# Lumateperone (Caplyta®)

## Classification

Atypical antipsychotic

## Pharmacology

The mechanism of action of lumateperone tosylate (Caplyta, ITI-007) in the treatment of schizophrenia is unknown but it's thought to simultaneously modulate serotonin, dopamine, and glutamate neurotransmission. Specifically, lumateperone acts as a potent 5-$HT_{2A}$ receptor antagonist, a $D_2$ receptor presynaptic partial agonist and postsynaptic antagonist, a $D_1$ receptor-dependent modulator of glutamate, and a serotonin reuptake inhibitor.

## Indication

Treatment of schizophrenia in adults

## Boxed Warning

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Caplyta is not approved for the treatment of patients with dementia-related psychosis.

## Pharmacokinetics

| Pharmacokinetic Parameter | Details |
|---|---|
| **Absorption** | Rapidly absorbed. Absolute bioavailability is about 4.4%. $C_{max}$ reached approximately 1 (fasting) to 2 h (food) post dosing. Ingestion of high fat meal lowers mean $C_{max}$ by 33% and increases mean AUC by 9% |
| **Distribution** | Protein binding = 97.4%. Volume of distribution (IV) = 4.1 L/kg |
| **Metabolism** | Extensively metabolized. $T_{1/2}$ = 13-21 hours for lumateperone and metabolites |
| **Excretion** | Less than 1% excreted unchanged in urine |

# Dosage/Administration

42 mg by mouth once daily with food. Dose titration is not required.

# Use in Special Population

Pregnancy

Neonates exposed to antipsychotic drugs during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Available data from Caplyta 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 untreated schizophrenia and with exposure to antipsychotics, including Caplyta, during pregnancy. The expected background risk of major birth defects and miscarriage for the indicated population is unknown. All 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.

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including Caplyta, 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/clinical-and-researchprograms/pregnancyregistry/.

Lactation

There are no available data on the presence of lumateperone or its metabolites in human milk or animal milk, the effects on the breastfed infant, or the effects on milk production. Toxicity in animals has been linked to the formation of aniline metabolites of lumateperone. Although aniline metabolites were not present in (adult) humans at quantifiable levels, it is unknown whether infants exposed to lumateperone will exhibit comparable lumateperone metabolism and elimination pathways as adults. In addition, there are published reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to antipsychotics. Based on findings of toxicity in animal studies and the potential for serious adverse reactions in the breastfed infant, **breastfeeding is not recommended during treatment with Lumateperone**.

Females and Males of Reproductive Potential

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

Pediatric Use

Safety and effectiveness of Caplyta have not been established in pediatric patients.

Geriatric Use

Controlled clinical studies of Caplyta did not include any patients aged 65 or older to determine whether or not they respond differently from younger patients.

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

Hepatic Impairment

Use of Caplyta is not recommended for patients with moderate (Child-Pugh class B) to severe hepatic impairment (Child-Pugh class C). Patients with moderate and severe hepatic impairment experienced higher exposure to lumateperone. No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A).

# Contraindication

Patients with history of hypersensitivity reaction to lumateperone. Reactions have included pruritus, rash (e.g. allergic dermatitis, popular rash, and generalized rash), and urticaria.

# Precautions

### 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. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in placebo treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Caplyta is not approved for the treatment of patients with dementia-related psychosis.

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

In placebo-controlled trials in elderly subjects with dementia, patients randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and

transient ischemic attack, including fatal stroke. Caplyta is not approved for the treatment of patients with dementia-related psychosis.

### Neuroleptic Malignant Syndrome (NMS)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, delirium, and autonomic instability. Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If NMS is suspected, immediately discontinue Caplyta and provide intensive symptomatic treatment and monitoring.

### Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk appears to be highest among the elderly, especially elderly women, but it is not possible to predict which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of tardive dyskinesia and the likelihood that it will become irreversible increase with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia 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 tardive dyskinesia is unknown.

Given these considerations, Caplyta should be prescribed in a manner most likely to reduce the risk of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: 1) who suffer from a chronic illness that is known to respond to antipsychotic drugs; and 2) for whom alternative, effective, but potentially less harmful treatments are not available or appropriate. 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.

