Teva and Medincell Announce FDA Acceptance of Supplemental New Drug Application for UZEDY® (risperidone) Extended-Release Injectable Suspension as a Treatment for Patients with Bipolar I Disorder

- **UZEDY is currently approved in the US as a subcutaneous long-acting injectable (LAI) for use every one or two months for the treatment of schizophrenia in adults[1]**
- **LAI treatment options may help address unmet needs of people living with bipolar I disorder (BP-I)**
- **BP-I filing acceptance for UZEDY represents Teva's commitment to pursuing new advances in neuroscience**

PARSIPPANY, N.J., TEL AVIV & PARIS, February 25, 2025 - Teva Pharmaceuticals, a U.S. affiliate of Teva Pharmaceutical Industries Ltd. (NYSE and TASE: TEVA), and Medincell (Euronext: MEDCL), announced today that the supplemental New Drug Application (sNDA) for UZEDY extended-release injectable suspension for the maintenance treatment of BP-I in adults has been accepted for filing by the U.S. Food and Drug Administration (FDA).

The sNDA is based on leveraging the existing clinical data for UZEDY coupled with the Agency's previous findings of safety and efficacy of past risperidone formulations approved for the treatment of BP-I.

"Since the FDA approval of UZEDY almost two years ago, it has proven to be an important treatment option for people living with schizophrenia," said Eric Hughes, MD, PhD, Executive Vice President of Global R&D and Chief Medical Officer at Teva. "Today's filing demonstrates the potential of UZEDY's clinical profile as a long-acting treatment for bipolar-I, a complex mental health disorder that significantly affects a person's mood, behavior, and overall state of mind. Debilitating manic and depressive symptoms and signs can also occur."

Teva will lead the regulatory process and be responsible for potential commercialization of UZEDY for BP-I, with Medincell eligible for royalties on net sales.

"Long-acting injectables are key drivers of innovation in the CNS field today," said Dr. Richard Malamut, Chief Medical Officer at Medincell. "In bipolar I disorder, as in schizophrenia, nonadherence remains a major barrier to effective care, one that UZEDY has the potential to help. We are proud to partner with Teva to deliver treatment options aimed at meeting unmet medical needs."

UZEDY was approved in the U.S. for the treatment of schizophrenia in adults in 2023.[2]

The efficacy and long-term safety and tolerability of UZEDY for the treatment of schizophrenia have been evaluated in two Phase 3 pivotal studies: TV46000-CNS-30072 (the RISE Study – The Risperidone Subcutaneous Extended-Release Study)[3] and TV46000-CNS-30078 (the SHINE Study – Safety in Humans of TV-46000 sc INjection Evaluation)[2].

The safety and efficacy of UZEDY for BP-I are not established and UZEDY is not approved by any regulatory authority for this indication.

About Bipolar I Disorder

Bipolar Disorder I (BP-I) is a manic-depressive condition that leads to large swings in mood and actions that greatly impact quality of life and ability to complete day-to-day tasks. It is challenging to diagnose and is often accompanied by other psychiatric comorbidities. BP-I is associated with poor long-term outcomes and a substantial increase in mortality compared to the general population from both suicide and cardiovascular disease. An estimated 1% or 3,400,000+ of U.S. adults will develop BP-I in their lifetime.[4]

About the RISE Study

RISE, Teva's Phase 3 study, was a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy of risperidone extended-release injectable suspension for subcutaneous use as a treatment in patients (ages 13-65 years) with schizophrenia.[3] 544 patients were randomized to receive a subcutaneous injection of UZEDY once monthly (q1M), once every two months (q2M), or placebo in a 1:1:1 ratio. The primary endpoint was time to impending relapse.[3]

About the SHINE Study
The second of Teva's Phase 3 studies; designed to evaluate the long-term safety, tolerability and effectof UZEDY subcutaneously administered q1M or q2M for up to 56 weeks in 331 patients (ages 13-65 years) with schizophrenia. The primary endpoint was the frequency of all adverse events, including serious adverse events.[2]

About UZEDY
UZEDY (risperidone) extended-release injectable suspension for subcutaneous use is indicated for the treatment of schizophrenia in adults. In clinical trials, UZEDY significantly reduced the risk of schizophrenia relapse.[1,2] UZEDY administers risperidone through copolymer technology under license from Medincell that allows for absorption and sustained release after subcutaneous injection. UZEDY is the only long-acting, subcutaneous formulation of risperidone available in both one- and two-month dosing intervals.[1] For full prescribing information, visit https://www.uzedy.com/globalassets/uzedy/prescribing-information.pdf.

