For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

LUMAVIBE

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Lumateperone is not approved for the treatment of patients with dementia-related psychosis.**
- **Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients. Closely monitor all antidepressant-treated patients for worsening and emergence of suicidal thoughts and behaviors. Safety and effectiveness of Lumateperone have not been established in pediatric patients**.

1. Generic Name

Lumateperone Capsules 42 mg

2. Qualitative and quantitative Composition:

Each hard gelatine capsule contains:

Lumateperone tosylate eq. to

Lumateperone…….42 mg

Excipients …… q. s.

Colour: Approved colors used in capsule shell.

The excipients used are Mannitol, Microcrystalline cellulose, Croscarmellose Sodium, Colloidal silicon dioxide, Purified Talc.

3. Dosage form and strength

Dosage form: Hard gelatine capsule

Strength: 42 mg

4. Clinical particulars

4.1. Therapeutic indication

Indicated for the treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate.

4.2. Posology and method of administration

Posology

The recommended dosage of Lumateperone is 42 mg once daily with or without food. Dose titration is not required.

Method of administration

For oral use.

4.3. Contraindications

It is contraindicated in patients with history of hypersensitivity reaction to lumateperone or any components of lumateperone. Reactions have included pruritus, rash (e.g. allergic dermatitis, papular rash, and generalized rash), and urticaria.

4.4. Special warnings and precautions for use

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. In an analysis of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, the risk of death in antipsychotic drug-treated patients was 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 incidence of death in antipsychotic-treated patients was about 4.5%, compared to an incidence of about 2.6% in placebo-treated patients. Although the causes of death varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia). Lumateperone is not approved for the treatment of patients with dementia-related psychosis.

Suicidal Thoughts and Behaviours in Pediatric and Young Adult Patients

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviours in antidepressant treated pediatric and young adult patients was greater than in placebo-treated patients. There were differences in absolute risk of suicidal thoughts and behaviours across the different uses, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviours per 1,000 patients treated are provided in the Table.

Table: Risk Differences of the Number of Patients with Suicidal Thoughts and Behaviours in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated Increases Compared to Placebo
< 18 years old	14 additional points
18 24 years old	5 additional points
Decreases Compared to Placebo	
25-64 years old	1 fewer patient
≥ 65 years old	6 fewer patients

*Lumateperone is not approved for use in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviours in pediatric and young adult patients extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviours.

Monitor all antidepressant-treated patients, especially during the initial few months of anti-depressant drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behaviour and to alert the health care provider. Consider changing

the therapeutic regimen, including possibly discontinuing Lumateperone, in patients whose depression is persistently worse, or who experience suicidal thoughts or behaviours**.**

Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials, elderly patients with dementia-related psychosis treated with antipsychotics had a higher incidence of stroke and transient ischemic attack, including fatal stroke compared to those treated with placebo.

Lumateperone is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, delirium, and autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue lumateperone and provide intensive symptomatic treatment and monitoring.

Tardive Dyskinesia

Tardive dyskinesia (TD) may develop in patients treated with antipsychotic drugs, including lumateperone. TD can develop after a relatively brief treatment period at low dosages and may also occur after discontinuation of treatment. If antipsychotic treatment is discontinued, TD may partially or completely remit. Antipsychotic treatment, however, may suppress or partially suppress the signs and symptoms of TD, and may mask the underlying process. The effect that symptomatic suppression has upon the long-term course of TD is unknown.

The TD risk appears to be highest among the elderly, especially elderly women, but it is not possible to predict which patients are likely to develop TD. The TD risk and the likelihood that TD will become irreversible increase with the duration of antipsychotic drug treatment and the cumulative dosage.

Periodically reassess the need for continued treatment. If signs and symptoms of TD appear in lumateperone -treated patients, consider drug discontinuation. However, some patients may require lumateperone treatment despite the presence of TD.

Metabolic Changes

Antipsychotic drugs have caused metabolic changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, has been reported in patients treated with antipsychotics. There have been reports of hyperglycemia in patients treated with lumateperone. Assess fasting plasma glucose before or soon after initiation of lumateperone and monitor periodically during long term treatment.

- In pooled data from short-term (4- to 6-week), placebo-controlled trials of adult patients with schizophrenia, mean changes from baseline and the proportion of patients with shifts from normal to greater than normal levels of fasting glucose were similar in lumateperone -treated and placebo-treated patients. In an uncontrolled open label trial of lumateperone for up to 1 year in adult patients with stable schizophrenia, the percentages of patients with shifts in fasting glucose and insulin values from normal to high were 8% and 12%, respectively. In this trial, 5% of lumateperone -treated patients with normal hemoglobin A1c.

- In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, mean changes from baseline and the proportion of patients with shifts from normal to greater than normal levels of fasting glucose and insulin were similar in lumateperone-treated and placebo-treated patients.
- In pooled data from short-term (6-week), placebo-controlled adjunctive therapy MDD trials, mean changes from baseline and the proportion of patients with shifts from normal to greater than normal levels of fasting glucose were similar in lumateperone treated and placebo-treated patients.

Dyslipidemia

Antipsychotics have caused adverse alterations in lipids. Before or soon after initiation of antipsychotic medications, obtain a fasting lipid profile at baseline and monitor periodically during treatment.

- In pooled data from short-term (4- to 6-week), placebo-controlled trials of adult patients with schizophrenia, mean changes from baseline and the proportion of patients with shifts to higher levels of fasting total cholesterol and triglycerides were similar in lumateperone -treated and placebo-treated patient. In an uncontrolled open-label trial of lumateperone for up to 1 year in patients with stable schizophrenia, the percentages of patients with a shift from normal to high were 8%, 5%, and 4% for total cholesterol, triglycerides, and LDL cholesterol, respectively.
- In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, mean changes from baseline and the proportion of patients with shifts to higher levels of fasting total cholesterol and triglycerides were similar in lumateperone -treated and placebo-treated patients. In an uncontrolled open label trial of lumateperone for up to 6 months in patients with bipolar depression, the proportion of patients with a shift from normal to high were 10%, 5%, and 2% for total cholesterol, triglycerides, and LDL cholesterol, respectively.
- In pooled data from short-term (6-week), placebo-controlled adjunctive therapy MDD trials, mean changes from baseline and the proportion of patients with shifts to higher levels of fasting total cholesterol and triglycerides were similar in lumateperone treated and placebo-treated patients.

Weight Gain

Weight gain has been observed with use of antipsychotics. Monitor weight at baseline and frequently thereafter.

- In pooled data from placebo-controlled trials of adult patients with schizophrenia, mean changes from baseline and the proportion of patients with an increase in weight ≥7% from baseline to end of study was similar in lumateperone -treated and placebo-treated patients. In an uncontrolled open-label trial of lumateperone for up to one year in patients with stable schizophrenia, the mean change in body weight was approximately -2 kg (SD 5.6) at Day 175 and approximately - 3.2 kg (SD 7.4) at Day 350.
- In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, mean changes from baseline and the proportion of patients with an increase in weight ≥7% from baseline to end of study were similar in lumateperone -treated and placebo-treated patients. In an uncontrolled open-label trial of lumateperone for up to 6 months in patients with bipolar depression, the mean change in body weight was -0.01 kg (SD 3.1) at Day 175.

