Risperidone Extended-Release Injectable Suspension for Subcutaneous Use (UZEDY)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action[1]

- Risperidone is an atypical antipsychotic in which the mechanism of action in the treatment of schizophrenia is unknown. The efficacy of risperidone may be mediated through high 5-HT_2 and D_2 receptor antagonist activity.

Indication(s) Under Review in This Document[1]

- Risperidone SC 1-2 month (UZEDY) is indicated for the treatment of schizophrenia in adults.

Dosage Form(s) Under Review[1]

- 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; 250 mg/0.7 mL single-dose prefilled syringes.

Clinical Evidence Summary

Efficacy Considerations[2,3]

- The efficacy of risperidone SC 1-2 month (TV-46000) for the treatment of schizophrenia in adults is based, in part, on the established effectiveness of oral risperidone as well as in a 108 week, multicenter, randomized, double-blind, placebo-controlled withdrawal study (RISE, NCT03503318) in adults who met DSM-5 criteria for schizophrenia.
- The study populations included participants that had a diagnosis of schizophrenia for greater than one year and had one or more episode of relapse in the last 24 months, and participants that had a response to an antipsychotic treatment (other than clozapine) in the past year.
- 544 patients were included, 181 in the placebo group, 183 in the risperidone SC 1-2 month every four weeks treatment group, and 180 participants in the risperidone SC 1-2 month every eight weeks treatment group (Table 1).
- The primary outcome was time to impending relapse (number of participants with impending relapse).

- There was a statistically significant difference between risperidone SC 1-2 month and placebo using a stratified Cox proportional hazard model and a stratified log rank test p-value for time to relapse for both risperidone SC 1-2 month every four weeks treatment group and risperidone SC 1-2 month every eight weeks treatment group.
- 53 (29.3%) participants in the placebo group, 13 (7.1%) in the risperidone SC 1-2 month every four weeks, and 23 (12.8%) in the risperidone SC 1-2 month every eight weeks experienced relapse (Table 2).

Table 1. Baseline Characteristics of RISE Study[2]

	Placebo*	Risperidone SC 1-2 month q1m*^	Risperidone SC 1-2 month q2m*^	Total
Arm/Group Description	Participants received an SC injection of placebo matched to risperidone SC 1-2 month at baseline and q4w thereafter.	Participants received an SC injection of risperidone SC 1-2 month at baseline and q4w thereafter.	Participants received an SC injection of risperidone SC 1-2 month at baseline and q8w thereafter, and a placebo SC injection 4 weeks after baseline and q8w thereafter.	
Baseline Participants, n	181	183	180	544
Age, mean years (SD)	49.2 (11.43)	50.6 (10.30)	48.1 (11.09)	49.3 (10.98)
Male, n (%)	110 (60.8)	112 (61.2)	110 (61.1)	332 (61.0)
Black or African American, n (%)	104 (57.5)	108 (59.0)	110 (61.1)	322 (59.2)

SC = subcutaneous; q1m = every 1 month; q2m = every 2 months; q4w = every 4 weeks; q8w = every eight weeks; SD = standard deviation
** Participants continued treatment until they experienced a relapse event; met 1 or more of the study discontinuation or withdrawal criteria; or remained relapse-free during the double-blind phase until the study was terminated.*
^The maximal dose administered to adult participants was comparable to an oral risperidone dose of 5 mg/day, and the maximal dose administered to adolescents was comparable to 4 mg/day.

Table 2. Primary Endpoint – RISE Study[2]

	Placebo	Risperidone SC 1-2 month q1m	Risperidone SC 1-2 month q2m
Overall # of Participants Analyzed	181	183	179
Participants with Impending Relapse, n (%)	53 (29.3)	13 (7.1)	23 (12.8)
P-value		<0.0001	<0.0001
HR (95% CI)		0.200 (0.109 to 0.367)	0.375 (0.227 to 0.618)

SC = subcutaneous; q1m = every 1 month; q2m = every 2 months; HR = hazard ratio; CI = confidence interval