If signs and symptoms of tardive dyskinesia appear in a patient on Caplyta, drug discontinuation should be considered. However, some patients may require treatment with Caplyta despite the presence of the syndrome.

### Metabolic Changes

Hyperglycemia and Diabetes Mellitus

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 in patients treated with Caplyta were similar to those in patients treated with placebo.
In an uncontrolled open-label trial of Caplyta for up to 1 year in 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. 4.7% of patients with normal hemoglobin A1c (<6.5%) at baseline developed elevated levels (≥6.5%) post-baseline.

Dyslipidemia

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 patients treated with Caplyta and placebo.
In an uncontrolled open-label trial of Caplyta 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.

Weight Gain

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 patients treated with Caplyta and placebo.
In an uncontrolled open-label trial of Caplyta for up to 1 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.

### Leukopenia, Neutropenia, and Agranulocytosis

Leukopenia and neutropenia have been reported during treatment with antipsychotic agents, including Caplyta. Agranulocytosis (including fatal cases) has been reported with other agents in the class.
Possible risk factors for 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 a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of Caplyta 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 Caplyta in patients with absolute neutrophil count < 1000/mm and follow their WBC until recovery.

### Orthostatic Hypotension and Syncope

Atypical antipsychotics cause orthostatic hypotension and syncope. Generally, the risk is greatest during initial dose administration. In these clinical trials the frequencies of orthostatic hypotension for Caplyta and placebo were 0.7% and 0%, respectively. The rates of syncope for Caplyta and placebo were 0.2% and 0.2%. 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 medications), patients with known cardiovascular disease (history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease. Caplyta 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.

### Falls

Antipsychotics, including Caplyta, may cause somnolence, postural hypotension, and motor and sensory instability, which may lead to falls and, consequently, fractures and other injuries. For patients with diseases, conditions or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and periodically during long-term treatment.

### Seizures

Like other antipsychotic drugs, Caplyta may cause seizures. The risk 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.

## Adverse Effects

The safety of Caplyta has been evaluated in 1724 adult patients with schizophrenia exposed to one or more doses. Of these patients, 811 participated in short-term (4- to 6-week), placebo-controlled trials with doses ranging from 14 to 84 mg/day. A total of 329 Caplyta-exposed patients had at least 6 months of exposure and 108 had at least 1 year of exposure to the 42-mg dose of Caplyta.

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

The most common adverse reactions (incidence of at least 5% of patients exposed to Caplyta and greater than twice the rate of placebo) are somnolence/sedation and dry mouth.

Adverse reactions associated with Caplyta (incidence of at least 2% in patients exposed to Caplyta and greater than placebo) are shown in the table below. The following findings are based on the pooled short-term (4- to 6-week), placebo-controlled studies in adult patients with schizophrenia in which Caplyta was administered at a daily dose of 42 mg (N=406).

| Adverse Reaction | Caplyta 42 mg (n = 406) | Placebo (n = 412) |
|---|---|---|
| Somnolence/sedation | 24% | 10% |
| Nausea | 9% | 5% |
| Dry mouth | 6% | 2% |
| Dizziness | 5% | 3% |
| Creatinine Phosphokinase Increased | 4% | 1% |
| Fatigue | 3% | 1% |
| Vomiting | 3% | 2% |
| Hepatic Transaminases Increased | 2% | 1% |
| Decreased Appetite | 2% | 1% |

**Extrapyramidal Symptoms**

In the 4- to 6-week, placebo-controlled trials, the frequency of reported events related to extrapyramidal symptoms (EPS), 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 Caplyta and 6.3% for placebo.

In the 4- to 6-week trials, data were collected using 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). The mean changes from baseline for Caplyta-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.

# Monitoring

See HHS Atypical Antipsychotic Audit Criteria

# Interactions

**Moderate or Strong CYP3A4 Inhibitors**

Concomitant use with moderate or strong CYP3A4 inhibitors increases lumateperone exposure which may increase the risk of adverse reactions. Avoid concomitant use.

