

New Formulation – Risperidone Subcutaneous LAI (Uzedy®)
FDA Approved April 2023
Teva Neuroscience, Inc.

Indication: Uzedy Subcutaneous LAI is indicated for the treatment of schizophrenia in adults

Mechanism: Risperidone functions as a potent 5-HT₂ & dopamine-D₂ receptor antagonist. Alpha₁, α₂ adrenergic, & histaminergic receptors are also antagonized with high affinity. Risperidone exhibits low to moderate affinity for 5-HT_{1C}, 5-HT_{1D}, & 5-HT_{1A} receptors and weak affinity for D₁ receptors. The clinical effect results from the concentrations of both risperidone and its major metabolite 9-hydroxyrisperidone (paliperidone)

Dosage

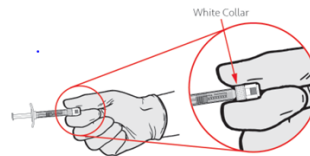
- Establish tolerability with oral risperidone
- Start Uzedy at the clinically appropriate dose using the table below
- Loading dose or supplementation with oral risperidone is not recommended
- Renal or hepatic impairment: Cautiously titrate on oral risperidone to at least 2 mg QDay.
Recommended dose 50 mg once monthly based on clinical response and tolerability

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

Administration

- Administer by subcutaneous injection in the abdomen or upper arm by a healthcare professional.
 - Allow to come to room temperature for at least 30 minutes before use.
 - Hold the syringe firmly by its white collar. Use a strong downward arm flick to position the bubble at the syringe cap, repeating thrice. This is crucial for accurate dosing (viscosity requires forceful flicks to position the bubble correctly) and failure to do so may result in an incomplete dose

Firmly hold the syringe by the white collar.

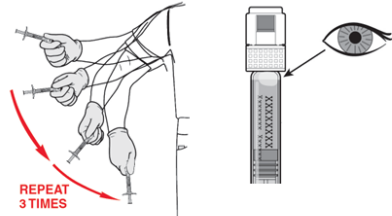


Flick Syringe Forcefully Three Times to Move the Bubble to the Cap

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

Check that the Bubble is at the Cap of the Syringe

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



Flick downwards forcefully with your full arm

STEP 6

Hold the syringe vertically by the white collar. Bend and snap off the cap. Do not touch the syringe tip to avoid contamination.



STEP 7

Attach the Needle to the Syringe

- Hold the syringe vertically with the white collar at the top.
- Push the green hub of safety needle inside the white collar of syringe and rotate the safety needle while holding the white collar until secure and tight.

Inspect the needle connection to check that the hub is not damaged.



STEP 8

Select Injection Site from the Following Areas:

- Stomach area (abdomen) around the belly button
- Back and outer area of the upper arms

Do not inject UZEDY anywhere except in the areas specified above.

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



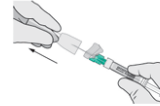
STEP 9

Clean the Injection Site with an alcohol wipe.

STEP 10

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

Do not expel any visible air bubble.



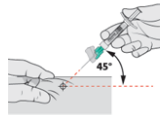
STEP 11

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



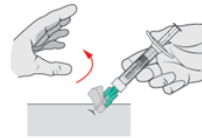
STEP 12

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



STEP 13

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

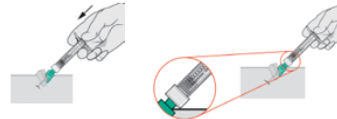


STEP 14

Inject the Medication

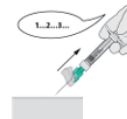
- Push on the plunger using a slow, firm, and steady push until the entire dose is delivered.
- Inject the entire dose at one time, without interruption.
- Check that the plunger stopper is at the White Collar.

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



STEP 15

Wait 2-3 seconds after the entire dose is delivered before removing the needle. Slowly pull the needle out from the injection site at the same angle as insertion.



How supplied: ER injectable suspension prefilled syringes

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

Storage: Store the kit in refrigerator in the original carton to protect from light. Unopened kits may be stored at room temp for up to 90 days. If unopened, Uzedy can be re-refrigerated within 90 days.

DDI

- Strong CYP3A4 inducers decrease risperidone plasma concentrations (eg. carbamazepine)
- Strong CYP 2D6 inhibitors increase risperidone plasma concentrations (eg. paroxetine & fluoxetine)

Pharmacokinetics

Onset	therapeutic levels reached 6-24 hours post-first injection
Half-life elimination	14 to 22 days
Metabolism	<ul style="list-style-type: none">▪ extensive hepatic metabolism via CYP2D6 to 9-hydroxyrisperidone, with minor involvement of CYP3A4 and N-dealkylation▪ the main metabolite, 9-hydroxyrisperidone, exhibits similar activity to risperidone▪ the effect originates from combined concentrations of risperidone & 9-hydroxyrisperidone
T_{max}	8 to 14 days
Steady state	approached within 2 months of initiation
Excretion	urine (70%); feces (14%)

Clinical Studies

Uzedy's efficacy for treating schizophrenia is based on oral risperidone's proven effectiveness and the results from the RISE and SHINE studies. The RISE study was a randomized, double-blind, placebo-controlled trial involving 544 adult patients diagnosed with schizophrenia. The study comprised a 12-week open-label oral risperidone stabilization phase, followed by a placebo-controlled phase in which patients were randomized 1:1:1 to receive monthly Uzedy, bimonthly Uzedy, or placebo. This treatment continued until an impending relapse or study completion. Relapse was defined by criteria such as an increased CGI-I and specified PANSS items, hospitalization for psychotic symptoms, high CGI-SS scores, or violent behavior causing significant harm.