- In pooled data from short-term (6-week), placebo-controlled adjunctive therapy MDD trials, mean changes from baseline and the proportion of patients with an increase in weight ≥7% from baseline to end of study were similar in lumateperone-treated and placebo-treated patients.
- In a long-term open-label adjunctive therapy MDD trial of lumateperone for up to 6 months, the mean change in body weight was -0.16 kg (SD 3.7) at Week 26**.**

Leukopenia, Neutropenia, and Agranulocytosis

Leukopenia and neutropenia have been reported during treatment with antipsychotic drugs, including lumateperone. Agranulocytosis (including fatal cases) has been reported with other antipsychotic drugs.

Possible risk factors for antipsychotic drug-leukopenia and neutropenia include pre-existing low white blood cell count (WBC) or absolute neutrophil count (ANC) and history of drug-induced leukopenia or neutropenia.

In patients with a pre-existing low WBC or ANC or a history of drug-induced leukopenia or neutropenia, perform complete blood count (CBC) monitoring during the first few months of lumateperone therapy. Consider discontinuing lumateperone in patients who have a clinically significant decline in WBC in the absence of other causative factors. Discontinue lumateperone in patients with clinically significant neutropenia or ANC < 1000/mm^3 and monitor closely until the neutropenia resolves**.**

Orthostatic Hypotension and Syncope

Atypical antipsychotics cause orthostatic hypotension and syncope. Generally, the risk is greatest during initial dose administration.

Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension (e.g., elderly patients, patients with dehydration, hypovolemia, and concomitant treatment with antihypertensive drugs), patients with known cardiovascular disease (history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease. Lumateperone has not been evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease. Such patients were excluded from pre-marketing clinical trials.

- In pooled data from short-term (4- to 6-week), placebo-controlled schizophrenia trials, the frequencies of orthostatic hypotension in lumateperone-treated and placebo treated patients were 0.7% and 0%, respectively. The incidence of syncope for lumateperone-treated and placebo-treated patients were 0.2% and 0.2%.
- In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, the frequencies of orthostatic hypotension for lumateperone -treated and placebo-treated patients were both 0%. The incidence of syncope for lumateperone and placebo were 0.3% and 0.5%, respectively in the monotherapy trials, and there were no reports of syncope in the adjunctive therapy trial.
- In pooled data from short-term (6-week), placebo-controlled adjunctive therapy MDD trials, the frequencies of orthostatic hypotension for lumateperone -treated and placebo treated patients were 6.6% and 6.2%, respectively. The incidence of syncope for lumateperone -treated and placebo-treated patients were 0.2% and 0%, respectively.

Falls

Antipsychotics, including lumateperone, may cause somnolence, postural hypotension, and motor and sensory instability, which may lead to falls and, consequently, fractures and other injuries.

If patients have a condition (or take concomitant drugs) that could exacerbate these effects, complete fall risk assessments when initiating lumateperone treatment and periodically during long-term treatment.

Seizures

Like other antipsychotic drugs, lumateperone may cause seizures. The risk of antipsychotic drug-associated seizures is greatest in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in older patients.

Use lumateperone cautiously in patients with a history of seizures or with other conditions that lower seizure threshold.

Potential for Cognitive and Motor Impairment

Lumateperone, like other antipsychotics, may cause somnolence and has the potential to impair judgment, thinking, and motor skills. Patients should be cautioned about operating hazardous machinery and motor vehicles until they are reasonably certain that therapy with lumateperone does not affect them adversely.

- In short-term (i.e., 4- to 6-week), placebo-controlled clinical trials of patients with schizophrenia, somnolence and sedation were reported in 24% of lumateperone-treated patients, compared to 10% of placebo-treated patients.
- In short term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression clinical trials, somnolence and sedation were reported in 13% of lumateperone-treated patients, compared to 3% of placebo-treated patients.
- In short term (6-week), placebo-controlled adjunctive therapy MDD trials, somnolence and sedation were reported in 12% of lumateperone-treated patients, compared to 2% of placebo-treated patients.

Body Temperature Dysregulation

Atypical antipsychotics may disrupt the body's ability to reduce core body temperature. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic drugs may contribute to an elevation in core body temperature. Use lumateperone with caution in patients who may experience these conditions.

Dysphagia

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

4.5. Drugs interactions

CYP3A4 Inducers*	
Prevention or Management	Avoid concomitant use of lumateperone with CYP3A4 inducers.
Clinical Impact	Concomitant use of lumateperone with CYP3A4 inducers decreases the exposure of lumateperone.
Moderate or Strong CYP3A4 Inhibitors*	
Prevention or Management	Reduce the lumateperone dosage when used concomitantly with moderate or strong CYP3A4 inhibitors.

Clinical Impact	Concomitant use of lumateperone with moderate or strong CYP3A4 inhibitors increases lumateperone exposure, which may increase the risk of adverse reactions.
Serotonin Reuptake Inhibitors	
Prevention or Management	Increased monitoring for SRI- associated adverse reactions is recommended.
Clinical Impact	Although no clinically significant drug interactions with adjunctive SSRI/SNRIs in MDD were observed in lumateperone clinical trials, lumateperone's moderate serotonin transporter (SERT) activity may increase the risk of SRI-associated adverse reactions (e.g., serotonin syndrome, hyponatremia).

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Available data from case reports on lumateperone use in pregnant women are insufficient to establish any drug associated risks for birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother associated with exposure to antipsychotics, including lumateperone, during pregnancy. In animal reproduction studies, no malformations were observed with oral administration of lumateperone to pregnant rats and rabbits during organogenesis at doses up to 2.4 and 9.7 times, respectively, the maximum recommended human dose (MRHD) of 42 mg/day on a mg/m basis. When pregnant rats were administered lumateperone during the period of organogenesis through lactation, the number of perinatal deaths of pups was increased at 4.9 times the MRHD, with no adverse effects on pups at 2.4 times the MRHD.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Al 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 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 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

Animal Data

Pregnant rats were treated with oral doses of 3.5, 10.5, 21, and 63 mg/kg/day lumateperone (0.8, 2.4, 4.9, and 14.6 times the MRHD on a mg/m basis) during the period of organogenesis. No malformations were observed with lumateperone at doses up to 2.4 times the MRHD. Findings of decreased body weight were observed in fetuses at 4.9 and 14.6 times the MRHD. Findings of incomplete ossification and increased incidences of visceral and skeletal variations were recorded in fetuses at 14.6 times the MRHD, a dose that induced maternal toxicity.

Pregnant rabbits were treated with oral doses of 2.1, 7, and 21 mg/kg/day lumateperone (1.0, 3.2, and 9.7 times the MRHD on a mg/m basis) during the period of organogenesis. Lumateperone did not cause adverse developmental effects at doses up to 9.7 times the MRHD.

In a study in which pregnant rats were administered oral doses of 3.5, 10.5, and 21 mg/kg/day lumateperone (0.8, 2.4, and 4.9 times the MRHD on a mg/m basis) during the period of organogenesis and through lactation, the number of live-born pups was decreased at 2.4 and 4.9 times the MRHD, and early postnatal deaths increased at a dose 4.9 times the MRHD. Impaired nursing and decreased body weight gain in pups were observed at 4.9 times, but not at 2.4 times, the MRHD.

Pregnant rats were treated with a human metabolite of lumateperone (reduced ketone metabolite) at oral doses of 15, 60, and 100 mg/kg/day (1.2, 19, and 27 times the exposure to this metabolite at the MRHD of lumateperone based on AUC plasma exposure) during the period of organogenesis. This metabolite did not cause adverse developmental effects at a dose 1.2 times the exposure at the MRHD of lumateperone; however, it caused an increase in visceral malformations (cleft palate) at 27 times and skeletal malformations at 19 times the exposure at the MRHD of lumateperone, a dose that induced maternal toxicity.

