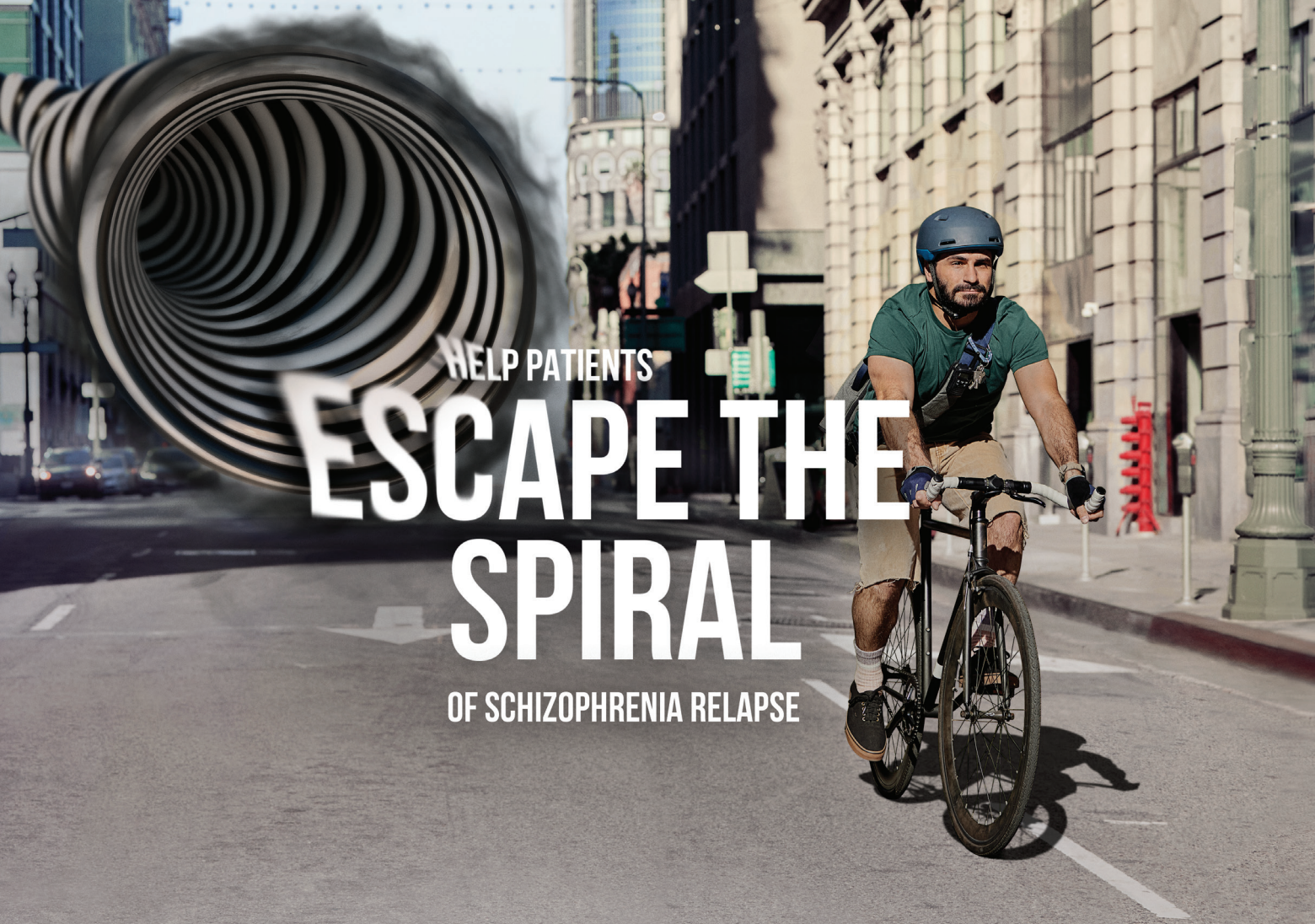

INDICATION AND USAGE

UZEDY (risperidone) extended-release injectable suspension for subcutaneous use is indicated for the treatment of schizophrenia in adults.

IMPORTANT SAFETY 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 use in patients with dementia-related psychosis and has not been studied in this patient population.

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.