- Moderate inhibitors: amprenavir, ciprofloxacin, cyclosporine, diltiazem, erythromycin, fluconazole, fluvoxamine, verapamil.
- Strong inhibitors: clarithromycin, grapefruit juice, itraconazole, voriconazole, nefazodone, ritonavir, nelfinavir

**CYP3A4 Inducers**

Concomitant use with CYP3A4 inducers decreases the exposure of lumateperone. Avoid concomitant use. Examples: Carbamazepine, phenytoin, rifampin, St. John's wort, bosentan, efavirenz, etravirine, modafinil, nafcillin, aprepitant, armodafinil, pioglitazone, prednisone

**UGT Inhibitors**

Concomitant use may increase the exposure of lumateperone and/or its metabolites. Avoid concomitant use. Examples: valproic acid, probenecid

# Efficacy

## Lieberman study

In a phase II, randomized, double-blind, placebo- and active-controlled trial, Lieberman and colleagues randomized 335 adults (18 to 55 yo) with schizophrenia to a four-week inpatient trial of one of four treatment options.

| **Safety Population** | **Placebo** n = 85 | **Caplyta 42 mg** n = 84 | **Caplyta 84 mg** n = 83 | **Risperidone 4 mg** n = 82 |
|---|---|---|---|---|
| Male, n (%) | 65 (76.5) | 66 (78.6) | 72 (86.7) | 73 (89.0) |
| Age (years, mean ± SD), percent ≤ 40 years | 40.5 ± 9.8, 47.1 | 38.3 ± 10.0, 54.8 | 41.1 ± 8.9, 43.4 | 40.7 ± 9.3, 43.9 |
| Race, n (%) Black | 65 (76.5) | 70 (83.3) | 62 (74.7) | 64 (78.0) |
| Race, n (%) White | 17 (20.0) | 13 (15.5) | 16 (19.3) | 16 (19.5) |
| Race, n (%) Asian | 1 (1.2) | 0 | 0 | 2 (2.4) |
| Race, n (%) Other | 2 (2.4) | 1 (1.2) | 5 (6.0) | 0 |

Study participants had a history of previous treatment response to antipsychotics and were experiencing an acute episode of psychosis which started within four weeks of study screening. Antipsychotics were discontinued at the start of the screening period. Eighty-one percent of the subjects completed study treatment.

| **Parameter** | **Placebo n = 80** | **Caplyta 42 mg n = 76** | **Caplyta 84 mg n = 80** | **Risperidone 4 mg n = 75** |
|---|---|---|---|---|
| BL TOTAL PANSS, mean ± SD | 86.3 ± 13.1 | 88.1 ± 11.0 | 84.6 ± 11.6 | 86.1 ± 12.2 |

| Parameter | Placebo n = 80 | Caplyta 42 mg n = 76 | Caplyta 84 mg n = 80 | Risperidone 4 mg n = 75 |
|---|---|---|---|---|
| BL Positive symptoms subscale, mean ± SD | 24.6 ± 4.6 | 24.8 ± 4.2 | 23.8 ± 4.5 | 24.2 ± 4.1 |
| BL Negative symptoms subscale, mean ± SD | 19.8 ± 4.8 | 21.0 ± 4.1 | 19.8 ± 4.1 | 20.7 ± 5.1 |

Patients who met any of the following criteria were excluded from the study: inability to provide informed consent; pregnant/breastfeeding; dementia/delirium/mental retardation/epilepsy/drug-induced psychosis/brain trauma; schizoaffective disorder/bipolar disorder/acute mania/major depression with psychotic features; imminent danger to self or others; suicidal ideation/behavior; unstable living environment; use of depot antipsychotic within one treatment cycle before baseline; use of any antipsychotic within seven-day screening period; use of specific agents with known interaction with 5-HT2A receptors; clinically significant abnormal lab values or clinical findings; uncontrolled angina/recent history of myocardial infarction/clinically significant cardiac arrhythmia;
hematological/renal/hepatic/endocrinological/neurological/cardiovascular disease; history of neuroleptic malignant syndrome; HIV; hepatitis B or C with evidence of active liver disease; substance abuse/dependence; positive drug/alcohol screen; likely drug allergy/sensitivity; prior participation in a study with ITI-007 or recent exposure to any investigational product; unable to be safely discontinued from current antipsychotic or other psychotropic medications.