Lactation

Risk Summary

Lumateperone and its metabolites are present in human breast milk in low amounts. In a clinical lactation study, lumateperone was detected in human milk at an estimated daily infant dose 0.0004 mg/kg, with a relative infant dose (RID) of 0.06% the maternal weight-adjusted dosage. Several major circulating metabolites were similarly detected in breast milk in low amounts; however, aniline metabolites were not present in milk or maternal plasma at quantifiable levels. There are no data on the effects of lumateperone on the breastfed infant or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for lumateperone and any potential adverse effects on the breastfed child from lumateperone or from the underlying maternal condition.

Data

A lactation study in 17 lactating women evaluated the concentrations of lumateperone and its metabolites in plasma and mature breast milk following a single dose of 42 mg lumateperone. The estimated daily infant dose of lumateperone in human milk was 0.0004 mg/kg/day (with assumed average milk consumption of 200 ml/kg/day). The mean relative infant dose (RID) (with assumed mean milk consumption of 200 mL/kg/day and average maternal weight of 71 kg) was 0.06% of the maternal weight-adjusted dosage. Several major circulating metabolites were also present in breast milk at estimated daily infant dose of 0.0004 mg/kg/day. Aniline metabolites were not present in milk or maternal plasma at quantifiable levels.

Females and Males of Reproductive Potential

Infertility

Based on findings from animal studies, lumateperone may impair male and female fertility.

Pediatric Use

Safety and effectiveness of lumateperone have not been established in pediatric patients. Antidepressants increased the risk of suicidal thoughts and behaviours in pediatric patients.

Geriatric Use

Controlled clinical studies of lumateperone for the treatment of schizophrenia and as adjunctive therapy with antidepressants for the treatment of MDD did not include any patients aged 65 or older to determine whether or not they respond differently from younger adult patients.

Among the lumateperone -treated patients in clinical studies for the treatment of depressive episodes associated with bipolar depression, 20 (6%) were 65 to 74 years of age, and none were 75 years of age or older. These clinical studies did not include sufficient numbers of patients aged 65 years of age or older to determine whether or not they respond differently from younger adult patients.

Antipsychotic drugs increase the risk of death in elderly patients with dementia-related psychosis. Lumateperone is not approved for the treatment of patients with dementia-related psychosis.

Elderly patients with dementia-related psychosis treated with antipsychotics have an increased risk of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack) including fatalities, compared to those treated with placebo.

Antipsychotic drugs increase the risk of tardive dyskinesia, and this risk appears to be highest among the elderly, particularly elderly women.

The use of serotonin reuptake inhibitors (SRIs) has been associated with clinically significant hyponatremia in geriatric patients, who may be at greater risk for this adverse reaction. The concomitant use of lumateperone with an SRI may increase this risk.

Hepatic Impairment

Patients with moderate hepatic impairment (HI) (Child-Pugh class B) and severe HI (Child-Pugh class C) generally had higher exposure to lumateperone than patients with normal hepatic function; therefore, the recommended lumateperone dosage in patients with moderate or severe HI is lower than those with normal hepatic function.

The recommended dosage in patients with mild HI (Child-Pugh class A) is the same as those with normal hepatic function.

4.7. Effects on ability to drive and use machines

Patients are advised not to drive a vehicle, operate complex machinery, or engage in other potentially hazardous activities until it is known whether lumateperone affects their ability to perform these tasks.

4.8. Undesirable effects

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

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- Suicidal Thoughts and Behaviours
- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-related Psychosis.

- Neuroleptic Malignant Syndrome
- Tardive Dyskinesia
- Metabolic Changes
- Leukopenia, Neutropenia, and Agranulocytosis
- Orthostatic Hypotension and Syncope
- Falls
- Seizures
- Potential for Cognitive and Motor Impairment
- Body Temperature Dysregulation
- Dysphagia

Clinical Trials Experience

Based on reported clinical trial the safety of lumateperone has been evaluated in placebo-controlled clinical trials that included 3575 adult patients with schizophrenia, bipolar depression, or major depressive disorder, exposed to one or more lumateperone doses. A total of 852 lumateperone-treated patients had at least 6 months of treatment and 108 had at least 1 year of treatment with the 42-mg once daily dosage.

Adverse Reactions in Patients with Schizophrenia

The following adverse reactions are based on the pooled short-term (4- to 6-week), placebo-controlled studies in adult patients with schizophrenia in which lumateperone was administered at a dosage of 42 mg once daily (N=406).

There was no single adverse reaction that led to discontinuation that occurred at a rate of >2% in lumateperone -treated patients. The most common adverse reactions (incidence of at least 5% of lumateperone -treated patients and greater than twice the rate of placebo treated patients) were somnolence/sedation and dry mouth. Adverse reactions (incidence of at least 2% in lumateperone-treated patients and greater than in placebo treated patients) are shown in the Table.

Table: Adverse Reactions Reported in ≥2% of lumateperone Treated Patients and Greater Incidence Than in Placebo Treated Patients in 4- to 6-week Schizophrenia Trials

	LUMATEPERONE 42 mg (N=372)	**Placebo (N=374)**
Somnolence/Sedation	24%	10%
Nausea	9%	5%
Dry mouth	6%	2%
Dizziness[1]	5%	3%
Creatine Phosphokinase Increased	4%	1%
Fatigue	3%	1%
Vomiting	3%	2%
Hepatic Transaminases Increased [2]	2%	1%
Decreased Appetite	2%	1%

[1]Dizziness, dizziness postural

[2]ALT, AST, "hepatic enzymes" increased, or liver function test abnormal

Adverse Reactions in Patients with Bipolar Depression (Lumateperone Monotherapy)

The following adverse reactions are based on the pooled short-term (6-week), placebo-controlled monotherapy bipolar depression studies in adult patients treated with lumateperone 42 mg once daily (N=372)

There was no single adverse reaction leading to discontinuation that occurred at a rate of >2% in lumateperone-treated patients.

The most common adverse reactions (incidence of at least 5% of lumateperone-treated patients and greater than twice the rate in placebo-treated patients) were somnolence/sedation, dizziness, nausea, and dry mouth.

Adverse reactions associated with lumateperone (incidence of at least 2% in lumateperone-treated patients and greater than placebo-treated patients) are shown in the Table.

Table: Adverse Reactions Reported in ≥2% of lumateperone Treated Patients and Greater Incidence than in Placebo Treated Patients in Pooled 6-week Monotherapy Bipolar Depression Trials

	LUMATEPERONE 42 mg (N=372)	**Placebo (N=374)**
Headache	14%	8%
Somnolence/Sedation	13%	3%
Dizziness[1]	8%	4%
Nausea	8%	3%
Dry mouth	5%	1%
Diarrhea	4%	2%
Vomiting	4%	0%
Abdominal pain[2]	2%	1%
Upper respiratory tract infection	2%	1%

[1]Dizziness, dizziness postural

[2]Abdominal discomfort, abdominal pain, abdominal pain upper and lower

Adverse Reactions in Patients with Bipolar Depression (Concomitant Treatment with lumateperone and Lithium or Valproate)

The adverse reactions below are based on a 6-week, placebo-controlled adjunctive therapy bipolar depression study in adult patients treated with lumateperone 42 mg once daily + lithium or valproate OR placebo + lithium or valproate (N=177).

