HHSC Psychiatric Executive Formulary Committee Minutes

The HHSC Psychiatric Executive Formulary Committee (PEFC) convened on January 29, 2021 via MS Teams. The meeting was called to order by Dr. Moron, Interim Chair at 9:33 a.m.

Members

Member Names	Attendance	Member Names	Attendance
Yekini Adeyemi, RN	Present	Glenn Shipley, DO	Present
Angela Babin, RPh	Present	Lesia Trickett, MD	Present
Jean Baemayr, PharmD- Secretary	Present	Ashton Wickramasinghe, MD	Present
John Bennett, MD	Present		
Bonnie Burroughs, PharmD	Present	Tim Bray (non-voting)	Absent
German Corso, MD	Absent	Brad Fitzwater, MD (non-voting)	Present
Catherine Hall, PharmD	Present	Connie Horton, APRN (non-voting)	Absent
Jeanna Heidel, PharmD	Present	Raul Luna, RN (non-voting)	Absent
Dana Hopkins, RN	Present	Mike Maples (non-voting)	Absent
David Moron, MD- Interim Chair	Present	Jeffery Matthews, MD (non-voting)	Absent
Kenda Pittman, PharmD	Present	Peggy Perry (non-voting)	Absent
Rishi Sawhney, MD	Present	Rachel Samsel, (non-voting)	Absent

Guests Present: Patricia Dominguez, PharmD, El Paso Psychiatric Center; Chris Feller, PharmD, SE Clinic Pharmacy at The Harris Center for Mental Health and IDD; Rania Kattura, PharmD, Austin State Hospital; Erendira Orozco, MD, Resident, Rio Grande State Center; Brittany Parmentier, PharmD, UT Health East Texas.

Opening

Introduction and Other Information

Dr. Matthews has been named the new Chief Medical Officer for the State Hospitals.

Annual Conflict of Interest Disclosures

A signed disclosure form has been received from each committee member. None of the forms reviewed indicated any issues with conflict of interest.

Review of Minutes

The minutes from the October 30, 2020 meeting were approved as previously distributed.

Unfinished Business

TAC Title 26, Part 1, Chapter 306, Subchapter G (April 2017)

The revised rules were published for public comment on October 23 in the Texas Register. The first comment of the two received was discussed at the October PEFC meeting. The second comment received was reviewed by the committee prior to this meeting. By email vote, the committee agreed with the commenter's recommended revision of the term "prescribing physician" to "prescribing practitioner" in section 306.354. The anticipated rule effective date is early 2021.

HHSC Psychiatric Drug Formulary Tables Annual Review

The committee reviewed and approved recommended updates to the Therapeutic Reference Range tables, as presented by Dr. Feller. The committee noted that the therapeutic ranges for some medications differed depending on the indication for use and the reference cited. Levels for oxcarbazepine will be removed from the table as this medication is also listed in the table of anticonvulsants that do not have an established therapeutic serum concentration range.
The tables will be updated and the revised formulary will be posted to the PEFC website.

New Business

Adverse Drug Reaction Reports

ADR: clozapine/ myoclonus

A 38-year-old Caucasian male admitted to a state hospital for management of his psychiatric symptoms. Since admission he had been managed with haloperidol long-acting injection (LAI). He was still showing psychotic symptoms and aripiprazole was later added to augment haloperidol treatment. After an adequate treatment trial with aripiprazole, it was deemed ineffective and the team planned to transition him to clozapine approximately 4.5 months post admission. The patient had continuously refused laboratory monitoring and diagnostics since admission and had declined to meet or talk with any member of his treatment team. Prior to initiating clozapine, an approval for non-behavioral restraints for lab draw was obtained from the clinical director of the hospital.
Clozapine was initiated per the facility titration protocol after all laboratory and diagnostic evaluations were deemed within normal limits. Aripiprazole was tapered and discontinued and eventually haloperidol decanoate was discontinued after six months of hospitalization. About a month after initiation of clozapine, the patient was noted to have involuntary jerking of his upper extremities. He was given oral diphenhydramine 50 mg and an hour later the involuntary jerking was noted to "have lessened". Of note he was on benztropine for management of extrapyramidal symptoms (EPS) until around the time clozapine was initiated, at which time the benztropine medication order was allowed to expire due to concern for additive risk

of constipation when used along with clozapine. He received a haloperidol decanoate dose approximately 1 week prior to when the involuntary movements were identified and at the time it was attributed to the discontinuation of benztropine and recent administration of haloperidol decanoate. Scheduled oral benztropine 1 mg twice daily was subsequently restarted and the patient was closely monitored for involuntary movements and constipation. Ten days after the restart of benztropine, the patient was still noted to have intermittent jerky movements in upper extremities, although it had improved.