On the primary end point (change from baseline on the total PANSS to day 28), Caplyta 42 mg significantly improved schizophrenia symptoms compared with placebo (least squares[LS] mean change -13.2 points vs. 7.4 points; p = 0.017, effect size = 0.4. Caplyta 84 mg did not significantly separate from placebo on the total PANSS at day 28 (LS mean change -8.3 vs. -7.4; p = 0.708). In a demonstration of assay sensitivity, risperidone (4 mg) differed from placebo on the total PANSS, (LS mean change -13.4 points vs. -7.4 points; p = 0.013, effect size = 0.4). Negative symptoms improved with Caplyta 42 mg (not statistically significant).

| Total PANSS | LS Mean (± SEM) change from BL on Day 28 | LS Mean Difference from placebo (rounded) | p value | Effect size |
|---|---|---|---|---|
| Placebo | -7.4 ± 1.68 | na | na | na |
| Caplyta 42 mg | -13.2 ± 1.69 | -5.8 | 0.017 | 0.4 |

| Total PANSS | LS Mean (± SEM) change from BL on Day 28 | LS Mean Difference from placebo (rounded) | p value | Effect size |
|---|---|---|---|---|
| Caplyta 84 mg | -8.3 ± 1.68 | -0.9 | 0.708 | .07 |
| Risperidone 4 mg | -13.4 ± 1.72 | -6.0 | 0.013 | 0.4 |

| PANSS Positive subscale | LS Mean (± SEM) change from BL on Day 28 | LS Mean Difference from placebo (rounded) | p value | Effect size |
|---|---|---|---|---|
| Placebo | -2.3 ± 0.5 | na | na | na |
| Caplyta 42 mg | -4.7 ± 0.5 | -2.4 | 0.002 | .50 |
| Caplyta 84 mg | -3.2 ± 0.5 | -0.8 | 0.272 | .17 |
| Risperidone 4 mg | -4.8 ± 0.5 | -2.4 | 0.002 | .51 |

| PANSS Negative subscale | LS Mean (± SEM) change from BL on Day 28 | LS Mean Difference from placebo (rounded) | p value | Effect size |
|---|---|---|---|---|
| Placebo | -0.3 ± 0.5 | na | na | na |
| Caplyta 42 mg | -1.2 ± 0.5 | -0.9 | 0.230 | .19 |
| Caplyta 84 mg | 0.5 ± 0.5 | 0.7 | 0.319 | .16 |
| Risperidone 4 mg | -0.4 ± 0.5 | -0.1 | 0.914 | .02 |

Response was defined as a > 30% reduction in PANSS score. Responder rates were similar between the Caplyta 42 mg and risperidone 4 mg groups.

| Comparator | n (%) | Rate Difference % (95% CI) | p value |
|---|---|---|---|
| Placebo (n = 80) | 18 (22.5) | na | na |
| Caplyta 42 mg (n = 76) | 31 (40.8) | 18.3 (3.9, 32.6) | 0.014 |
| Caplyta 84 mg (n = 80) | 20 (25.0) | 2.5 (-10.7, 15.7) | 0.711 |
| Risperidone 4 mg (n = 75) | 30 (40.0) | 17.5 (3.1, 31.9) | 0.019 |

At baseline (a priori), Lieberman and colleagues also identified subgroups of patients with prominent negative and depressive symptoms. About a third of study participants had prominent negative symptoms (see table below), defined as a score of ≥ 4 on ≥ 3 items on the PANSS negative symptoms subscale (blunted affect, emotional withdrawal, poor rapport, passive apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking). In this subgroup of patients, Caplyta 42 mg reduced symptom severity compared to placebo. The aim of the subgroup analyses was to

illustrate magnitude of response (effect size); they were not powered to detect statistically significant differences.

| Parameter | Placebo n = 29 | Caplyta 42 mg n = 33 | Caplyta 84 mg n = 25 | Risperidone 4 mg n = 33 |
|---|---|---|---|---|
| Negative symptoms subscale, mean ± SD | 23.3 ± 4.2 | 23.5 ± 3.1 | 23.9 ± 3.0 | 23.2 ± 3.9 |

| Comparator | Mean (± SEM) change from BL on Day 28 | Mean difference from placebo (rounded) | p value | Effect size |
|---|---|---|---|---|
| Placebo (n = 29) | -1.3 ± 0.92 | na | na | na |
| Caplyta 42 mg (n = 33) | -3.0 ± 0.88 | -1.6 | 0.206 | 0.34 |
| Caplyta 84 mg (n = 25) | -1.1 ± 0.93 | 0.2 | 0.865 | 0 |
| Risperidone 4 mg (n = 33) | -1.2 ± 0.80 | 0.2 | 0.893 | 0 |