Uzedy significantly delayed the time to relapse compared to placebo, with the risk of relapse reduced by 80% for monthly and 62.5% for bimonthly dosing.

The SHINE study, a 56-week open-label trial, evaluated Uzedy's safety and tolerability among 336 schizophrenia patients also stable on oral risperidone for at least four months. Patients received Uzedy either monthly or bimonthly based on individual needs, exhibiting good tolerance and a safety profile consistent with oral risperidone. The safety profile of Uzedy was consistent across both RISE and SHINE trials.

Role in Therapy

- Uzedy® the 2nd SC risperidone-containing long-acting injection and the first bi-monthly subcutaneous LAI appears to be effective and offers a new once-monthly and bi-monthly injectable treatment option that does not require a loading dose or a supplemental oral dose
- Monthly administration results in 2-2.5 times higher steady-state plasma exposure of risperidone & 9-hydroxyrisperidone compared to a single dose. Bi-monthly administration is 1.5 times higher
 - plasma levels increase proportionally with dosage
- Uzedy employs MedinCell's SteadyTeq copolymer technology for a controlled steady release, enabling rapid absorption and maintaining consistent dosage over one to two months
 - a quicker time to therapeutic concentration (6-24 hours after first injection), however other LAI options available which do not require concurrent oral therapy
- Selecting an LAI involves various considerations, including injection site options, administration frequency, need for reconstitution, requirement for oral supplementation, storage, ease of administration, needle gauge, injection volume, as well as the permissible grace period for missed doses
- Currently there are 11 FDA-approved atypical long-acting injectables, including aripiprazole, risperidone, paliperidone, and olanzapine
 - All of them must be administered by a healthcare professional
 - None of them are FDA-approved for pediatric use
 - All have a black box warning due to the increased risk of mortality in elderly patients with dementia-related psychosis
 - Zyprexa Relprevv specifically, is subject to a REMS program due to risk of severe sedation /delirium
 - Uzedy and Abilify Asimtufii
 - both risperidone and aripiprazole have established safety with primary literature and post-marketing experience
 - common adverse events of Abilify Asimtufii include weight gain, akathisia, pain at the injection site, and sedation
 - Uzedy's common adverse events include parkinsonism, akathisia, tremor, blurred vision, nausea/vomiting, stomach discomfort, constipation, increased appetite / weight, fatigue, rash, nasal congestion, and upper respiratory tract infections. The most common reactions at the injection site were itching and nodules
 - both have warnings for increased mortality in elderly patients with dementia-related psychosis, cerebrovascular adverse reactions, neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, orthostatic hypotension and syncope, falls, leukopenia, neutropenia, agranulocytosis, seizures, cognitive and motor impairment, body temperature regulation, and dysphagia
 - Abilify Asimtufii also has a warning for pathological gambling & other compulsive behaviors
 - Uzedy has extra warnings & precautions for hyperprolactinemia and priapism

- Abilify Asimtufii is being marketed as a longer-lasting formulation of aripiprazole which offers a more convenient reliable treatment for schizophrenia and as a maintenance monotherapy for adults with bipolar I disorder, providing two months of sustained therapeutic concentrations per dose
- Uzedy is being marketed as an important treatment option for patients with schizophrenia, aimed at addressing specific treatment challenges and potentially reducing the risk of relapse
- In comparison to Perseris® SC, Uzedy® SC offers a broader range of dosing and utilizes a smaller gauge needle
 - Perseris available in 90 mg & 120 mg dosage strengths only
 - 90-mg dose corresponds to 3 mg/day oral risperidone and 120-mg dose corresponds to 4 mg/day oral risperidone
 - Clts on stable oral risperidone doses <3 mg/day or >4 mg/day may not be candidates for risperidone Perseris
- For further comparison, please refer to the second-generation antipsychotic Long-Acting Injectables table
- Uzedy may improve adherence, but like other LAI antipsychotics, its effects cannot be reversed if toxicity occur. Use of risperidone SC may lead to side-effects like weight gain, constipation, akathisia, sedation, dizziness, GI issues, respiratory infections, and possible injection site rash

Formulary Recommendation

Add to BHRS, CareAdvantage, and HealthWorx formulary with PA criteria:

Indication—FDA approved diagnoses

Age—Adults

Documentation—

Patient has tried and failed oral antipsychotic therapy Or

Transferred from hospital/facility/another provider stabilized on this medication

Quantity Limit --

#1/30DS for 50mg, 75mg, 100mg, 125mg

#1/60DS for 150mg, 200mg, 250mg

References upon request