Two months after clozapine initiation, progress notes indicated that the patient continued to have "intermittent twitching in his UE". Nursing report observing the patient having "brief episodes of closing his eyes and dropping things from his hands, intermittently for the past one month [i.e. early November] but this was not documented or reported to the main treatment team up until now". Based on this finding, the patient was evaluated by a neurologist. An ammonia level and EEG were recommended. The ammonia level was drawn and was within normal limits. An EEG completed 2.5 months after the initiation of clozapine showed that the patient was having seizure like activity every time he had a jerky movement. Of note, one day prior to his scheduled EEG, the patient experienced a fall where he reported losing control of his muscle of his left leg. He bent his left knee and fell to the floor sustaining superficial scrapes to the knee. He was also observed to have jerky movements in his upper extremities.

Medications administered within 24 hours:

Vitamin D3 1000 units oral every other day, fluticasone nasal spray 1 spray in each nostril twice daily, clozapine oral 100 mg in the morning and 200 mg at bedtime, benztropine 1 mg oral twice daily, atropine 1% eye drops 1 drop sublingually twice daily for sialorrhea, acetaminophen 650 mg oral every 4 hours as needed for pain or fever.

Upon identification of myoclonic movements, the clozapine dose was reduced from 100 mg in the morning and 250 mg at bedtime to 100 mg in the morning and 200 mg at bedtime and levetiracetam 500 mg oral twice daily was added at the recommendation of the neurologist, as findings of the EEG suggested myoclonic seizures with high suspicion due to clozapine use. The patient persistently refused levetiracetam and was still reporting jerky movements, but no actual seizure activity was documented per chart review. Clozapine taper was continued and eventually discontinued after 3.5 months of use.

The chance of this patient being a slow metabolizer was ruled out as each time a clozapine level was obtained his level was steady at around 400 ng/mL.

Clozapine-induced myoclonus has been reported during post marketing use of clozapine, but its incidence is not well defined. Available studies record the occurrence of myoclonus in clozapine treated patients to range from 0.9% to 12.5%, suggesting a difficulty in recognizing and diagnosing this event. There are case reports attributing the development of myoclonus to clozapine use with symptoms appearing within the first month of treatment. (Ther Adv Psychopharmacol 2015). Symptoms of myoclonus can be misinterpreted in the mental health setting, as was

the case for our patient, since he had been receiving haloperidol which is known to cause EPS-like symptoms and dyskinesia. Given the timeline of events, and objective findings on EEG, the myoclonus experienced by this patient was caused by clozapine.

ADR: bamlanivimab/ myoclonus

A 37-year-old Hispanic female resident of a state supported living center (SSLC) received bamlanivimab IV treatment under an Emergency Use Authorization (EUA). The individual left the SSLC campus at 0745 on January 19 for an infusion of bamlanivimab and returned to the campus at 1300. Staff reported at 1745 that individual seemed warm to the touch and had redness to knees, elbows, and heels. An RN assessed the individual at 1810 and notified the physician on call at 1825. The physician gave instructions to monitor the individual every two hours for four hours and then decrease monitoring to every 4 hours if there had been no increase in redness or other symptoms. At 2300 it was reported that heels were no longer red. Knees were warm and pink. By 1000 on January 20 it was reported that there was no more redness.

Relevant History:

A COVID-19 nasal swab polymerase chain reaction (PCR) test was positive on January 11 and results were received by the SSLC on January 13.

Allergies include cefuroxime, Coban, and latex. No smoking or alcohol use. The individual has alopecia, cerebral palsy, chronic constipation, GERD, profound intellectual disabilities, hyperglyceridemia, major depressive disorder, and seizure disorder.