Individuals in the prominent depressive symptoms subgroup (see table below) had a Calgary Depression Scale for Schizophrenia (CDSS) score > 6) and higher baseline PANSS scores. Caplyta 42 mg significantly reduced total PANSS score and the CDSS score in the subgroup of patients with prominent depressive symptoms.

| Parameter | Placebo n = 14 | Caplyta 42 mg n = 7 | Caplyta 84 mg n = 13 | Risperidone 4 mg n = 11 |
|---|---|---|---|---|
| **Baseline PANSS** | 91.9 ± 10.9 | 95.1 ± 11.1 | 85.3 ± 15.4 | 92.7 ± 12.5 |

| Comparator | Mean (± SEM) change from BL on Day 28 | Mean Difference from Placebo (Rounded) | p value | Effect size |
|---|---|---|---|---|
| Placebo | -12.4 ± 3.89 | n/a | n/a | n/a |
| Caplyta 42 mg | -31.7 ± 7.31 | -19.4 | 0.018 | 1.13 |
| Caplyta 84 mg | -14.2 ± 3.51 | -1.8 | 0.736 | .14 |
| Risperidone 4 mg | -20.6 ± 3.89 | -8.3 | 0.152 | .60 |

| Parameter | Placebo n = 14 | Caplyta 42 mg n = 7 | Caplyta 84 mg n = 13 | Risperidone 4 mg n = 11 |
|---|---|---|---|---|
| Baseline CDSS | 9.3 ± 2.8 | 8.0 ± 1.0 | 8.9 ± 1.7 | 9.8 ± 2.6 |

| Comparator | Mean (± SEM) change from BL on Day 28 | Mean Difference from Placebo (Rounded) | p value | Effect size |
|---|---|---|---|---|
| Placebo | -5.4 ± 1.00 | n/a | n/a | n/a |
| Caplyta 42 mg | -7.7 ± .42 | -2.4 | 0.044 | .99 |

| Comparator | Mean (± SEM) change from BL on Day 28 | Mean Difference from Placebo (Rounded) | p value | Effect size |
|---|---|---|---|---|
| Caplyta 84 mg | -5.6 ± .74 | -.3 | 0.839 | .09 |
| Risperidone 4 mg | -7.2 ± 1.31 | -1.8 | 0.271 | .48 |

Because of the above improvements in negative and depressive symptoms, the authors performed a post hoc analysis of the PANSS-derived prosocial factor. Caplyta 42 mg significantly ($p < 0.001$) improved prosocial behavior with an effect size of 0.6.

| Post Hoc Analysis of PANSS-Derived Prosocial Factor | LS Mean (± SEM) change from BL on Day 28 | LS Mean Difference from placebo (rounded) | p value | Effect size |
|---|---|---|---|---|
| Placebo (n = 80) | -2.5 ± .5 | n/a | n/a | n/a |
| Caplyta 42 mg (n = 76) | -5.0 ± .5 | -2.5 | < .001 | .59 |
| Caplyta 84 mg (n = 80) | -3.3 ± .5 | -0.8 | 0.243 | .19 |
| Risperidone 4 mg (n = 75) | -4.2 ± .5 | -1.7 | 0.01 | .42 |

## Correll study

In a phase 3, randomized, 4-week, double-blind, placebo-controlled inpatient trial, Correll and colleagues examined the efficacy and safety of lumateperone for the short-term treatment of schizophrenia. Eligible participants were aged 18 to 60 years who had been diagnosed with schizophrenia (DSM-5) and were experiencing an acute exacerbation of schizophrenia (onset within four weeks of screening).

Inclusion criteria at baseline included the following: Positive and Negative Syndrome Scale (PANSS) total score of 70 or higher indicating moderate to extreme symptoms; previous response to antipsychotic therapy; CGI-S score of 4 or higher.

