg daily) before initiating treatment with UZEDY *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

UZEDY has not been studied in patients with hepatic impairment; however, such effect has been investigated with oral risperidone.

8.8 Patients with Parkinson's Disease or Dementia with Lewy Bodies

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

Reference ID: 5166001

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 overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms 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 hyponatremia, 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 overdosage 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 Overdosage

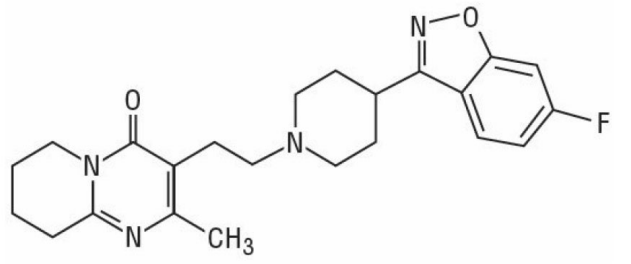
There is no specific antidote to risperidone. Provide supportive care including close medical supervision and monitoring. Treatment should consist of general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdosage. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs.

Consider contacting the Poison Help Line (1-800-222-1222) or medical toxicologist for additional overdosage management recommendations.

11 DESCRIPTION

UZEDY contains risperidone, an atypical antipsychotic. Risperidone belongs to the chemical class of benzisoxazole derivatives. The chemical designation 3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl) piperidin-1yl] ethyl]-2-methyl-6,7,8,9-tetrahydropyrido[1,2-a] pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.5 g/mol.

The structural formula is:



Reference ID: 5166001

Risperidone is a white to off-white powder. It is practically insoluble in water and soluble in methanol and 0.1 N HCl. It has the following pKa values: 8.28 (piperidine moiety) and 3.12 (pyrimidine moiety).

UZEDY is a sterile, white to off-white opaque viscous extended-release injectable suspension, intended for subcutaneous administration in the following strengths of risperidone (and deliverable volumes from a single-dose prefilled syringe): 50 mg (0.14 mL), 75 mg (0.21 mL), 100 mg (0.28 mL), 125 mg (0.35 mL), 150 mg (0.42 mL), 200 mg (0.56 mL), and 250 mg (0.7 mL). The inactive ingredients include dimethyl sulfoxide (45% w/w), methoxy-poly(ethylene glycol)-*co*-poly(D,L-lactide) (15% w/w), and poly(D,L-lactide)-*co*-poly(ethylene glycol)-*co*-poly(D,L-lactide) (10% w/w).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of risperidone, in schizophrenia, is unclear. The drug's therapeutic activity in schizophrenia could be mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism. The clinical effect from risperidone results from the combined concentrations of risperidone and its major metabolite, 9-hydroxyrisperidone (paliperidone) *[see Clinical Pharmacology (12.3)]*. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of risperidone.

12.2 Pharmacodynamics

Risperidone is a monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. Risperidone showed low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-5}$ M) for cholinergic muscarinic or β_1 and β_2 adrenergic 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 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 1.5-fold higher than the respective single dose exposure. After administration of UZEDY, plasma levels of risperidone, 9-hydroxyrisperidone, and risperidone and 9-hydroxyrisperidone combined ($AUC_{0\text{-}tau}$ and C_{max}) increase in a dose-proportional manner.

Reference ID: 5166001

The average exposure values ($C_{avg,ss}$) over the dosing period are comparable for UZEDY administered once monthly and once every 2 months at corresponding doses. Following both once monthly (50 mg to 125 mg) and once every 2 months dosing (100 mg to 250 mg), the mean exposure of risperidone and 9-hydroxyrisperidone combined ($AUC_{0\text{-}tau}$) 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 two absorption peaks for risperidone in plasma. After subcutaneous administration, median t_{max} 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 α_1-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 ($t_{½}$) 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, antiarrhythmics, and other drugs. CYP2D6 is subject to genetic polymorphism (about 6 to 8% of Caucasians, and a very low percentage of Asians, have little or no activity and are “poor metabolizers”) and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone; whereas, poor CYP2D6 metabolizers convert it much more slowly.