Other medications:

Citalopram, ethinyl estradiol-norethindrone, gabapentin, lansoprazole, lorazepam, quetiapine, trazodone, polyethylene glycol 3350, calcium carbonate, cholecalciferol, docusate, fructooligosaccharide-polydextrose, lactulose, multivitamin with minerals, fluticasone nasal as needed, ibuprofen as needed, acetaminophen as needed, and bisacodyl as needed.

New Drug Applications

Lumateperone (Caplyta®)

Presented by Dr. Hall. Please refer to Appendix A for the monograph that was considered when determining action by the committee.

After discussion of the monograph, the committee approved the addition of lumateperone to the formulary in the Psychotropic Agents-Antipsychotics section and to the antipsychotic tier schedule as a Tier 3 agent. Caplyta will also be added to the Psychotropic Monitoring Inpatient Guidelines document in the Atypical Antipsychotics section and to the Classes of Medications Frequently Used for Psychiatric Indications (the "consent drug list") document under Antipsychotics.

The formulary check list was completed and no issues were detected.

Canagliflozin (Invokana®) Pended until next meeting

Empagliflozin (Jardiance®) Pended until next meeting

Hepatitis C Drug Purchases

For the first quarter of fiscal year 2021 (September 2020 to November 2020), the following purchases for drugs to treat hepatitis C were made:

State Hospitals: $45,778

State Supported Living Centers: $18,889

The committee discussed the history of tracking this information and determined that routine reporting by this committee was no longer necessary.

Quarterly Non-Formulary Drug Justification Report

For the first quarter of fiscal year 2021 (September 2020 to November 2020), only the state hospitals reported use of non-formulary agents. The SSLCs currently do not have the capability to obtain non-formulary drug usage reports from their computer system but are working with the vendor to make this reporting possible. The following were the top five non-formulary agents, by number of orders, that were prescribed in the state hospitals during the first quarter of fiscal year 2021:

- Quercetin (plant flavonoid dietary supplement)
- Zinc gluconate
- Acetaminophen/caffeine/pyrilamine (Midol Menstrual Complete)
- Dexmethylphenidate (Focalin)
- Listerine Zero

Drug Formulary Sectional Review

In reviewing the formulary drug listings for analgesic, antipyretic, and anti-inflammatory agents and anticonvulsant agents, the following changes were approved:

- Ophthalmics
  - Gentamicin: remove trade name Garamycin
  - Homatropine: remove trade name Isopto Homatropine
  - Scopolamine (Isopto Hyoscine): remove from formulary
  - Naphazoline: remove trade name AK-Con; change trade name Naphcon to Naphcon-A
  - Fluorescein sodium: add trade names Bio-Glo, FUL-GLO; remove injection dosage form
  - Fluorescein-benoxinate: remove trade name Flurox; add trade name Altafluor Benox
  - New listing: Mineral oil-petrolatum (Akwa Tears, Refresh Lacri-Lube)
    - Ointment, ophthalmic
  - Opthalmic Irrigating Solution: add Balanced Salt Solution to name; remove trade name AK-Rinse
  - Ophthalmic Lubricant: change to Polyvinyl Alcohol; remove trade names Liquitears, HypoTears, HypoTears PF; add trade name Akwa Tears
- Otics
  - Acetic Acid: remove trade names Acetasol, VoSol

    - Acetic acid-aluminum acetate (Domboro Otic): remove from formulary
    - Carbamide peroxide-glycerin-propylene glycol-sodium stannate: change name to carbamide peroxide
- Mouth/Throat
    - Benzocaine: Remove "Topical, for mucous membranes" listings, add "Topical" to "Mouth-Throat Preparations" heading; add lozenge dosage form
    - Clotrimazole: remove trade name Fungoid
    - Doxycycline: remove trade name Periostat
    - Fluoride: remove trade name OmniMed; remove liquid dosage form
    - Nystatin: remove trade name Mycostatin
    - Saliva substitute OTC: remove OTC; remove toothpaste dosage form
    - Saliva substitute Rx: remove from formulary
    - Sodium chloride: remove from formulary
- Nasal
    - Azelastine: remove trade name Astelin
    - Beclomethasone: change trade name QVAR to Beconase
    - Triamcinolone: remove trade name Azmacort

The updated formulary will be posted on the PEFC website.

