Preparing a Letter of Appeal for Treatment with UZEDY® (risperidone) extended-release injectable suspension

Submitting an appeal to a patient's health plan can help explain the rationale and clinical decision-making behind the choice of a specific therapy. A **Letter of Appeal** may be needed when a patient's health plan denies a request for prior authorization or coverage for UZEDY.

INDICATIONS AND USAGE

UZEDY® (risperidone) extended-release injectable suspension for subcutaneous use is indicated in adults for the treatment of schizophrenia and as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder.

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.

Please see the full Prescribing Information for UZEDY, including Boxed WARNING.

Tips and approaches:

Understand the reason(s) for a denial by reviewing the explanation of benefits (EOB) or the denial letter. Coverage can be denied for a variety of reasons:

- For administrative denials caused by errors such as incorrect coding, missing clinical documentation, or failure to obtain necessary prior authorizations, contact the payer and inquire about re-submission
- For clinical denials, or those indicating the treatment may not be considered medically necessary, a more detailed appeal will be required. Follow the plan's specific guidance on how to submit a formal appeal

Deadlines must be met for plan-specific appeals processes.

Comprehensive details are essential when composing a Letter of Appeal.

Specific information may include:

- Patient information:
  - Full name and date of birth
  - Policy and group numbers
  - Case ID number (if available)
- Introductory statement describing the purpose of the Letter of Appeal that indicates familiarity with the health plan's coverage policy or formulary restrictions
- Overview of the prescriber's credentials, experience in their specialty, and relevant professional affiliations
- Date of the denial letter and the reason given for denial
- Patient diagnosis and indication for UZEDY
- Severity of patient's condition and symptoms, including functional status and limitations
- Lack of patient caregiver support that may negatively influence short- and long-term treatment goals (eg, medication adherence, transportation, treatment follow-up)
- Summary of previous treatments, including oral and other long-acting injectable medications, duration and response to treatment, and reason for discontinuation
- Recent emergency treatment, hospitalization, and number of prior relapses and re-hospitalizations
- **Clinical rationale for treatment with UZEDY specific to the patient's history and current functioning. Rationale may include:**
  - Clinical trial outcomes supporting FDA approval (eg, reduction in risk of relapse)
  - Need for a treatment with subcutaneous administration versus oral or intramuscular administration
  - Patient's capacity to compliantly receive the required loading dose or oral supplementation needed with other long-acting injectable medications

IMPORTANT SAFETY INFORMATION (continued)

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.

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.

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  - Patient's history with treatment adherence/non-adherence including ongoing oral maintenance therapy
  - Need for multiple dosing options and administration intervals (1- or 2-months) for patients with schizophrenia
- Summary of recommendation and request for treatment
- Additional enclosures to support the request may include:
  - UZEDY® (risperidone) extended-release injectable suspension prescribing information
  - Clinical chart notes/medical records including scores of symptom rating scales and screening tools (eg, Positive and Negative Syndrome Scale (PANSS) for schizophrenia, Rapid Mood Screener (RMS) or Mood Disorder Questionnaire (MDQ) for bipolar 1 disorder)
  - Pharmacogenomic/psychotropic testing results for drug metabolism

Keep records of all documentation sent, calls placed, and the names, phone numbers, and titles of specific individuals who have been contacted at the patient's health insurance plan.

Template instructions:

When using the template on the next page, replace bracketed text with customized content related to the specific patient and the healthcare provider's clinical opinion.

Please note that this template is intended only as an example. Teva recommends confirming the information that is required to include in an appeal letter with individual health plans.

IMPORTANT SAFETY INFORMATION (continued)

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 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 D2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents.

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.

Please see the full Prescribing Information for UZEDY, including Boxed WARNING.

[Provider/Practice Letterhead]

[Date]
[Name of health insurance]
[Address]
[City, State, ZIP Code]

Insured: [Name]
DOB: [MM/DD/YYYY]
Policy Number: [Number]
Group Number: [Number]
Case ID: [Number]

Dear [Medical/Pharmacy Director's name],
I am writing this letter to appeal the denial of coverage for UZEDY on behalf of my patient, [patient full name] who was diagnosed with [ICD-10-CM code and condition] on [date].

Your reason[s] for the denial [is/are] [list reason(s) for the denial].

This letter provides a summary of my patient's diagnosis, medical history, and the clinical rationale for treatment with UZEDY.

Clinical History and Diagnosis
[Summarize the patient's clinical history. Include a description of:

- Patient's current functioning, including severity of condition and relevant scores of symptom rating scales and screening tools administered
- Lack of patient caregiver support that may have historically impacted treatment goals
- Recent emergency treatment, hospitalization, and number of prior relapses and re-hospitalizations
- Previous treatments, including duration and response, and reason for discontinuation]

Clinical Rationale and Treatment Plan
[Summarize the clinical rationale for treatment with UZEDY for this patient. Include the specific reasons for choosing UZEDY and the factors related to treatment selection. For example, include:

- Patient's history with treatment adherence/non-adherence including loading dose, oral supplementation requirements, or ongoing oral maintenance therapy
- Need for multiple dosing options, administration intervals for schizophrenia treatment, and subcutaneous administration

Describe the plan for UZEDY treatment, including dosing interval and dose prescribed. Cite any clinical practice guidelines that support the use of UZEDY.]

Based on my expertise and the clinical rationale outlined, I believe treatment with UZEDY is indicated and medically necessary for [patient full name] and request that you reconsider your denial. If you have any questions, please feel free to reach me at [provider phone number] or via email at [provider email] to discuss. Thank you in advance for your immediate attention to this request.

Sincerely,
[Provider name, credentials, NPI, and relevant insurance provider number]

[List enclosures]

IMPORTANT SAFETY INFORMATION (continued)

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 in patients with **schizophrenia** (≥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 adverse reactions with risperidone in patients with **bipolar disorder** were weight increased (5% in monotherapy trial) and tremor and parkinsonism (≥10% in adjunctive therapy trial).

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.

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