WARNINGS AND PRECAUTIONS

Cerebrovascular Adverse Reactions: In trials of elderly patients with dementia-related psychosis, there was a significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, in patients treated with oral risperidone compared to placebo. UZEDY is not approved for use in patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): 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.

Tardive Dyskinesia (TD): TD, 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 TD is unknown.

The risk of developing TD 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. TD 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.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information for UZEDY, including Boxed WARNING, on the following pages.

UZEDY™ (risperidone) extended-release injectable suspension

50 mg 75 mg 100 mg 125 mg
150 mg 200 mg 250 mg

NOW APPROVED

AN LAI THAT CLINICIANS AND PATIENTS AGREE ON†*

RAPID ABSORPTION

UZEDY rapidly achieves therapeutic levels† in plasma within 6 to 24 hours of administration with a single dose[1,2]

DEMONSTRATED EFFICACY‡

UZEDY demonstrated significant reductions in the risk of relapse vs placebo[1,2]

STREAMLINED INITIATION

No loading dose or oral supplementation is required[2]

SUBCUTANEOUS INJECTION

UZEDY is for subcutaneous injection administered only by a healthcare professional and comes in a single-dose, prefilled syringe with a short, 5/8-inch needle[2]

FLEXIBLE 1- AND 2-MONTH DOSING INTERVALS

With 2 dosing intervals and 8 dosing options, you can tailor the dosing regimen to the individual patient needs[2]

IMPORTANT SAFETY INFORMATION (CONTINUED)

Tardive Dyskinesia (TD) (Continued):
If signs and symptoms of TD 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. 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.

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 (DM), in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics, including risperidone. Patients with an established diagnosis of DM who are started on atypical antipsychotics, including UZEDY, should be monitored regularly for worsening of glucose control. Patients with risk factors for DM (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics, including UZEDY, should undergo fasting blood glucose (FBG) 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

(continued on next page)

Please see additional Important Safety Information and Brief Summary of full Prescribing Information for UZEDY, including Boxed WARNING, on the following pages.

LAI, long-acting injectable.

*Data were collected from 63 patients, 24 physicians, and 25 nurses in a prospective, cross-sectional companion survey assessing the perceptions regarding ease of use and satisfaction with UZEDY. The survey was administered after a minimum of 2 experiences prescribing, administering, or receiving UZEDY. Ninety-six percent of clinicians and 92% of patients reported that they were satisfied with UZEDY. Ninety-two percent of clinicians and 89% of patients reported that administration of UZEDY was easy. Eighty percent of clinicians and 94% of patients reported that if given a choice, they would choose a shorter needle over a longer needle.[1]

†The threshold for clinically relevant plasma concentrations of risperidone is defined as levels ≥10 ng/mL.[1]

‡The RISE phase 3 study was a randomized, double-blind, multicenter, placebo-controlled, relapse prevention study evaluating the safety and efficacy of UZEDY once monthly or once every 2 months vs placebo once monthly in 542 patients with schizophrenia.[2]

teva

UZEDY™ 50 mg 75 mg 100 mg 125 mg 150 mg 200 mg 250 mg
(risperidone) extended-release injectable suspension

IMPORTANT SAFETY INFORMATION (CONTINUED)

Metabolic Changes (Continued):

develop symptoms of hyperglycemia during treatment with atypical antipsychotics, including UZEDY, should undergo FBG testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic, including risperidone, was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of risperidone.

Dyslipidemia has been observed in patients treated with atypical antipsychotics.

Weight gain has been observed with atypical antipsychotic use. Monitoring weight is recommended.

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.

Orthostatic Hypotension and Syncope: UZEDY may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope. UZEDY should be used with particular caution in patients with known cardiovascular disease, cerebrovascular disease, and conditions which would predispose patients to hypotension and 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.

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.

Leukopenia, Neutropenia, and Agranulocytosis have been reported with antipsychotic agents, including risperidone. In patients with a pre-existing history of a clinically significant low white blood cell count (WBC) or absolute neutrophil count (ANC) or a history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of UZEDY at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue UZEDY in patients with ANC < 1000/mm^3) and follow their WBC until recovery.

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. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that treatment with UZEDY does not affect them adversely.

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.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Antipsychotic drugs, including UZEDY, should be used cautiously in patients at risk for aspiration.

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.

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 experience these conditions.

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.

The most common injection site reactions with UZEDY (≥5% and greater than placebo) were pruritus and nodule.

