Lumateperone (**Caplyta**®)
FDA approved December 2019
Intra-Cellular Therapies, Inc.

Indication: Lumateperone is an atypical antipsychotic indicated for the treatment of schizophrenia in adults

Mechanism of Action: Not fully understood, however, the efficacy could be mediated through a combination of antagonist activity at central serotonin 5-HT2A receptors and postsynaptic antagonist activity at dopamine D2 receptors. Lumateperone has greater affinity for serotonin 5-HT_{2A} and moderate affinity for D_1, D_2, and serotonin transporters

Dosage	• 42 mg once daily • Dose titration not required
Moderate or severe hepatic impairment	Avoid use
Administration	Administer with food
How Supplied	42 mg capsules

Interactions

Concomitant Medication	**Effect**
CYP3A4 inducers	• ↓ lumateperone exposure • Avoid use • Eg. Carbamazepine, phenytoin, St. John's wort, modafinil, prednisone
Moderate or strong CYP3A4 inhibitors	• ↑ lumateperone exposure, ↑ r/o AEs • Avoid use • Eg. Cipro, diltiazem, fluconazole, fluvoxamine, voriconazole, nefazodone
Drug-Food Interactions	• Avoid grapefruit juice (CYP3A4 inhibitor)

Adverse Effects (see table 1)

Most frequently reported AEs (≥5% & at least twice of placebo)	• somnolence/sedation (24% vs. 10% placebo group) • dry mouth (6% vs. 2% placebo)

Warnings & Precautions

- Cerebrovascular adverse reactions in elderly patients with Dementia Related Psychosis
- Neuroleptic malignant syndrome • Tardive dyskinesia • Metabolic changes • Leukopenia, Neutropenia and Agranulocytosis • Orthostatic hypotension and syncope • Seizures • Potential for cognitive and motor impairment

Pharmacokinetics

Effect of Food	high-fat meal lowers mean Cmax by 33%
Tmax	1 to 2 hours
Half-life	about 18 hours after IV administration
Steady state	• attained in about 5 days • dose-proportional (21 to 56 mg) • large inter-subject variability (coefficients of variation Cmax & AUC 68% to 97%)
Excretion	58% urine, 29% feces

Clinical Studies
Efficacy: evaluated in two 4-week multicenter, randomized, placebo-controlled double-blind trials in adult patients with a diagnosis of schizophrenia. The primary efficacy measure was change in the Positive and Negative Syndrome Scale (PANSS) total score from baseline to Day 28

- Study 1: 335 pts were randomized to receive lumateperone 42 mg, 84 mg, an active comparator, or placebo
- Study 2: 450 pts were randomized to receive lumateperone 28 mg, 42 mg, or placebo
- lumateperone 42 mg treatment group showed a statistically significant reduction from baseline to Day 28 in the PANSS total score compared to the placebo group
    - Study 1: the least-squares mean change from baseline PANSS total score in pts receiving lumateperone 42 mg/day was -13.2 vs -7.4 in placebo
        - the 42-mg dose significantly improved PANSS positive but not negative subscales compared with placebo
    - Study 2: the least-squares mean change from baseline PANSS total score in pts receiving lumateperone 42 mg/day was -14.5 vs -10.3 in placebo
- the treatment effect in the lumateperone 28 or 84 mg group was not statistically significant

Safety: The safety of lumateperone has been evaluated in 1,724 pts with schizophrenia

- 811 pts had 4 to 6 week exposure to 14 to 84 mg daily dose, 329 pts had at least 6 months & 108 pts had at least 1 year of exposure to 42-mg dose
- No single adverse reaction led to discontinuation at a rate of >2% in lumateperone treated pts
- Most common AEs (≥5% & at least twice of placebo): Somnolence/sedation & dry mouth
- Other AEs based on the pooled short-term studies are shown in table 1 below

Table 1: Adverse Reactions Reported in ≥2% of CAPLYTA-Treated Patients in 4- to 6-week Schizophrenia Trials

	CAPLYTA 42 mg (N=406)	Placebo (N=412)
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%

Role in Therapy

- Lumateperone will likely be marketed as an important therapeutic option for schizophrenia patients with "favorable safety and tolerability profile in addition to a unique mechanism of action"
    - "unique pharmacological profile" designed to target 3 neurotransmitters in the brain - serotonin, dopamine & glutamate
        - potent 5-HT2a receptor antagonism with cell-type-specific dopamine and glutamate receptor modulation & serotonin reuptake inhibition
        - acts as a post-synaptic antagonist and pre-synaptic partial agonist at dopamine D_2 receptors
        - stimulates phosphorylation of glutamatergic NMDA-NR2B receptors, downstream of D1 receptor intracellular signaling
        - synergistic modulation of serotonergic, dopaminergic, and glutamatergic neurotransmission

- Lumateperone appears to have favorable cardiometabolic profile compared to other antipsychotics
    - Results of Phase II and III studies indicate that lumateperone did not cause significant cardiometabolic AEs