There was no single adverse reaction leading to discontinuation that occurred at a rate of >2% in patients in the lumateperone + lithium or valproate group.

The most common adverse reactions (incidence of at least 5% in patients treated with lumateperone + lithium or valproate and greater than twice the rate of patients treated with placebo + lithium or valproate) were somnolence/sedation, dizziness, nausea, and dry mouth.

Adverse reactions associated with lumateperone + lithium or valproate (incidence of at least 2% in patients treated with lumateperone + lithium or valproate and greater than with patients treated with placebo + lithium or valproate) are shown in the Table.

Table: Adverse Reactions Reported in ≥2% of Lumateperone Treated Patients and that Occurred at Greater Incidence than in the Placebo-Treated Patients in a 6-Week Adjunctive Therapy Bipolar Depression Trial

	LUMATEPERONE 42 mg + lithium or valproate (N=177)	**Placebo + lithium or valproate (N=175)**
Somnolence/Sedation	13%	3%
Dizziness[1]	11%	2%
Nausea	9%	4%
Dry mouth	5%	1%
Vomiting	4%	0%
Diarrhea	3%	2%
Upper respiratory tract infection	3%	1%
Blurred vision	3%	1%
Increased blood prolactin	2%	0%

[1]Dizziness, dizziness postural

Adverse Reactions in Studies for Adjunctive Treatment of Major Depressive Disorder

The following adverse reactions are based on pooled short-term (6-week), placebo controlled adjunctive therapy MDD studies in adult patients treated with lumateperone 42 mg orally once daily and background antidepressant therapy (ADT) or placebo and background ADT (N=483).

There was no single adverse reaction leading to discontinuation that occurred at an incidence of >2% in patients treated with lumateperone and background ADT.

The most common adverse reactions (incidence of at least 5% of patients treated with lumateperone and background ADT and greater than twice the incidence in patients treated with placebo and background ADT) were dizziness, dry mouth, somnolence/sedation, nausea, fatigue, and diarrhea.

Adverse reactions in the adjunctive therapy MDD studies (incidence of at least 2% of patients treated with lumateperone and background ADT and greater than in patients treated with placebo and background ADT) are shown in the Table.

Table: Adverse Reactions Reported in ≥2% of Patients Treated with Lumateperone + Background ADT and at Greater Incidence than in Patients Treated with Placebo + Background ADT in Pooled 6-Week Adjunctive MDD Trials

	LUMATEPERONE 42 mg + lithium or valproate (N=177)	**Placebo + lithium or valproate (N=175)**
Headache[1]	19%	13%
Dizziness[2]	17%	5%
Dry mouth	13%	3%
Somnolence/Sedation	12%	2%
Nausea	9%	4%

	LUMATEPERONE 42 mg + lithium or valproate (N=177)	Placebo + lithium or valproate (N=175)
Fatigue	8%	2%
Diarrhea	5%	1%
Tremor	4%	<1%
Vomiting	3%	2%
Vertigo	3	<1
Insomnia	3	2%

[1]Headache, migraine, tension headache
[2]Dizziness, postural dizziness

Additional Adverse Reactions

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. Although these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Extrapyramidal Symptoms: In the short-term, placebo-controlled schizophrenia, bipolar depression, and adjunctive MDD studies, extrapyramidal (EPS) symptom data was objectively collected on the Simpson-Angus Scale (SAS) for EPS (total score ranges from 0 to 40), the Barnes Akathisia Rating Scale (BARS) for akathisia (total score ranges from 0 to 14), and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesia (total score ranges from 0 to 28).

- In the 4- to 6-week, placebo-controlled schizophrenia trials, the frequency of EPS related reported events including akathisia, extrapyramidal disorder, muscle spasms, restlessness, musculoskeletal stiffness, dyskinesia, dystonia, muscle twitching, tardive dyskinesia, tremor, drooling, and involuntary muscle contractions was 6.7% for the lumateperone -treated patients and 6.3% for placebo-treated patients. In these trials, the mean changes from baseline for lumateperone-treated patients and placebo treated patients were 0.1 and 0 for the SAS, -0.1 and 0 for the BARS, and 0.1 and 0 for the AIMS, respectively.
- In the 6-week, monotherapy bipolar depression trials, the frequency of reported EPS related reactions including muscle spasms, dyskinesia, extrapyramidal disorder, movement disorder, tremor, restlessness, and akathisia was 1.3% for lumateperone treated patients and 1.1% for placebo-treated patients. In these trials, the mean changes from baseline for lumateperone -treated patients and placebo-treated patients were 0 and 0 for the SAS, -0.1 and -0.1 for the BARS, and 0 and 0 for the AIMS, respectively.
- In a 6-week, adjunctive therapy bipolar depression trial, the frequency of reported EPS-related reactions, including tremor, muscle spasms, akathisia, extrapyramidal disorder, gait disturbance, and restlessness was 4% for lumateperone -treated patients and 2.3% for placebo-treated patients. In the 6-week, monotherapy bipolar depression trials, the mean changes from baseline for lumateperone -treated patients and placebo-treated patients were 0 and 0 for the SAS, -0.1 and -0.1 for the BARS, and 0 and 0 for the AIMS, respectively. In this trial, the mean changes from baseline for lumateperone -treated patients and placebo-

treated patients were 0 and 0 for the SAS, 0 and -0.1 for the BARS, and 0 and 0 for the AIMS, respectively.

- In the 6-week, adjunctive MDD trials, the frequency of reported EPS-related adverse reactions (tremor, bradykinesia, muscle spasms, gait disturbance, tongue spasm, muscle tightness and dyskinesia), excluding akathisia and restlessness, was 5% for lumateperone -treated patients and 0.8% for placebo-treated patients. The combined incidence of akathisia and restlessness was 1% for lumateperone -treated patients and 0.8% for placebo-treated patients. In these trials, the mean changes from baseline for lumateperone -treated patients and placebo-treated patients were 0 and 0 for the SAS, 0 and -0.1 for the BARS, and 0 and 0 for the AIMS, respectively.

Post marketing Experience

The following adverse reaction has been identified during post-approval use of lumateperone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure.

Central and Peripheral Nervous System Disorders: burning sensation, including skin burning sensation.

Reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

4.9. Overdose

No specific antidotes for lumateperone are known. In managing lumateperone overdose, provide supportive care, including close medical supervision and monitoring and consider the possibility of multiple drug involvement.

5. Pharmacological properties

5.1. Mechanism of Action

The mechanism of action of lumateperone for the treatment of depressive episodes associated with bipolar depression (as monotherapy or as adjunctive therapy with lithium or valproate), is unknown. However, the mechanism of action of lumateperone could be mediated through a combination of antagonist activity at central serotonin 5-HT_{2A} receptors, and partial agonist activity at central dopamine D_2 receptors.

5.2. Pharmacodynamic properties

Lumateperone has high binding affinity for serotonin 5-HT_{2A} receptors (K_i = 0.54 nM) and moderate binding affinity for dopamine D_2 (K = 32 nM) receptors. Lumateperone has moderate binding affinity for dopamine D_1 (K = 41 nM) and D_4 and adrenergic $alpha_{1A}$ and $alpha_{1B}$ receptors ($K \leq 100$ nM), serotonin transporters (K_i = 33 nM), and inhibits uptake of serotonin in cells expressing the human SERT (IC = 150 nM). Lumateperone has low binding affinity (less than 50% inhibition at 100 nM) for muscarinic and histaminergic receptors.