Safety Considerations

- The safety of risperidone SC 1-2 month 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 (Table 3).
- Additionally, the long-term safety and tolerability of risperidone SC 1-2 month was evaluated in a randomized, industry-sponsored study (SHINE, NCT03893825). The study included 336 patients: risperidone SC 1-2 month every four weeks treatment group (n= 172) and risperidone SC 1-2 month every eight weeks treatment group (n= 162).
- The primary outcome measure was the number of participants with adverse events (AEs) and number of participants with serious adverse events (SAEs). Baseline characteristics are displayed in Table 4.
- In the risperidone SC 1-2 month every four weeks treatment group, 37.2% of participants reported an AE and 4.7% of participants reported an SAE, and in the risperidone SC 1-2 month every eight weeks treatment group, 45.7% of participants reported an AE and 6.8% of participants reported an SAE (Table 5).

Table 3. – Adverse Reactions in ≥2% of Oral Risperidone-Treated Adult Patients (and greater than placebo) with Schizophrenia in Three 4- to 8-Week, Double-Blind, Placebo-Controlled Trials[1]

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

Rash	1	4	1
Dry Skin	1	3	0
Vascular Disorders			
Orthostatic Hypotension	2	1	0

Table 4. Baseline Characteristics of SHINE Study[3]

	Risperidone SC 1-2 month q1m*	Risperidone SC 1-2 month q2m*	Total
Arm/Group Description	Participants received an SC injection of risperidone SC 1-2 month at baseline and q4w thereafter for up to 56 weeks.	Participants received an SC injection of risperidone SC 1-2 month at baseline and q8w thereafter, and a placebo SC injection 4 weeks after baseline and q8w thereafter for up to 56 weeks.	Total of all reporting groups
Baseline Participants, n	174	162	336
Age, mean years (SD)	51.3 (10.28)	49.8 (11.51)	50.6 (10.90)
Male, n (%)	113 (64.9)	103 (63.6)	216 (64.3)
Black or African American, n (%)	91 (52.3)	90 (55.6)	181 (53.9)

SC = subcutaneous; q1m = every 1 month; q2m = every 2 months; q4w = every 4 weeks; q8w = every eight weeks; SD = standard deviation
**The maximal dose administered to adult participants was comparable to an oral risperidone dose of 5 mg/day, and the maximal dose administered to adolescents was comparable to 4 mg/day.*

Table 5. Primary Endpoints – SHINE Study[3]

	Risperidone SC 1-2 month q1m	Risperidone SC 1-2 month q2m
Overall # of Participants Analyzed	172	162
Participants with AEs, n (%)	64 (37.2)	74 (45.7)
Participants with SAEs, n (%)	8 (4.7)	11 (6.8)

SC = subcutaneous; q1m = every 1 month; q2m = every 2 months; AEs = adverse events; SAEs = serious adverse events

Other Warnings / Precautions [1]

- Increased mortality in elderly patients with dementia-related psychosis
- Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis
- Neuroleptic malignant syndrome
- Tardive dyskinesia
- Metabolic changes such as hyperglycemia and diabetes mellitus, dyslipidemia, and weight gain
- Hyperprolactinemia
- Orthostatic hypotension, syncope, and falls
- Leukopenia, neutropenia, and agranulocytosis
- Potential for cognitive and motor impairment

- Seizures
- Dysphagia
- Priapism
- Body temperature regulation
- Pregnancy considerations:
    - Risperidone SC 1-2 month has not been studied in pregnancy
    - Neonates exposed to antipsychotic medications during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery
    - 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
    - Pregnancy exposure registry: 18669612388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/
- Lactation:
    - Limited data from published literature reports the presence of risperidone and its metabolite, 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 EPS in breastfed infants exposed to risperidone
    - The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for risperidone SC 1-2 month and any potential adverse effects on the breastfed child from risperidone SC 1-2 month or from the underlying maternal condition

Dosing

- Initiate risperidone SC 1-2 month, as either a once monthly injection or a once every 2-month injection, the day after last dose of oral therapy.
- Neither a loading dose nor supplemental oral risperidone doses are recommended when switching.

Oral risperidone to risperidone SC 1-2 month dosing conversions[1]:

Table 7.