Investigators randomized 450 patients (1:1:1) to 42 mg of lumateperone (60 mg lumateperone tosylate), 28 mg of lumateperone (40 mg lumateperone tosylate), or placebo. Treatments were administered once daily in the morning. The primary efficacy end-point was the mean change from baseline to day 28 on the PANNS total score versus placebo. Secondary efficacy measures included CGI-S score, PANSS positive, negative, and general psychopathology subscales, the Personal and Social performance (PSP) scale, the PANSS-derived prosocial factor (P3, P6, N2, N4, N7, and G16), and the Calgary Depression Scale for Schizophrenia.

Study completion rates were 85.3%, 80.0%, and 74.0% in the lumateperone 42 mg, 28 mg, and placebo groups, respectively. A follow-up safety assessment was performed approximately two weeks after the last dose of study medication.

Demographic and baseline characteristics were similar across groups. See below.

| Demographic Characteristic | Lumateperone 42 mg (n = 150) | Lumateperone 28 mg (n = 150) | Placebo (n = 149) | Total (n = 449) |
|---|---|---|---|---|
| Male | 110 (73.3) | 113 (75.3) | 123 (82.6) | 346 (77.1) |
| Age, mean (SD), y | 42.4 (10.3) | 43.5 (10.1) | 41.4 (10.3) | 42.4 (10.2) |
| Age $\leq$ 40 y | 62 (41.3) | 56 (37.3) | 71 (47.7) | 189 (42.1) |
| Race/ethnicity | | | | |
| Black | 108 (72.0) | 94 (62.7) | 96 (64.4) | 298 (66.4) |
| White | 33 (22.0) | 42 (28.0) | 42 (28.2) | 117 (26.1) |
| Other | 9 (6.0) | 14 (9.3) | 11 (7.4) | 34 (7.6) |
| BMI, mean (SD) | 28.7 (5.4) | 28.4 (5.1) | 28.2 (5.3) | 28.4 (5.3) |
| PANSS total score, mean (SD) | 90.1 (9.5) | 89.3 (10.2) | 90.1 (11.1) | 89.8 (10.3) |
| PANSS + symptom subscale score, mean (SD) | 26.0 (3.5) | 25.8 (3.9) | 25.8 (3.9) | 25.9 (3.8) |
| PANSS - symptom subscale score, mean (SD) | 20.6 (3.8) | 20.4 (4.2) | 21.0 (4.4) | 20.7 (4.1) |
| PANSS prosocial subscale score, mean (SD) | 25.0 (3.4) | 24.5 (3.5) | 24.3 (3.3) | 24.6 (3.4) |
| PSP scale score, mean (SD) | 47.8 (11.9) | 48.2 (12.2) | 47.7 (12.4) | 47.9 (12.2) |

The study's primary outcome was the mean change from baseline to day 28 on the PANSS total score vs placebo. After four weeks, the least squares mean change (SE) was -14.5 (1.3) in patients treated with lumateperone 42 mg, -12.9 (1.3) in patients treated with lumateperone 28 mg, -10.3 (1.3) in patients treated with placebo (least squares mean difference = -4.2 (95% CI -7.8 to -0.6; effect size, 0.3; multiplicity-adjusted P = 0.04). In patients treated with lumateperone 42 mg, statistically significant differences from placebo in PANSS total score were observed at day 8 and continued through day 28. Response was defined as > 30% improvement in PANSS total score. 54 patients (36.5%) treated with lumateperone 42 mg, 53 patients (36.3%) treated with lumateperone 28 mg, and 36 placebo treated patients (25.5%) met the criterion for response.

Compared to placebo, patients treated with lumateperone 42 mg demonstrated statistically significant improvement on the PANSS-derived prosocial factor (centrally rated) and the Personal and Social Performance scale (PSP, site-rated). The PANSS-derived prosocial factor is made up of the following six items: active social avoidance (G16), passive social withdrawal (N4), emotional withdrawal (N2), stereotyped thinking (N7), hallucinatory behavior (P3), and suspiciousness/persecution (P6). Being that this was an acutely ill population, it's possible that the improvement on the prosocial factor was secondary to improvement in positive symptoms.

Compared to placebo, neither the 42 mg nor the 28 mg cohorts demonstrated statistically significant improvement on the Calgary Depression Scale for Schizophrenia.