In healthy human volunteers the mean cortical 5-HT_{2A} receptor occupancy and the mean striatal D_2 receptor occupancy were greater than 80% and approximately 12%, respectively, after a single 7 mg dose of lumateperone. D receptor occupancy increased with a dose from 7 mg to 28 mg.

Cardiac Electrophysiology

QTcF interval was evaluated in a randomized, placebo- and active- (moxifloxacin 400 mg) controlled, four-arm crossover study utilizing concentration-QTc effect modeling in 33 patients with schizophrenia. The placebo-corrected change from baseline QTcF (90% two-sided upper confidence interval) values of 4.9 (8.9) and 15.8 (19.8) ms for a lumateperone 42 mg once daily oral dosage for five days and a lumateperone 126 mg once daily oral dosage (three times the recommended daily dosage) for five days, respectively.

Clinical Studies

Schizophrenia

Lumateperone was evaluated for the treatment of schizophrenia in adults in two placebo-controlled trials.

Study 1 (Adults with Schizophrenia)

Study 1 Design:

Study 1 (NCT01499563) was a four-week, randomized, double-blind, placebo-controlled, multi-center study in adult patients with a diagnosis of schizophrenia according to the DSM-IV-TR criteria. The primary efficacy measure was change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score at Week 4. The PANSS is a 30-item scale used to measure symptoms of schizophrenia. Each item is rated by a clinician on a seven-point scale. A score of 1 indicates the absence of symptoms, and a score of 7 indicates extremely severe symptoms. The PANSS total score ranges from 30 to 210 with higher scores reflecting greater overall symptom severity.

A total of 335 patients were randomized to receive oral lumateperone 42 mg, lumateperone 84 mg (two times the recommended daily dose), an active comparator, or placebo once daily. The study was not designed to allow for efficacy comparison of lumateperone and the active comparator.

Study 1 Baseline Demographics:

Demographic and baseline disease characteristics were similar for the lumateperone, active comparator, and placebo groups. Median age was 42 years (range 20 to 55 years). 17% were female, 19% were White, and 78% were Black.

Study 1: Summary of Primary Efficacy Results:

Compared to the placebo group, patients randomized to lumateperone 42 mg once daily showed a statistically significant reduction from baseline to Day 28 in the PANSS total score. The treatment effect in the lumateperone 84 mg once daily treatment group (vs. placebo group) was not statistically significant. The results of Study 1 are shown in the Table.

Study 2 (Adults with Schizophrenia)

Study 2 Design:

Study 2 (NCT02282761) was a four-week, randomized, double-blind, placebo-controlled, multi-center study in adult patients with a diagnosis of schizophrenia according to the DSM-5 criteria. The primary efficacy measure was change from baseline in the PANSS total score at Week 4.

A total of 450 patients were randomized to receive oral lumateperone 28 mg (two-thirds the recommended daily dose), lumateperone 42 mg, or placebo once daily.

Study 2 Baseline Demographics:

Demographic and baseline disease characteristics were similar for the lumateperone and placebo groups. Median age was 44 years (range 19 to 60 years); 23% were female, 26% were White and 66% were Black.

Study 2: Summary of Primary Efficacy Results:

Compared to the placebo group, patients in the lumateperone 42 mg group showed a statistically significant reduction from baseline to Day 28 in the PANSS total score. The treatment effect in the lumateperone 28 mg group (vs. placebo group) was not statistically significant. The results of Study 2 are shown in the Table.

Efficacy Results in Studies 1 and 2 (Adults with Schizophrenia)

Studies 1 and 2 did not include any patients aged 65 or older. Examination of subgroups by sex and race did not suggest differences in response in either study.

Table: Primary Efficacy Results for Change from Baseline in PANSS Total Score in Adult Patients with Schizophrenia (Studies 1 and 2)

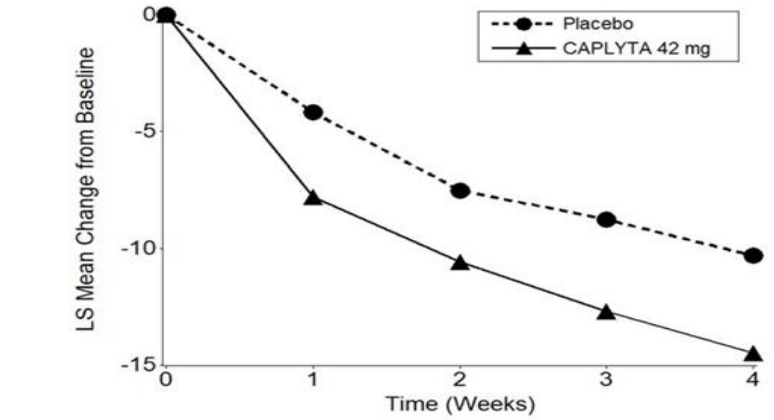
			Primary Efficacy Endpoint: PANSS Total Score		
Study Number	**Treatment Group**	**N**	**Mean Baseline Score (SD)**	**LS Mean Change from Baseline (SE)**	**Placebo subtracted Difference (95% CI)**
1.	Lumateperone (42 mg once daily)*	84	88.1 (11.0)	-13.2 (1.7)	-5.8(10.5, -1.1)[a]
	Placebo	85	86.3 (13.1)	-7.4 (1.7)	-
2.	Lumateperone (42 mg once daily)*	150	90.0 (9.6)	-14.5 (1.3)	-4.2 (-7.8, -0.6)
	Placebo	150	89.0 (10.3)	-10.3 (1.3)	-

The PANSS total score may range from 30 to 210; higher scores reflect greater symptom severity.
SD: standard deviation; SE: standard error; LS Mean: least squares mean; CI: unadjusted confidence interval.

[a] Difference (lumateperone minus placebo) in LS mean change from baseline not adjusted for sample size increase after unblinded interim analysis.

[*] Lumateperone statistically significantly superior to placebo**.**

Figure: Change from Baseline in PANSS Total Score by Time (Weeks) in Adult Patients with Schizophrenia in Study 2.



Depressive Episodes Associated with Bipolar I or II Disorder (Bipolar Depression)

Clinical Study of lumateperone Monotherapy for Bipolar I or II Disorder

Study 3 Design:

The efficacy of lumateperone, as monotherapy, for the treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults was established in a 6-week, randomized, double-blind, placebo-controlled, multi-center study in adult patients who met DSM-5 criteria for depressive episodes associated with bipolar I or bipolar II disorder (Study 3; NCT03249376). The primary efficacy measure was the change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score at Week 6. The MADRS is a 10-item clinician-rated scale with total scores ranging from 0 (no depressive features) to 60 (maximum score). The secondary endpoint was the change from baseline in Clinical Global Impression-Bipolar-Severity of Illness scale (CGI-BP-S) total score at Week 6. The CGI-BP-S total score is a clinician rated scale that measures the patient's current illness state on a 21-point scale that assesses depression, mania, and overall illness, where a higher score is associated with greater illness severity.

A total of 381 patients were randomized to receive oral lumateperone 42 mg or placebo once daily.

Study 3 Baseline Demographic Characteristics:

Demographic and baseline characteristics were similar for the lumateperone and placebo groups. Median age was 45 (range 18 to 72). 58% were female, 91% were White, and 8% were Black.

