CLINICAL UPDATE

Brand Name	Caplyta®
Generic Name	lumateperone
Drug Manufacturer	Intra-Cellular Therapies, Inc.

Clinical Update

TYPE OF CLINICAL UPDATE

New Strengths

FDA APPROVAL DATE

April 26, 2022

LAUNCH DATE

July 26, 2022

REVIEW DESIGNATION

Standard

TYPE OF REVIEW

N/A

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Caplyta® is an atypical antipsychotic indicated for the treatment of:

- Schizophrenia in adults.
- Depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate.

MECHANISMS OF ACTION

The mechanism of action of lumateperone in the treatment of schizophrenia and depressive episodes associated with bipolar I or II disorder is unknown. However, 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.

DOSAGE FORM(S) AND STRENGTH(S)

Capsules: 42 mg, 21 mg, 10.5 mg

DOSE & ADMINISTRATION

The recommended dosage of Caplyta® is 42 mg once daily with or without food. Moderate or severe hepatic impairment: Recommended dosage is 21 mg once daily.

CLINICAL UPDATE

EFFICACY

1. Schizophrenia

Caplyta® was evaluated for the treatment of schizophrenia in two placebo-controlled trials.

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 may range from 30 to 210 with higher scores reflecting greater overall symptom severity. A total of 335 patients were randomized to receive Caplyta® 42 mg, Caplyta® 84 mg (two times the recommended daily dose), an active comparator, or placebo.

Compared to the placebo group, patients randomized to Caplyta® 42 mg showed a statistically significant reduction from baseline to Day 28 in the PANSS total score. The treatment effect in the Caplyta® 84 mg group (vs. placebo) was not statistically significant.

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 Caplyta® 28 mg (two-thirds the recommended daily dose), Caplyta® 42 mg, or placebo.

Compared to the placebo group, patients randomized to Caplyta® 42 mg showed a statistically significant reduction from baseline to Day 28 in the PANSS total score. The treatment effect in the Caplyta® 28 mg group (vs. placebo) was not statistically significant.

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 1: Primary Efficacy Results for Change from Baseline in PANSS Total Score in 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	Caplyta® (42 mg)*	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	Caplyta® (42 mg)*	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 (drug minus placebo) in LS mean change from baseline not adjusted for sample size increase after unblinded interim analysis. * Statistically significantly superior to placebo.

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

Monotherapy

The efficacy of Caplyta®, as monotherapy, 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 Reference ID: 4973162 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 Caplyta® 42 mg or placebo.

Compared to the placebo group, patients randomized to Caplyta® 42 mg showed a statistically significant improvement from baseline to Day 43 in the MADRS total score and CGI-BP-S total score.

Adjunctive Therapy with Lithium or Valproate

The efficacy of Caplyta®, as adjunctive therapy with lithium or valproate, 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 Caplyta® 28 mg (two-thirds the recommended daily dose), Caplyta® 42 mg, or placebo.

Compared to the placebo group, patients randomized to Caplyta® 42 mg 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 Caplyta® 28 mg group (vs. placebo) was not statistically significant.

Table 2: 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)**
3	Caplyta® (42 mg)*	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)	---
4	Caplyta® (42 mg)* + 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 (drug minus placebo) in LS mean change from baseline * Statistically significantly superior to placebo.