INDICATION AND USAGE

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

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.

See below for additional Important Safety Information.

IMPORTANT SAFETY INFORMATION CONTINUED

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.

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 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 the full Prescribing Information for UZEDY, including Boxed WARNING.

About Teva

Teva Pharmaceutical Industries Ltd. (NYSE and TASE: TEVA) is a different kind of global pharmaceutical leader, one that operates across the full spectrum of innovation to reliably deliver medicines to patients worldwide. For over 120 years, Teva's commitment to bettering health has never wavered. Today, the company's global network of capabilities enables its 37,000 employees across 57 markets to advance health by developing medicines for the future while championing the production of generics and biologics. If

patients have a need, we're already working to address it. To learn more about how Teva is all in for better health, visit www.tevapharm.com.

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, which are based on management's current beliefs and expectations and are subject to substantial risks and uncertainties, both known and unknown, that could cause our future results, performance or achievements to differ significantly from that expressed or implied by such forward-looking statements. You can identify these forward-looking statements by the use of words such as "should," "expect," "anticipate," "estimate," "target," "may," "project," "guidance," "intend," "plan," "believe" and other words and terms of similar meaning and expression in connection with any discussion of future operating or financial performance. Important factors that could cause or contribute to such differences include risks relating to: our ability to successfully develop and commercialize UZEDY (risperidone) extended-release injectable suspension for the maintenance treatment of BP-I in adult patients; our ability to successfully compete in the marketplace, including our ability to develop and commercialize additional pharmaceutical products; our ability to successfully execute our Pivot to Growth strategy, including to expand our innovative and biosimilar medicines pipeline and profitably commercialize the innovative medicines and biosimilar portfolio, whether organically or through business development, and to sustain and focus our portfolio of generic medicines; and other factors discussed in our Annual Report on Form 10-K for the year ended December 31, 2024, including in the section captioned "Risk Factors and "Forward Looking Statements." Forward-looking statements speak only as of the date on which they are made, and we assume no obligation to update or revise any forward-looking statements or other information contained herein, whether as a result of new information, future events or otherwise. You are cautioned not to put undue reliance on these forward-looking statements.

1. UZEDY® (risperidone) extended-release injectable suspension, for subcutaneous injection Current Prescribing Information. Parsippany, NJ. Teva Neuroscience, Inc.
2. Data on file. Parsippany, NJ: Teva Neuroscience, Inc.
3. Clinicaltrials.gov. Study to Evaluate TV-46000 as Maintenance Treatment in Adult and Adolescent Participants With Schizophrenia (RISE). https://clinicaltrials.gov/study/NCT03503318. Accessed November 2024.
4. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-Month Prevalence of Bipolar Spectrum Disorder in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2007;64(5):543–552. doi:10.1001/archpsyc.64.5.543

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Teva Media Inquiries:

TevaCommunicationsNorthAmerica@tevapharm.com

Teva Investor Relations Inquires

TevaIR@Tevapharm.com

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About Medincell

Medincell is a clinical- and commercial-stage biopharmaceutical licensing company developing long-acting injectable drugs in many therapeutic areas. Our innovative treatments aim to guarantee compliance with medical prescriptions, to improve the effectiveness and accessibility of medicines, and to reduce their environmental footprint. They combine active pharmaceutical ingredients with our proprietary BEPO® technology which controls the delivery of a drug at a therapeutic level for several days, weeks or months from the subcutaneous or local injection of a simple deposit of a few millimeters, entirely bioresorbable. The first treatment based on BEPO® technology, intended for the treatment of schizophrenia, was approved by the FDA in April 2023, and is now distributed in the United States by Teva under the name UZEDY® (BEPO® technology is licensed to Teva under the name SteadyTeq™). We collaborate with leading pharmaceutical companies and foundations to improve global health through new treatment options. Based in Montpellier, Medincell currently employs more than 140 people representing more than 25 different nationalities.

Contact: communication@medincell.com