Prior Oral Risperidone Therapy	Risperidone SC 1-2 month Dosage Once Monthly	Risperidone SC 1-2 month Dosage Once Every 2 Months
2 mg of oral risperidone / day	50 mg	100 mg
3 mg of oral risperidone / day	75 mg	150 mg
4 mg of oral risperidone / day	100 mg	200 mg
5 mg of oral risperidone / day	125 mg	250 mg

SC = subcutaneous

Other Therapeutic Options

Table 8.

Drug	Risperidone SC	Risperidone SC	Risperidone IM	Paliperidone palmitate IM	Paliperidone palmitate IM	Paliperidone palmitate IM
Brand name	**Uzedy**	**Perseris**	**Risperdal Consta**	**Invega Sustenna**	**Invega Trinza**	**Invega Hafyera**
Approved indications	Schizophrenia	Schizophrenia	Schizophrenia, monotherapy or adjunctive therapy for the maintenance of bipolar I disorder	Schizophrenia, schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants	Schizophrenia	Schizophrenia
Requires reconstitution	No	Yes	Yes	No	No	No
Injection type	Subcutaneous	Subcutaneous	Intramuscular	Intramuscular	Intramuscular	Intramuscular
Approved injection sites	Abdomen or back of upper arm	Abdomen or back of upper arm	Deltoid or gluteal muscle	Deltoid or gluteal muscle	Deltoid or gluteal muscle	Gluteal muscle
Needle gauge	21	18	20/21	22/23	22	20
Injection interval	4 or 8 weeks	4 weeks	2 weeks	4 weeks	12 weeks	26 weeks
Oral supplementation required	No	No	Yes; 21 days after initial injection	No	No	No
Early maintenance dose allowed	No data	No data	No data	Yes, one week before next dose due	Yes; 2 weeks before next dose due	Yes; 2 weeks before next dose due
Refrigeration required	Yes	Yes	Yes	No	No	No
Protect from light required	Yes	No	Yes	No	No	No

SC = subcutaneous; IM = intramuscular

Projected Place in Therapy

- Antipsychotics are the current gold standard of treatment for schizophrenia.
- Risperidone SC 1-2 month is the sixth risperidone derivative long-acting injectable approved for the management of schizophrenia. Neither a loading dose nor supplemental oral risperidone doses are recommended. Patients who are on stable oral risperidone doses lower than 2 mg/day or higher than 5 mg/day may not be candidates for risperidone SC 1-2 month since risperidone SC 1-2 month only has oral dose conversions for 2 mg through 5 mg.

- Risperidone SC 1-2 month provides clinicians with another option to treat adult patients with schizophrenia for whom a subcutaneous long-acting dosage form is preferred or those who prefer a longer duration (eight weeks as opposed to four weeks) between injections.
- Advantages to risperidone SC 1-2 month include the subcutaneous administration versus intramuscular administration with risperidone IM (Consta) and the paliperidone palmitate derivatives. Compared to risperidone extended-release suspension (Perseris) which is also administered subcutaneously, risperidone SC 1-2 month does not require reconstitution. The option to administer every four weeks or every eight weeks is another advantage, as Perseris is only administered every 4 weeks. Further, patients who are on stable oral risperidone doses lower than 3 mg/day or higher than 4 mg/day may not be candidates for risperidone extended-release suspension. Finally, risperidone SC 1-2 month allows patients to convert directly from oral risperidone to an 8 week administration window, without need to first trial every 4 week administration.
- Disadvantages to risperidone SC 1-2 month include the lack of data indicating if an early maintenance dose is allowed, as well as information on missed doses (currently only instruction is to administer missed dose as soon as possible).
- Staff education is imperative for proper storage and administration, including storage in an unopened package, protect from light, and to discard if package is opened.

References

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5. Risperdal Consta (risperidone) [prescribing information]. Janssen Pharmaceuticals, Inc. Titusville, NJ. 2007.
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Prepared October 2023. Authors: Jason S. Pol, PharmD; Colleen P. LeHew, PharmD, BCPP; Alison M. Dailey, PharmD, BCPS, BCPP; Matthew A. Fuller, PharmD, BCPP. Contact person: Matthew A. Fuller, PharmD, BCPP, National PBM Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services (12PBM)