Drug Monograph

Drug Name:	**Caplyta™ (lumateperone) capsules**
Drug Class:	**Antipsychotics, Atypical (2nd Generation) Oral and Transdermal Products, Reference Product**
Prepared For:	MO HealthNet
Prepared By:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Caplyta capsules are available as a 42 mg strength (equivalent to 60 mg lumateperone tosylate).
Manufacturer:	Distributed by Intra-Cellular Therapies, Inc. New York, NY 10016.
Summary of Findings:	The efficacy of Caplyta was assessed in two randomized, double-blind, placebo-controlled multicenter clinical trials in patients with schizophrenia. Both trials showed statistically significant improvements in the primary endpoint of Positive and Negative Syndrome Scale (PANSS) total score at a daily dose of 42mg when dosed for 4 weeks. 95% CI in each study were -5.8 (-10.5, -1.1) and -4.2 (-7.8, -0.6, P=0.02). Compared to placebo, treatment with Caplyta resulted in similar effects in terms of weight as well as other metabolic markers such as cholesterol, glucose and triglyceride levels. Side effects more prominent with Caplyta included constipation, fatigue, somnolence and sedation.

Status Recommendation:	☒ Clinical Edit	☐ PA Required
	☐ Open Access	☐ PDL
Type of PA Criteria:	☒ Appropriate Indications	☐ Non-Preferred
	☐ No PA Required	☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

The World Health Organization ranks schizophrenia in the top ten illnesses contributing to the global burden of disease. Higher rates of depression, suicide, anxiety, and substance use disorders are found in patients diagnosed with schizophrenia when compared to those without. Antipsychotic medications are used as first line treatment for schizophrenia. There has been a lack of evidence showing any difference in efficacy among antipsychotics currently available, with the exception of clozapine. Choice of antipsychotic medication is most often based on increasing patient adherence by balancing side effects and patient-specific factors.

Dosage Form [3]

Caplyta is available as a 42 mg capsule (equivalent to 60 mg lumateperone tosylate).

Manufacturer [3]

Distributed by: Intra-Cellular Therapies, Inc. New York, NY 10016.

Indication(s) [3]

Caplyta is an atypical antipsychotic indicated for the treatment of schizophrenia in adults.

Clinical Efficacy [3] (mechanism of action/pharmacology, comparative efficacy)

The mechanism of action of lumateperone in the treatment of schizophrenia 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.

Pharmacokinetics:

Absorption	Absolute bioavailability is about 4.4%. Cmax is reached approximately 1-2 hours after Caplyta dosing
Metabolism	Extensively metabolized with more than twenty metabolites identified in vivo. In vitro studies show that multiple enzymes, including but not limited to uridine 5'-diphosphoglucuronosyltransferases (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	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
Half-life	18 hours (IV administration)

Clinical Trials Experience

Study of a Novel Antipsychotic ITI-007 in Schizophrenia

STUDY 1 DESIGN	Four-week, randomized, double-blind, placebo-controlled, multi-center study (n = 335)
INCLUSION CRITERIA	• Patient's age is 18-55 • Patient has current diagnosis of schizophrenia and is experiencing an acute exacerbation of psychosis • Patient has a history of at least three months exposure to one or more antipsychotic therapy(ies) and a prior response to antipsychotic therapy within the previous five years
EXCLUSION CRITERIA	• Any female patient who is pregnant or breast-feeding • Any patient presenting with concurrent dementia, delirium, mental retardation, epilepsy, drug-induced psychosis, or history of significant brain trauma • Any patient presenting with schizoaffective disorder, bipolar disorder, acute mania, or major depression with psychotic features • Any patient considered to be an imminent danger to themselves or others • Any patient with hematological, renal, hepatic, endocrinological, neurological, or cardiovascular disease or substance abuse as defined by protocol • Any patient judged by the Investigator to be inappropriate for the study
TREATMENT REGIMEN	Randomized to receive Caplyta 42 mg, Caplyta 84 mg, an active comparator (risperidone), or placebo. The study was not designed to allow for efficacy comparison of Caplyta and the active comparator. The primary efficacy measure was the Positive and Negative Syndrome Scale (PANSS) total score.
RESULTS	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.
SAFETY	Discussed in the Adverse Effects section below.