Reference ID: 5166001

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 ^{14}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 α1-acid glycoprotein *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies

No specific drug interaction studies have been performed with UZEDY. The drug interaction data provided in this section is based on studies with oral risperidone. Effects of other drugs on the exposures of risperidone, 9-hydroxyrisperidone, and risperidone and 9-hydroxyrisperidone combined as well as the effects of risperidone on the exposures of other drugs is summarized below.

Effects of Other Drugs on Risperidone, 9-hydroxyrisperidone, and Risperidone and 9-hydroxyrisperidone Combined Pharmacokinetics

Strong 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.

Reference ID: 5166001

Moderate CYP3A4 Inhibitor (Erythromycin)

There were no significant interactions between oral risperidone and erythromycin, a moderate CYP3A4 inhibitor.

Strong CYP3A4 Inducer (Carbamazepine)

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

Amitriptyline, Cimetidine, Ranitidine, Clozapine

Clinically meaningful pharmacokinetic interaction between UZEDY and other drugs, such as amitriptyline, cimetidine, ranitidine, and clozapine, is not expected.

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

<u>Effects of Oral Risperidone on Pharmacokinetics of Other Drugs</u>

Lithium

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

Valproate

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

Topiramate

Oral risperidone administered at doses from 1 to 6 mg/day concomitantly with topiramate 400 mg/day resulted in a 23% decrease in risperidone C_{max} and a 33% decrease in risperidone $AUC_{0\text{-}12}$ hour at steady state. Minimal reductions in the exposure to risperidone and 9-hydroxyrisperidone combined, and no change for 9-hydroxyrisperidone were observed. This

Reference ID: 5166001

interaction is unlikely to be of clinical significance. There was no clinically relevant effect of oral risperidone on the pharmacokinetics of topiramate.

Digoxin

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

CYP2D6 Substrates

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP2D6. Therefore, UZEDY is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, oral risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP2D6.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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 10 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/m^2 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/m^2 (mg/kg) basis at which these tumors occurred.

Table 10: Summary of Tumor Occurrence at the Multiples of the Human Oral Dose on a mg/m^2 (mg/kg) Basis with Oral Risperidone Dosing

Tumor Type	Species	Sex	Multiples of Maximum Human Dose in mg/m^2 (mg/kg)	
			Lowest Effect Level	Highest No-Effect Level
Pituitary adenomas	mouse	Female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	Male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	Female	0.2 (2.4)	none
	rat	Female	0.4 (2.4)	none
	rat	Male	6.0 (37.5)	1.5 (9.4)
Mammary gland neoplasm, Total	rat	Male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however,

Reference ID: 5166001

measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5- to 6-fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unclear *[see Warnings and Precautions (5.6)]*.

Mutagenesis

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(D,L-lactide) and poly(D,L-lactide)-*co*-poly(ethylene glycol)-*co*-poly(D,L-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/m^2 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/m^2 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

Reference ID: 5166001

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
- Clinical Global Impression-Severity of Suicidality (CGI-SS) of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2
- violent behavior resulting in clinically significant self-injury, injury to another person, or property damage