DRUG INTERACTIONS

- Carbamazepine and other strong CYP3A4 inducers decrease plasma concentrations of risperidone.
- Fluoxetine, paroxetine, and other strong CYP2D6 inhibitors increase risperidone plasma concentration.
- Due to additive pharmacologic effects, the concomitant use of centrally-acting drugs, including alcohol, may increase nervous system disorders.
- UZEDY may enhance the hypotensive effects of other therapeutic agents with this potential.
- UZEDY may antagonize the pharmacologic effects of dopamine agonists.
- Concomitant use with methylphenidate, when there is change in dosage of either medication, may increase the risk of extrapyramidal symptoms (EPS)

USE IN SPECIFIC POPULATIONS

Pregnancy: May cause EPS and/or withdrawal symptoms in neonates with third trimester exposure. 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/.

Lactation: Infants exposed to risperidone through breastmilk should be monitored for excess sedation, failure to thrive, jitteriness, and EPS.

Fertility: UZEDY may cause a reversible reduction in fertility in females.

Pediatric Use: Safety and effectiveness of UZEDY have not been established in pediatric patients.

Renal or Hepatic Impairment: Carefully titrate on oral risperidone up to at least 2 mg daily before initiating treatment with UZEDY.

Patients with Parkinson's disease or dementia with Lewy bodies can experience increased sensitivity to UZEDY. Manifestations and features are consistent with NMS.

Please see Brief Summary of full Prescribing Information for UZEDY on the following pages.

References: 1. Data on file. Parsippany, NJ: Teva Neuroscience, Inc.
2. UZEDY™ (risperidone) extended-release injectable suspension Current Prescribing Information. Parsippany, NJ: Teva Neuroscience, Inc.

RIS-40437 May 2023

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR UZEDY (risperidone) extended-release injectable suspension, for subcutaneous use
SEE PACKAGE INSERT FOR 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.

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%, 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.

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, 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*.

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	**N=559**	**N=742**	**N=156**
Change from baseline	0.6	6.9	1.8
Triglycerides	**N=183**	**N=307**	**N=123**
Change from baseline	-17.4	-4.9	-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*.

CONTINUED ON NEXT PAGE

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%

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. 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.

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.

UZEDY™ (risperidone) extended-release injectable suspension

5.11 Seizures

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

5.12 Dysphagia

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

5.13 Priapism

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

5.14 Body Temperature Regulation

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

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Increased mortality in elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis *[see Warnings and Precautions (5.2)]*
- Neuroleptic malignant syndrome *[see Warnings and Precautions (5.3)]*
- Tardive dyskinesia *[see Warnings and Precautions (5.4)]*
- Metabolic changes *[see Warnings and Precautions (5.5)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.6)]*
- Orthostatic hypotension and syncope *[see Warnings and Precautions (5.7)]*
- Falls *[see Warnings and Precautions (5.8)]*
- Leukopenia/neutropenia and agranulocytosis *[see Warnings and Precautions (5.9)]*
- Potential for cognitive and motor impairment *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*
- Dysphagia *[see Warnings and Precautions (5.12)]*
- Priapism *[see Warnings and Precautions (5.13)]*
- Body temperature regulation *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

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

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

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

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

System/Organ Class Adverse Reaction	Percentage of Patients Reporting Reaction		
	Oral Risperidone		
	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
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
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.

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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

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

Discontinuations Due to Adverse Drug Reactions with Oral Risperidone

Approximately 7% (39/564) of oral risperidone-treated patients in double-blind, placebo-controlled trials discontinued treatment due to an adverse reaction, compared with 4% (10/225) who were receiving placebo. The adverse reactions associated with discontinuation in 2 or more oral risperidone-treated patients were:

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

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

CONTINUED ON NEXT PAGE

(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):

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.

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.

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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.
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 pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied *[see Clinical Pharmacology]*.
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.
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.
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 adjustment is necessary for lithium, valproate, topiramate, digoxin, and CYP2D6 substrates (donepezil and galantamine) when co-administered with UZEDY.

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

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 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.

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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 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)]*.

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.

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*]*.

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.

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Teva Neuroscience, Inc.
Parsippany, NJ 07054

This Brief Summary is based on the full Prescribing Information for UZEDY UZE-002.

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