The table below includes the efficacy end point measures in the intent-to-treat population. Changes in the PANSS negative subscale and CDSS score were not significantly different (versus placebo) in either active treatment group.

| **PANSS total score** | **Lumateperone 42 mg** | **Lumateperone 28 mg** | **Placebo** |
|---|---|---|---|
| Change from BL to day 28, LS mean (SE) | -14.5 (1.3) | -12.9 (1.3) | -10.3 (1.3) |
| Difference from placebo, LS mean (95% CI) | -4.2 (-7.8 to -0.6) | -2.6 (-6.2 to 1.1) | NA |
| Effect size | -0.30 | -0.18 | NA |
| Multiplicity adjusted p value | **0.04** | 0.18 | NA |

| **PANSS positive symptom subscale score** | **Lumateperone 42 mg** | **Lumateperone 28 mg** | **Placebo** |
|---|---|---|---|
| Change from BL to day 28, LS mean (SE) | -4.8 (0.42) | -4.4 (0.42) | -3.1 (0.43) |
| Difference from placebo, LS mean (95% CI) | -1.7 (-2.9 to -0.5) | -1.2 (-2.4 to -0.1) | NA |
| Effect size | 0.33 | .24 | NA |
| p value | **0.006** | **0.04** | NA |

| **PANSS negative symptom subscale score** | **Lumateperone 42 mg** | **Lumateperone 28 mg** | **Placebo** |
|---|---|---|---|
| Change from BL to day 28, LS mean (SE) | -1.4 (0.38) | -1.0 (0.38) | -0.5 (0.39) |
| Difference from placebo, LS mean (95% CI) | -0.9 (-2.0 to 0.2) | -0.5 (-1.6 to 0.6) | NA |

| PANSS negative symptom subscale score | Lumateperone 42 mg | Lumateperone 28 mg | Placebo |
|---|---|---|---|
| Effect size | 0.20 | 0.11 | NA |
| p value | 0.09 | 0.36 | NA |

| PANSS-derived prosocial factor score | Lumateperone 42 mg | Lumateperone 28 mg | Placebo |
|---|---|---|---|
| Change from BL to day 28, LS mean (SE) | -4.7 (0.39) | -4.5 (0.39) | -3.6 (0.40) |
| Difference from placebo, LS mean (95% CI) | -1.1 (-2.2 to 0) | -1.0 (-2.1 to 0.2) | NA |
| Effect size | 0.24 | 0.20 | NA |
| p value | **0.04** | 0.09 | NA |

| PSP | Lumateperone 42 mg | Lumateperone 28 mg | Placebo |
|---|---|---|---|
| Change from BL to day 28, LS mean (SE) | 11.0 (1.13) | 10.5 (1.16) | 7.7 (1.22) |
| Difference from placebo, LS mean (95% CI) | 3.3 (0.1 to 6.6) | 2.9 (-0.4 to 6.2) | NA |
| Effect size | 0.26 | 0.23 | NA |
| p value | **0.05** | 0.09 | NA |

# Dosage Forms/Cost

| Name/strength | Wholesale Acquisition Cost (WAC) |
|---|---|
| 42 mg capsule (60 mg lumateperone tosylate) | $44/capsule, $1320/month |

# Special Considerations

| Parameter | Lurasidone | Brexpiprazole | Cariprazine | Lumateperone |
|---|---|---|---|---|
| **Indication** | Adult /adolescent with SCZ<br><br>Adult/ped (10 to 17 yo) with bipolar depression (monotherapy)<br><br>Adjunctive tx with lithium or valproate in adults with bipolar depression | Adjunctive tx of MDD<br>SCZ | SCZ<br>acute tx of manic or mixed epis. in bipolar I in adults<br>bipolar depression | SCZ in adults |
| **MOA** | D2, $5HT_{2a}$, **$5HT_7$** antagonist; 5-HT1A partial agonist | Partial agonist at $D_2$, 5-HT1A; 5-HT2A antagonist | Dopamine 3 preferring D3/D2 partial agonist; 5-HT1A partial agonist; 5-HT2A antagonist | Potent 5-HT2A antagonist, D2 receptor presynaptic partial agonist and postsynaptic antagonist, D1 rec-dependent modulator of glutamate, 5HT reuptake inhibitor |
| **Possible therapeutic benefit** | Depressive symptoms, cognition | | Negative symptoms, depression, cognition | |
| **Cost per mo (WAC)** | ? | $1160 | $1225 | $1320 |
| **Tier** | 1 | 2 | 2 | See below |