A Trial to Assess the Antipsychotic Efficacy of ITI-007

STUDY 2 DESIGN	Four-week, randomized, double-blind, placebo-controlled, multi-center study (n=450)
INCLUSION CRITERIA	• Male or female subjects of any race, ages 18-60 inclusive, with a clinical diagnosis of schizophrenia • Experiencing an acute exacerbation of psychosis
EXCLUSION CRITERIA	• Any subject unable to provide informed consent • Any female subject who is pregnant or breast-feeding • Any subject judged to be medically inappropriate for study participation
TREATMENT REGIMEN	Randomized to receive Caplyta 28 mg, Caplyta 42 mg, or placebo. Primary efficacy measure was the PANSS total score
RESULTS	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
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [(3)]

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

Warnings and Precautions [(3)]

- Boxed Warning: Increased mortality in elderly patients with dementia-related psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Caplyta is not approved for the treatment of patients with dementia-related psychosis
- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse reactions (e.g., stroke and transient ischemic attack).
- Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring.
- Tardive Dyskinesia: Discontinue treatment if clinically appropriate.
- Metabolic Changes: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain.
- Leukopenia, Neutropenia, and Agranulocytosis: Perform complete blood counts (CBC) in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Consider discontinuing CAPLYTA if clinically significant decline in WBC occurs in absence of other causative factors.
- Orthostatic Hypotension and Syncope: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope.
- Seizures: Use cautiously in patients with a history of seizure or with conditions that lower seizure threshold.
- Potential for Cognitive and Motor Impairment: Use caution when operating machinery.

Adverse Effects [(3)]

Most common, ≥ 2%	Caplyta 42mg (n =406) %	Placebo (n =406) %
Somnolence/ Sedation	24	10
Nausea	9	5
Dry Mouth	6	2
Dizziness	5	3
Creatine Phosphokinase Increased	4	1
Fatigue	3	1
Vomiting	3	2
Hepatic Transaminases Increased	2	1
Decreased Appetite	2	1

Drug Interactions [3]

- CYP3A4 inducers: Avoid concomitant use.
- Moderate or strong CYP3A4 inhibitors: Avoid concomitant use.

Dosage and Administration [3]

The recommended dosage of Caplyta is 42 mg administered orally once daily with food. Dose titration is not required.
Avoid use in patients with moderate or severe hepatic impairment (Child-Pugh B or C)

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Month
lumateperone	Caplyta	Intra-Cellular Therapies, Inc	42mg Boxes of 30	$1,320

** Wholesale Acquisition Cost

Conclusion [1,2,3]

Two clinical trials of Caplyta showed statistically significant improvements in the Positive and Negative Syndrome Scale (PANSS) at a daily dose of 42mg. The two most common adverse effects were somnolence/ sedation and dry mouth with a relatively low incidence of metabolic side effects (weigh gain, hyperglycemia, hyperlipidemia). There have no head to head trials with other antipsychotic medications.

Recommendation

The MO HealthNet Division recommends adding this drug to the current atypical (2nd generation) antipsychotics clinical edit, polypharmacy clinical edit, and 15 day fiscal edit.

References

1) Fischer, Bernard, Buchanan, Robert. Schizophrenia in adults: Clinical manifestations, course, assessment, and diagnosis. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on April 15, 2020.)
2) IPD Analytics Payer & Provider Insights_New Drug Review_Caplyta™_01 2020.pdf
3) Product Information: Caplyta™ Intra-Cellular Therapies, Inc. New York, NY 10016 12/2019.

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