Study 3 Efficacy Results:

Compared to the placebo group, patients in the lumateperone 42 mg group showed a statistically significant improvement from baseline to Day 43 in the MADRS total score and CGI-BP-S total score. Examination of subgroups by age, sex, and race did not suggest differences in response in the study.

Clinical Study of lumateperone Adjunctive Therapy with Lithium or Valproate for Bipolar I or II Disorder

Study 4 Design:

The efficacy of lumateperone, as adjunctive therapy with lithium or valproate, for the treatment of depressive episodes associated with bipolar I or II disorder in adults was established in a 6-week, randomized, double-blind, placebo controlled, multi-center study in adult patients who met DSM-5 criteria for depressive episodes associated with bipolar I or bipolar II disorder (Study 4; NCT02600507). The primary efficacy measure was the change from baseline in MADRS total score at Week 6. The secondary endpoint was the change from baseline in CGI-BP-S depression score at Week 6. The CGI-BP-S depression score is a clinician-rated scale that measures the patient's current illness state on a 7-point scale, where a higher score is associated with greater illness severity.

A total of 529 patients were randomized to receive oral lumateperone 28 mg (two-thirds the recommended daily dosage), lumateperone 42 mg, or placebo once daily. Patients in al treatment groups continued treatment with lithium or valproate.

Study 4 Baseline Demographic

Characteristics: Demographic and baseline characteristics were similar for the lumateperone and placebo groups. Median age was 46 (range 18 to 74). 58% were female, 88% were White, and 11% were Black.

Study 4 Efficacy Results:

Compared to the placebo + lithium or valproate group, patients in the lumateperone 42 mg + lithium or valproate group showed a statistically significant improvement from baseline to Day 43 in the MADRS total score and CGI-BP-S depression score. The treatment effect in the lumateperone 28 mg + lithium or valproate group (vs. placebo + lithium or valproate group) was not statistically significant. The results of Study 4 are shown in the table.

Examination of subgroups by age, sex, and race did not suggest differences in response in the study.

Table: Primary Efficacy Results from Bipolar Depression Trials (Studies 3 and 4)

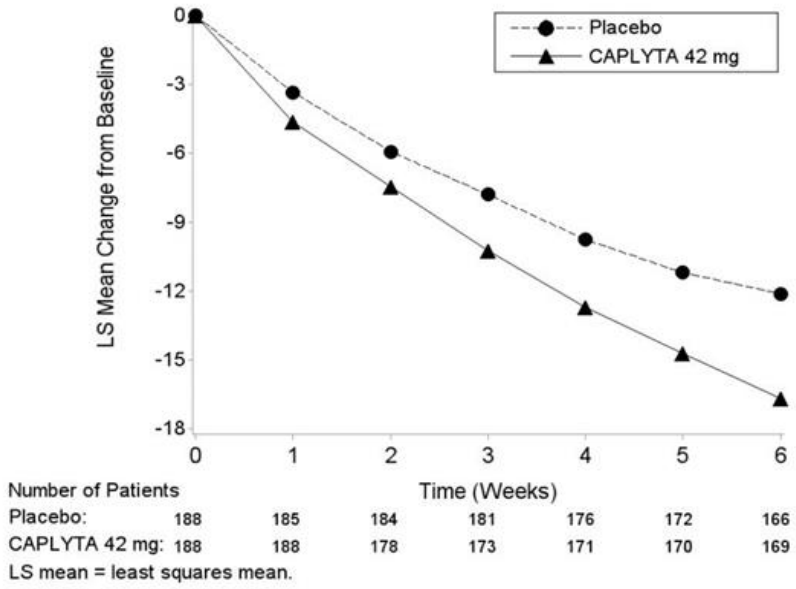
			Primary Efficacy Endpoint: MADRS Total Score		
Study Number	**Treatment Group**	**N**	**Mean Baseline Score (SD)**	**LS Mean Change from Baseline (SE)**	**Placebo subtracted Difference (95% CI)**
Monotherapy					
3	Lumateperone (42 mg) once daily*	188	30.8 (4.9)	-16.7 (0.7)	-4.6 (-6.3, -2.8)
	Placebo	188	30.3 (4.6)	-12.1 (0.7)	
Adjunctive Therapy					
4	Lumateperone (42 mg) once daily* + lithium or valproate	174	32.2 (5.0)	-16.9 (0.8)	-2.4 (-4.4, -0.4)
	Placebo + lithium or valproate	174	32.1 (5.2)	-14.5 (0.8)	

The MADRS total score ranges from 0 to 60; higher scores reflect greater symptom severity SD: standard deviation; SE: standard error; LS Mean: least squares mean; CI: confidence interval

[a] Difference (lumateperone minus placebo) in LS mean change from baseline

*Lumateperone statistically significantly superior to placebo.

Figure: Change from Baseline in MADRS Total Score by Visits (Study 3) in Adult Patients with Depressive Episodes Associated with Bipolar I or II Disorder (Monotherapy)



Adjunctive Treatment of Major Depressive Disorder in Adults Studies 5 and 6 Designs:

The effectiveness of LUMATEPERONE, as adjunctive therapy with antidepressants, for the treatment of major depressive disorder (MDD) in adults was established in two 6-week, randomized, double-blind, placebo-controlled, multi-center trials in adult patients who met DSM-5 criteria for MDD, with or without symptoms of anxiety who had inadequate response to one to two courses of prior antidepressant therapy (ADT) (Study 5 NCT04985942 and Study 6 NCT05061706). Inadequate response to ADT was defined as having less than 50% improvement after at least six weeks of treatment with selective serotonin or serotonin norepinephrine reuptake inhibitors or bupropion at the minimum effective ADT dosage or greater. Patients were randomized to receive oral lumateperone 42 mg or placebo once daily and al patients continued their background ADT.

Studies 5 and 6 Endpoints:

In Study 5 and 6, the primary endpoint was change from baseline to Week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score in the lumateperone + ADT group compared to the placebo + ADT group. The key secondary endpoint was the change from baseline to Week 6 in the Clinical Global Impression Scale-Severity (CGI-S) score. The CGI-S is a validated clinician-rated scale that measures the patient's current illness state on a 1 (normal, not at all il) to 7-point (extremely ill) scale.

Studies 5 and 6 Baseline Demographics:

- In Study 5, a total of 485 patients were randomized to receive lumateperone 42 mg + ADT or placebo + ADT. Demographic and baseline characteristics were similar for the LUMATEPERONE and placebo groups. Median age was 46 (range 18 to 65). 66% were female, 77% were White, 15% were Asian, and 7% were Black.
- In Study 6, a total of 480 patients were randomized to receive lumateperone 42 mg + ADT or placebo + ADT. Demographic and baseline characteristics were similar for the lumateperone and placebo groups. Median age was 48 (range 18 to 65). 70% were female, 95% were White.

Studies 5 and 6 Efficacy Results:

In Studies 5 and 6, patients randomized to lumateperone 42 mg + ADT showed a statistically significant improvement from baseline to day 43 in the MADRS total score and CGI-S score compared to the placebo + ADT group. The results of Study 5 and Study 6 are shown in the Table.

