PDL DRUG REVIEW

Proprietary Name: Caplyta®
Common Name: lumateperone
PDL Category: Antipsychotics - Atypicals

Comparable Products	Preferred Drug List Status
Aripiprazole	Preferred
Quetiapine	Preferred
Risperidone	Preferred

Summary

Pharmacology/Usage: Lumateperone, the active ingredient of Caplyta®, is an atypical antipsychotic. While the exact mechanism of action is not known, the efficacy of lumateperone could be mediated through a combination of antagonist activity at central serotonin 5-HT2A receptors and postsynaptic antagonist activity at central dopamine D2 receptors.

Indication: For the treatment of schizophrenia in adults.

There is no pregnancy category for this medication; however, the risk summary indicates that neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Available data from case reports on use in pregnant women are not sufficient 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 during pregnancy. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including Caplyta®. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Capsules: 42mg

Recommended Dosage: Take one capsule PO QD with food. Dose titration is not required.

Dose adjustments are not required with mild hepatic impairment; however, use is not recommended for patients with moderate to severe hepatic impairment.

Drug Interactions: Avoid the concomitant use of Caplyta® with moderate or strong CYP3A4 inhibitors and with CYP3A4 inducers. Avoid the concomitant use of Caplyta® with UGT inhibitors.

Box Warning: Caplyta® has a box warning regarding the 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. Caplyta® is not approved for the treatment of patients with dementia-related psychosis.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Caplyta®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included somnolence/sedation (14%), nausea (4%), dry mouth (4%), dizziness (2%), creatine phosphokinase increased (3%), fatigue (2%), vomiting (1%), hepatic transaminases increased (1%), and decreased appetite (1%).

A potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. If NMS is suspected, immediately discontinue Caplyta® and provide intensive symptomatic treatment and monitoring.

Tardive dyskinesia (TD), a syndrome of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotics. 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. The risk of developing TD and the chance that it will become irreversible increases with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses, and it may occur after discontinuation of treatment. Caplyta® should be prescribed in a manner that is most likely to reduce the risk of TD. If signs and symptoms of TD appear in a patient being treated with Caplyta®, consider discontinuing treatment.

Atypical antipsychotics have caused metabolic changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and body weight gain. While all of the atypical antipsychotics have shown to produce some metabolic changes, each drug has its own specific risk profile.

Atypical antipsychotics cause orthostatic hypotension and syncope. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension, patients with known cardiovascular disease, and patients with cerebrovascular disease. Caplyta® has not been evaluated in patients with a recent history of MI or unstable cardiovascular disease.

Leukopenia and neutropenia have been reported during treatment with antipsychotic agents, including Caplyta®. Agranulocytosis, including fatal cases, has also been reported with other agents in the class. In patients with pre-existing low white blood cell (WBC) count or absolute neutrophil count (ANC) or history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) frequently during the first few months of treatment. In such patients, consider treatment discontinuation 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 symptoms occur. Discontinue treatment in patients with ANC <1000/mm^3 and follow their WBC until recovery.

Like other antipsychotics, 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.

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

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

Contraindications: In patients with a history of hypersensitivity reactions to lumateperone

Manufacturer: Intra-Cellular Therapies, Inc

Analysis: The efficacy of Caplyta® was assessed in two placebo-controlled trials. *Study 1* was a randomized, double-blind, multicenter, placebo-controlled 4-week trial that included adult patients with a diagnosis of schizophrenia per DSM-IV-TR criteria (N=335). Included patients had a median age of 42 years, while 17% were female and 19% were Caucasian. Patients were randomized to Caplyta® 42mg, Caplyta® 84mg, risperidone as an

active comparator, or placebo. (Note that information regarding the active comparator was not found in the prescribing information, and that the study was not designed to allow for efficacy comparison of Caplyta® and the active comparator.)

The primary outcome was the Positive and Negative Syndrome Scale (PANSS) total score, with the PANSS total score ranging from 30 to 210 with higher scores reflecting greater overall symptom severity. Results suggested that compared to placebo, patients randomized to Caplyta® 42mg demonstrated a statistically significant reduction from baseline to day 28 in the PANSS total score. The treatment effect in the Caplyta® 84mg group vs placebo was not statistically significant. Results can be seen in the table below, which was adapted from the prescribing information.

	Treatment	N	Mean Baseline Score	LS Mean Change from Baseline	Placebo-subtracted difference
Study 1	Caplyta® 42mg	84	88.1	-13.2	-5.8
	Placebo	85	86.3	-7.4	

Study 2 was a randomized, double-blind, placebo-controlled, multicenter 4-week study that included adults with a diagnosis of schizophrenia per the DSM-5 criteria (N=450). Included patients had a median age of 44 years, while 23% were female and 26% were Caucasian. Patients were randomized to receive Caplyta® 28mg, Caplyta® 42mg, or placebo.

The primary outcome was the change in the PANSS total score. Results suggested that compared with placebo, patients randomized to Caplyta® 42mg demonstrated a statistically significant reduction from baseline to day 28 in the PANSS total score. The treatment effect in the Caplyta® 28mg group was not statistically significant. Results are summarized in the table below, which was adapted from the prescribing information.

	Treatment	N	Mean Baseline Score	LS Mean Change from Baseline	Placebo-subtracted difference
Study 2	Caplyta® 42mg	150	90.0	-14.5	-4.2
	Placebo	150	89.0	-10.3	

Note that studies 1 and 2 did not include any patients aged 65 years or older.

Place in Therapy: Caplyta® is an oral atypical antipsychotic indicated for the treatment of schizophrenia in adults. In clinical trials compared with placebo, Caplyta® had statistically significantly greater reductions from baseline in PANSS total score. Regarding safety, the frequency of extrapyramidal symptoms (EPS) was similar to placebo (6.7% Caplyta® vs 6.3% for placebo). In addition, the mean change in body weight after 175 days of treatment with Caplyta® was -2kg. Studies with active comparators were not found.

There is no evidence at this time to support that Caplyta® is safer or more effective than the currently preferred, more cost-effective medications. It is therefore recommended that Caplyta® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred Step 3**

References

[1] Caplyta [package insert]. New York, NY: Intra-Cellular Therapies, Inc; 2019.