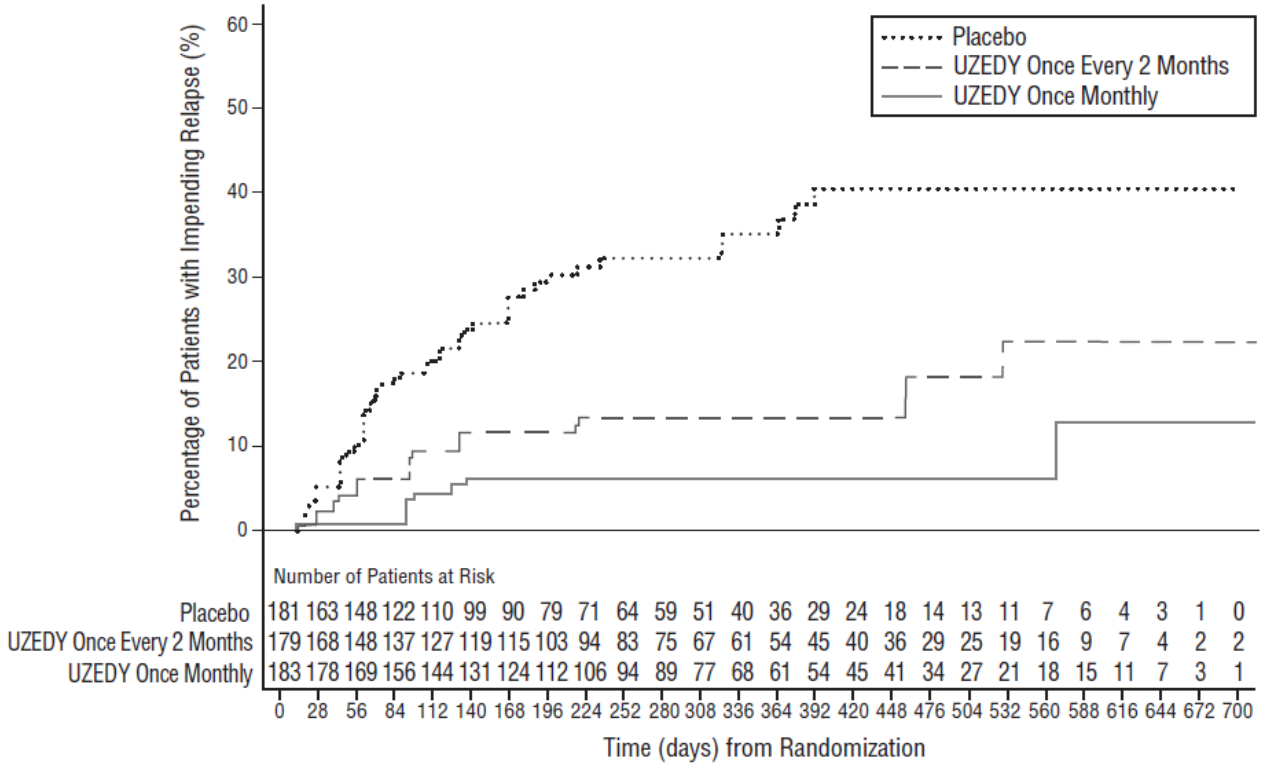
The mean baseline PANSS total score was similar across the groups (approximately 61 in each group). Most patients were male (61% per group) and the median age was 52 years. Most patients in this study were black or African American (57% to 61% per group). Of the 544 patients randomized to treatment, 543 were included in the intent-to-treat (ITT) population.

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.

Reference ID: 5166001

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/0.14 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 51759-410-10)
- 100 mg/0.28 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 51759-520-10)
- 125 mg/0.35 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 51759-630-10)
- 150 mg/0.42 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 51759-740-10)

Reference ID: 5166001

- 200 mg/0.56 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 51759-850-10)
- 250 mg/0.7 mL single-dose prefilled syringe, packaged in a carton with one 21 gauge, 5/8-inch needle (NDC 51759-960-10)

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

Storage and Handling

Store in refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.

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

17 PATIENT COUNSELING INFORMATION

Neuroleptic Malignant Syndrome (NMS)

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

Tardive Dyskinesia

Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their healthcare provider if these abnormal movements occur *[see Warnings and Precautions (5.4)]*.

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)]*.

Reference ID: 5166001

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-001

Manufactured for:
Teva Neuroscience, Inc.
Parsippany, NJ 07054

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