# Summary/Conclusion

In the Lieberman study, there was a small, non-statistically significant improvement in PANSS negative subscale score for patients treated with Caplyta 42 mg. Decreases were as follows for patients in the placebo, Caplyta 42 mg and risperidone 4 mg groups: -0.3 (± 0.5), -1.2 (± 0.5), -0.4 (± 0.5). Patients with prominent negative symptoms (n = 120) experienced a slightly bigger improvement, which was statistically significant (-1.3 ± 0.92, -3.0 ± 0.88, -1.2 ± 0.80). Lieberman et al also studied a small group (n = 45) of patients with prominent depressive symptoms. These patients had Calgary Depression Scale for

Schizophrenia (CDSS) scores around 8 or 9 (scores greater than 6 indicate the presence of a major depressive episode). After 28 days, mean changes with placebo, Caplyta 42 mg, and risperidone 4 mg were -5.4, -7.7, and -7.2, respectively.

In the Correll study, negative symptoms improved an average of -1.4 points (± 0.38) versus – 0.5 points (± 0.39) with placebo, not a statistically significant change. Patients in the Correll study did not demonstrate a statistically significant improvement on the CDSS.

Because of Caplyta's possible effects on negative symptoms and depression, researchers also looked The PANSS-derived prosocial factor and the Personal and Social Performance scale (PSP). Lieberman et al's post-hoc analysis of the prosocial factor showed an average improvement of 5 points in the Caplyta 42 mg group, 4.2 points in the risperidone 4 mg group, and 2.5 points in the placebo group. Correll et al showed average improvements of -4.7 (Caplyta 42 mg) and -3.6 (placebo). Since the prosocial factor includes negative symptoms and positive symptoms, it's possible that its improvement is secondary to positive symptoms in these acutely ill populations. In the Correll study, the PSP improved 11 points in the Caplyta 42 mg group versus 7.7 points in the placebo group.

In general, positive symptoms of schizophrenia respond better to antipsychotic therapy than negative and cognitive symptoms. Since the latter two symptom domains greatly interfere with patients' ability to function socially and occupationally, there is a significant unmet clinical need. Since 2010, the FDA has approved four new antipsychotics--lurasidone (Latuda), brexpiprazole (Rexulti), cariprazine (Vraylar), and lumateperone (Caplyta). Each has a unique receptor binding profile that may be associated with enhanced therapeutic effects (see table above). However, the exact mechanism of action of antipsychotic medications is unknown and it's hard to know the true clinical relevance of the receptor profiles mentioned above, the definition of which are mostly based on indirect comparisons and preclinical (animal) data rather than head to head clinical trials. The newest agent, lumateperone (Caplyta) has an interesting mechanism of action and is well tolerated but the available evidence does not demonstrate dramatic improvements in undertreated treatment domains.

# Recommendation

Lumateperone (Caplyta) should be added as a Tier 3 agent.

# References


1. Corponi F, Fabbri C, Bitter I, et al. Novel antipsychotics specificity profile: A clinically oriented review of lurasidone, brexpiprazole, cariprazine and lumateperone. European Neuropsychopharmacology (2019) 29, 971-985.
2. Correll CU, Davis RE, Weingart M, et al. Efficacy and Safety of Lumateperone for Treatment of Schizophrenia. *JAMA Psychiatry*. 2020;77(4): 349-358.
3. Greenwood J, Acharya RB, Marcellus V, Rey JA. Lumateperone: a Novel Antipsychotic for Schizophrenia. Annals of Pharmacotherapy 2021, Vol 55(I) 98-104.
4. Lieberman JA, Davis RE, Correll Cu, et al. ITI-007 for the Treatment of Schizophrenia: a 4-week Randomized, Double-Blind, Controlled Trial. Biological Psychiatry. June 15, 2016; 79:952-961.
5. Lumateperone (Caplyta™) prescribing information. Revised: 12/2019. Intra-Cellular Therapies, Inc.



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