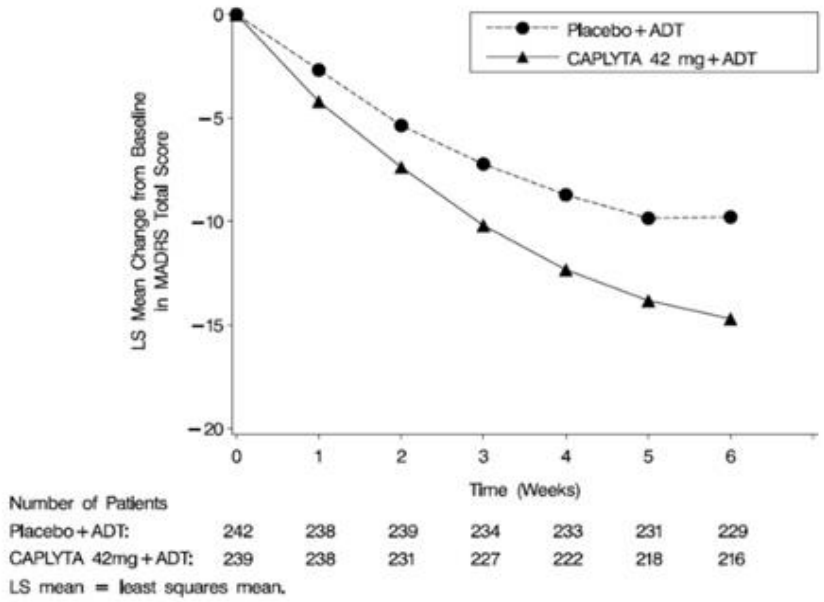
Examination of subgroups by age, sex, race, and ADT class did not suggest differences in response in these studies.

Table: Primary Efficacy Results from Adjunctive MDD Trials (Studies 5 and 6)

			Primary Efficacy Endpoint: PANSS Total Score		
Study Number	**Treatment Group**	**N**	**Mean Baseline Score (SD)**	**LS Mean Change from Baseline (SE)**	**Placebo subtracted Difference (95% CI)**
5.	Lumateperone (42 mg) + ADT*	239	30.4 (3.75)	-14.7 (0.54)	-4.9 (-6.38, -3.44)
	Placebo + ADT	242	30.1 (3.50)	-9.8 (0.53)	-
6.	Lumateperone (42 mg) + ADT*	232	30.8 (3.88)	-14.7 (0.56)	-4.5 (-6.03, -3.02)
	Placebo + ADT	237	31.5 (3.97)	-10.2 (0.54)	-

The MADRS total score ranges from 0 to 60; higher scores reflect greater symptom severity SD: standard deviation; SE: standard error; LS Mean: least squares mean; CI: confidence interval
a Difference (lumateperone + ADT minus placebo + ADT) in LS mean change from baseline
*Lumateperone + ADT statistically significantly superior to placebo + ADT.

Figure: Change from Baseline in MADRS Total Score by Time (Weeks) in Patients with MDD (Adjunctive Treatment) in Study 5



5.3. Pharmacokinetic properties

Following once daily oral administration of lumateperone, lumateperone steady state is reached in about 5 days. Lumateperone steady-state exposure is approximately dose proportional in the range of 3.5 mg to 56 mg (0.08 to 1.3 times the approved recommended daily dosage). A large inter-subject variability in lumateperone PK parameters was observed, with coefficients of variation for C_{max} (peak plasma concentration) and AUC (area under the concentration vs time curve) ranging from 68% to 97% at steady state.

Absorption

After lumateperone dosing, the absolute bioavailability of lumateperone is about 4.4%. C_{max} of lumateperone is reached approximately 1-2 hours after lumateperone dosing.

Effect of Food:

Ingestion of a high-fat meal with lumateperone lowered lumateperone mean C_{max} by 33% and increased mean AUC by 9%. Median T_{max} was delayed about 1 hour (from 1 hour at fasted state to 2 hours in the presence of food).

Distribution

Protein binding of lumateperone is 97.4% at 5 µM (about 70-fold higher than therapeutic concentrations) in human plasma. The volume of distribution of lumateperone following intravenous administration is about 4.1 L/kg.

Elimination

The clearance of lumateperone is approximately 27.9 L/hour and the terminal half-life is about 18 hours after intravenous administration.

Metabolism

Lumateperone is extensively metabolized with more than twenty metabolites identified in vivo. After a single ^{14}C-labelled oral dose, lumateperone and glucuronidated metabolites represent about 2.8% and 51% of the total plasma radioactivity, respectively. In vitro studies show that multiple enzymes, including but not limited to uridine 5'-diphospho-glucuronosyltransferases (UDP-glucuronosyltransferase, UGT) 1A1, 1A4, and 2B15, aldoketoreductase (AKR)1C1, 1B10, and 1C4, and cytochrome P450 (CYP) 3A4, 2C8, and 1A2, are involved in the metabolism of lumateperone.

Excretion:

In a human mass-balance study, 58% and 29% of the radioactive dose was recovered in the urine and feces, respectively. Less than 1% of the dose was excreted as unchanged lumateperone in the urine.

Specific Populations

No clinically significant differences in the pharmacokinetics of lumateperone were observed based on age, sex, or race.

Patients with Hepatic Impairment

The pharmacokinetics of lumateperone were evaluated in patients with varying degrees of hepatic impairment (HI) and in those with normal hepatic function following administration of a single 14 mg dose of lumateperone. The below table displays the geometric mean ratios (90% confidence intervals) of lumateperone pharmacokinetic parameters in lumateperone - treated patients with varying degrees of HI to those with normal hepatic function.

Table: Geometric Mean Ratios (90% confidence interval) of Lumateperone Pharmacokinetic Parameters in lumateperone-treated Patients with Hepatic Impairment

	AUC_t	**C_{max}**
Mild HI (Child-Pugh Class A)	1.1 (0.8, 1.7)	1.4 (0.8, 2.3)
Moderate HI (Child-Pugh Class B)	2.4 (1.6, 3.6)	2 (1.2, 3.2)
Severe HI (Child-Pugh Class C)	1.8 (1.2, 2.8)	1.6 (0.9, 2.6)

Patients with Renal Impairment

The pharmacokinetics of lumateperone were evaluated in patients with varying degrees of renal impairment (RI) and in those with normal renal function following administration of a single 14 mg dose of lumateperone. The below table displays the geometric mean ratios (90% confidence intervals) of lumateperone pharmacokinetic parameters in lumateperone-treated patients with varying degrees of RI to those with normal renal function (eGFR > 90 mL/minute/1.73 m^2).

Table: Geometric Mean Ratios (90% confidence interval) of Lumateperone Pharmacokinetic Parameters in lumateperone treated Patients with Renal Impairment

	AUC_t	**C_{max}**
Mild RI (eGFR of 60 - 89 mL/minute/1.73 m^2)	0.54 (0.31, 0.92)	0.62 (0.35, 1.10)
Moderate RI (eGFR of 30 - 59 mL/minute/1.73 m^2)	1 (0.6, 1.8) *	1 (0.6, 1.9) *
Severe RI (eGFR ≤ 29 mL/minute/1.73 m^2)	1.5 (0.8, 2.6)	1.4 (0.8, 2.4)

*****The pharmacokinetics were unchanged.

Drug Interaction Studies

Clinical Studies:

Strong CYP3A4 Inhibitors:

Itraconazole (strong CYP3A4 inhibitor) increased geometric mean (90% confidence interval) of lumateperone AUC_t by 3.8-fold (3.2, 4.5) and lumateperone C_{max} by 3.2-fold (2.8 – 3.7).

Moderate CYP3A4 Inhibitors:

Diltiazem (moderate CYP3A4 inhibitor) increased geometric mean (90% confidence interval) of lumateperone AUC by 2.3-fold (1.6, 3.3) and lumateperone C_{max} by 1.9-fold (1.3, 2.6).