- Pooled data from short-term trials suggests similar changes in weight gain, fasting glucose, triglycerides, total cholesterol & EPS in the lumateperone and placebo treated groups

- Lumateperone at 28 mg and 84 mg did not significantly improve symptoms compared with placebo
  - "unexplained narrow therapeutic window"
- Studies excluded patients with a history of seizure or other conditions
  - findings may not be generalizable to patients with certain comorbid conditions
- One phase 3 study (ITI-007-302) involving 696 patients failed in 2016
  - neither lumateperone 20 mg nor 60 mg showed significant change from baseline on the PANSS total score compared to placebo
  - the negative results however, did not impact the ability of lumateperone to separate from placebo when the 3 studies were pooled
- potential for lumateperone off-label use for bipolar depression, agitation associated with dementia, depression, and other neuropsychiatric disorders
- The company plans to initiate the commercial launch of lumateperone in the first quarter of 2020
- Unclear whether lumateperone is truly an innovative antipsychotic and clinically relevant or another moderately effective metabolically friendly "me too" med
  - Lumateperone efficacy compared with other effective antipsychotics such as olanzapine is unknown
- Future clinical trials utilizing molecular imaging are needed to confirm the target engagement of the various sites of action

Pricing Comparison:

Table 1: FDA-Approved Oral Atypical Antipsychotics for Schizophrenia and Comparative Cost*

Brand (generic)	Dosage Form(s) & Strength(s)	Dosing Regimen	Cost per 30 Days (AWP)[a]	Packaging/Storage Considerations
Caplyta (lumateperone)	Oral capsule: 42 mg	42 mg once daily with food	Not Available	Store at room temperature.
Abilify (aripiprazole)	• Oral tablets: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg • Orally disintegrating tablets (ODTs): 10 mg, 15 mg • Oral solution: 1 mg/mL	• Adults: 10 – 15 mg/day • Adolescents: 10 mg/day	• Tablets: $23.40 • ODTs: $450 • Oral solution: $720 - $1,080	Store at room temperature.
Rexulti (brexpiprazole)	Oral tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg	2 – 4 mg/day	$1,367.70	Store at room temperature.
Vraylar (cariprazine)	Oral capsules: 1.5 mg, 3 mg, 4.5 mg, 6 mg	1.5 – 6 mg/day	$1,441.20	Store at room temperature.
Latuda (lurasidone)	Oral tablets: 20 mg, 40 mg, 60 mg, 80 mg, 120 mg	• Adults: 40 – 160 mg/day • Adolescents: 40 – 80 mg/day	$1,468.20 - $2,936.40	Store at room temperature.
Zyprexa (olanzapine)	• Oral tablets: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg • ODTs: 5 mg, 10 mg, 15 mg, 20 mg	Adults and adolescents: 10 mg/day	• Oral tablets: $4.80 • ODTs: $36.90	Store at room temperature

Brand (generic)	Dosage Form(s) & Strength(s)	Dosing Regimen	Cost per 30 Days (AWP)[a]	Packaging/Storage Considerations
Seroquel (quetiapine fumarate), Seroquel XR (quetiapine fumarate extended-release)	• Oral tablets, immediate-release: 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg • Oral tablets, extended-release: 50 mg, 150 mg, 200 mg, 300 mg, 400 mg	• Oral tablets, immediate-release: Adults: 150 – 750 mg/day • Oral tablets, extended-release 400 – 800 mg/day • Adolescents: 400 – 800 mg/day	• Oral tablets, immediate-release: $33.48 - $55.57 • Oral tablets, extended-release: $39.68 – $79.35	Store at room temperature.
Invega (paliperidone)	Oral tablets, extended-release: 1.5 mg, 3 mg, 6 mg, 9 mg	• Adults: 3 – 12 mg/day • Adolescents: 3 -6 mg/day	• $366.75 – $733.50	Store at room temperature.
Risperdal (risperidone)	• Oral tablets: 0.35 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg • Oral solution: 1 mg/mL • ODTs: 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg	• Adults: 4 – 8 mg • Adolescents: 3 mg	• Oral tablets: $6.00 – $12.00 • Oral solution: $120.00 – $240.00 • ODTs: $378.98 - $757.96	Store at room temperature.
Geodon (ziprasidone)	Oral capsules: 20 mg, 40 mg, 60 mg, 80 mg	• 80 mg twice daily	• $85.80	Store at room temperature.

[a] Estimated cost per 30 days based on unit AWP per Medispan

*Highmark Preliminary Medication Review: New Molecular Entity: Caplyta (lumateperone)

Formulary Considerations:

Recommend adding to formulary with Prior Authorization requirement to promote first-line use of more cost-effective, generic products with a proven track record of safety and efficacy. Apply to BHRS and CMC formularies.

Approval Criteria:

- Medically accepted indications
- Age Limit: 18 years of age and older
- Quantity Limit: 1 tablet per day
- Documentation of two previous trials of formulary antipsychotics

References

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