Strong CYP3A4 Inducers:

Rifampin (strong CYP3A4 inducer) decreased geometric mean (90% confidence interval) of lumateperone AUC by 98% (96%, 99%) and lumateperone C_{max} by 92% (87%, 95%).

UGT inhibitors:

There were no clinically significant drug interactions with the UGT inhibitors probenecid and valproic acid.

CYP3A4 substrates:

No clinically significant differences in the pharmacokinetics of midazolam (CYP3A4 substrate) or its metabolite 1-hydroxymidazolam were observed when used concomitantly with single or multiple doses of lumateperone in patients with schizophrenia.

In Vitro Studies:

Lumateperone showed little to no inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. It showed no induction of CYP1A2, CYP2B6, or CYP3A4.

Lumateperone did not appear to be a P-gp or BCRP substrate. It showed little to no inhibition of OCT2, OAT1, OAT3, OATP1B3, or OATP1B1**.**

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in rats and mice, and results showed no carcinogenic potential in either species.

In Sprague-Dawley rats, males were administered lumateperone (free base) at oral doses of 3.5, 7 or 14 mg/kg/day and females were administered lumateperone at oral doses of 3.5, 10.5, or 21 mg/kg/day for the first 385 days, then doses were reduced for the two higher dose groups so that the females were administered 3.5, 7 or 14 mg/kg/day, respectively, for the duration of the study. In this study the no adverse effect level for neoplastic lesions was determined to be 14 mg/kg/day (84 mg/m^2 /day) for males and 10.5/7 mg/kg/day (42 mg/m^2 /day) for females, which are 1.6 times (females) to 3.2 times (males) the MRHD on a mg/m^2 basis.

Male and female CD-1 mice were administered lumateperone at oral doses of 3.5, 10.5 or 21 mg/kg/day for the first 35 days, then doses were reduced to 1.4, 4.9, and 14 mg/kg/day, respectively, for the duration of the study. In this study, the no adverse effect level for neoplastic lesions was determined to be 10.5/4.9 mg/kg/day (15 mg/m^2 /day) for each sex which is 0.6 times the MRHD on a mg/m^2 basis.

Mutagenesis

No evidence of mutagenic potential was found in the in vitro bacterial reverse mutation assay (Ames test) and the mouse lymphoma test without metabolic activation. Lumateperone was positive in the Ames test only in the presence of metabolic activation and only in the TA1537 strain and was positive in the mouse lymphoma test only in the presence of metabolic activation and only at high concentrations that inhibited cell growth; together these results were thought to be related to solubility limits and/or nonspecific effects on cellular function. Lumateperone was negative for clastogenic activity in the in vivo micronucleus assay in rats and was not genotoxic in the in vivo Comet assay in rats.

Impairment of Fertility

Female rats were treated with oral doses of 3.5, 10.5, 21 or 42 mg/kg/day lumateperone (free base) (0.8, 2.4, 4.9, and 9.7 times the MRHD on a mg/ m^2 basis) prior to mating and continuing through conception and implantation. Estrus cycle irregularities were observed at doses ≥10.5 mg/kg/day. Decreases in the median number of corpora lutea and implantation sites, and increases in the number of non-gravid uteruses, were recorded at 42 mg/kg/day. Decreased gestation body weight and body weight gain, and increases in time to mating, were observed at 21 and 42 mg/kg/day.

Male rats were treated with oral doses of 3.5, 10.5, 21 or 42 mg/kg/day lumateperone (0.8, 2.4, 4.9, and 9.7 times the MRHD on a mg/ m^2 basis) for 9 weeks prior to mating and throughout 14 days of mating. Decreased sperm motility, changes in sperm morphology, reduced epididymal counts, and adverse histopathology changes in testes and epididymides were observed at 21 and 42 mg/kg/day.

Animal Toxicology and/or Pharmacology

Oral administration of lumateperone caused systemic intracytoplasmic accumulation of pigmented material in dogs, rats, and mice at clinically relevant exposures (AUC). Intracytoplasmic pigmentation appeared to be localized in lysosomes. Accumulation of pigmented material persisted without reversal at the end of 1- to 2-month drug-free periods. Pigmented material was observed in the brain and spinal cord of all three species, and in the heart and eye of rats. Although the composition of the pigmented material was not established, the material is likely polymers or protein adducts formed from aniline metabolites of lumateperone.

In the dog, accumulation of pigmented material in the brain and spinal cord was associated with neuronal degeneration and necrosis, followed by axonal degeneration and histiocytic inflammation after oral administration of lumateperone for up to 9 months. In the rat, accumulation of pigmented material was associated with degenerative changes and signs of an inflammatory response in the spinal cord, peripheral nervous system, eye, and heart after oral administration of lumateperone for up to 2 years. Although overt degenerative changes were not observed in the rat brain, the presence of pigment-containing infiltrating macrophages is consistent with an inflammatory response.

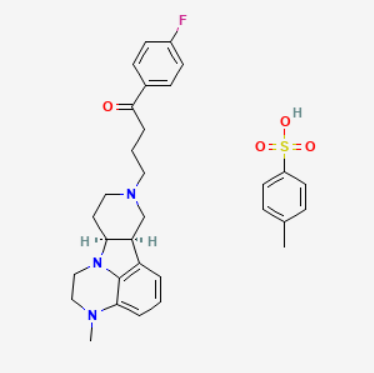
The role of intracytoplasmic pigmented material in causing these lesions was not definitively established; however, the colocalization of pigmented material in tissues with degenerative changes and signs of inflammation is supportive. Alternatively, the aniline metabolites of lumateperone may undergo metabolic activation forming reactive metabolites that contribute to the observed toxicities. The role of intracellular accumulation of lumateperone or its non-aniline metabolites in these toxicities could not be ruled out.

The aniline metabolites thought to be responsible for these toxicities were detected in dogs and rats but were not present in humans at quantifiable levels. Based on all the available evidence, these toxicities do not appear to be relevant to humans.

7. Description

Lumateperone tosylate:

Lumateperone tosylate is 1-(4-fluorophenyl)-4-[(10R,15S)-4-methyl-1,4,12-triazatetracyclo [7.6.1.05,16.010,15] hexadeca-5,7,9(16)-trien-12-yl] butan-1-one;4-methylbenzenesulfonic acid. The empirical formula is $C_{31}H_{36}FN_3O_4S$, and its molecular weight is 565.7 g/mol. The chemical structure of Lumateperone tosylate is:



Lumateperone tosylate:

Lumateperone tosylate capsule is a hard gelatin capsule of size "0" having maroon opaque cap and yellow opaque body containing off white powder. The excipients used are Mannitol, Microcrystalline cellulose, Croscarmellose Sodium, Colloidal silicon dioxide, Purified Talc.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

Lumateperone Capsules is available in pack of 10 Capsules.

8.4. Storage and handing instructions

Store at temperature not exceeding 30°C. Keep the medicine out of reach of children.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Exemed Pharmaceuticals

Plot No.133/1 & 133/2, G.I.D.C.,

Selvas Road, Vapi-396 195,

Dist.: Valsad, Gujarat State, INDIA

11. Details of permission or licence number with date

Mfg. License. No: G/25/2011. Issued on 09.12.2025.

12. Date of revision

NA

MARKETED BY

TORRENT PHARMA

TORRENT PHARMACEUTICALS LTD.

IN/LUMAVIBE/FEB-2026/01/PI