Other Formulary Changes

Dr. Dominguez presented a review of insulin detemir. After consideration, the committee approved changing insulin detemir from Reserved Drug to regular formulary status.

The committee also approved the following changes to the formulary:

- Formulary Appendix E- Adverse Drug Reaction Reporting- remove this document from the formulary and add the link to the FDA MedWatch Online Voluntary Reporting Form to the "Resource Links" document in the "Resources" section of the PEFC website.
- Formulary Appendix F- Foods Containing Tyramine- move this document to the "Resources" section of the PEFC website.
- Formulary Appendix G- Oral Morphine Conversion Table- move this document to the "Resources" section of the PEFC website.

The updated formulary will be posted on the PEFC website.

HHSC Psychotropic Medications Consent List Annual Review

The committee reviewed and approved the following changes to the list of psychotropic medications requiring consent:

- Add lumateperone (Caplyta) in the antipsychotics section
- Remove "nonformulary" from the eszopiclone listing
- Add "nonformulary" to the zaleplon listing

The updated document will be posted on the PEFC website.

Psychotropic Audit Criteria & Guidelines Review

The committee reviewed and approved recommended revisions to the following audit criteria documents:

- Carbamazepine
- Lamotrigine
- Oxcarbazepine
- Valproic acid, divalproex
- Lithium

The updated documents will be posted to the PEFC website.

Antipsychotic Long-acting Antipsychotic Injection (LAI)

State hospital operating procedure 05-03, which describes the coordination of LAI use between state hospitals and post-discharge providers, was discussed.

State Hospital Operating Procedures Update

Triennial review of state hospital operating procedures 03-01, which describes the guidelines for anti-androgen therapy for aggression, and 03-07, which describes the guidelines for anticoagulation therapy, have been reassigned to the state hospital Pharmacy and Therapeutics subcommittee of the System Medical Executive Committee). This does not preclude the PEFC from reviewing and providing feedback on these policies.

Issues from the Chief Medical Officer, State Hospitals

Dr. Matthews was not present to present a report.

Issues from the Medical Services Coordinator, SSLCs

Dr. Shipley discussed SSLC bamlanivimab use and ongoing progress with COVID-19 vaccination.

Drug Shortages, Recalls, and FDA Safety Communications

The FDA has issued the following safety communications and recalls that may impact our facilities:

Shortages

Loxapine: The FDA reports that the manufacturer currently has 5 mg, 10 mg, and 25 mg strengths available on allocation; the HSCS drug wholesaler only has 10 mg available.

Recalls

Metformin extended release tablets: Testing by the FDA which showed N-Nitrosodimethylamine (NDMA) concentrations in excess of the Acceptable Daily Intake Limit (ADI) resulted in the following recall:

- Nostrum Laboratories: two lots of 500 mg and three lots of 750 mg. To date, Nostrum Laboratories, Inc. has not received any reports of adverse events related to this recall.

Chlorhexidine Gluconate Oral Rinse, 0.12%: The following products have been recalled due to possible contamination with the bacteria Burkholderia lata. Use of the defective product in the immunocompetent host may result in oral and, potentially, systemic infections requiring antibacterial therapy. In the most at-risk populations, the use of the defective product may result in life-threatening infections, such as pneumonia and bacteremia.

- Lohxa, LLC: alcohol free products (NDC#: 70166-027-15) with an expiration date from 01/31/21 – 03/31/21. To date, no adverse events have been reported to Lohxa related to this recall.
- Sunstar Americas: Paroex products bearing an expiration date from 12/31/2020 – 9/30/2022. To date, 29 adverse events have been reported to Sunstar Americas related to this recall.
- Precision Dose: all lots of 15mL Unit Dose Cups with an expiration date from 1/31/2021 – 02/28/2022. Precision Dose was notified by the manufacturer of the product, Sunstar Americas, that this product may be contaminated. To date, no adverse events have been reported to Precision Dose related to this recall.

Sildenafil and trazodone: AvKARE is recalling one lot of sildenafil 100 mg tablets (Lot 36884 with an expiration date of 03/2022) and one lot of trazodone 100 mg tablets (Lot 36783 with an expiration date of 06/2022) due to a product mix-up of the listed two separate products inadvertently packaged together during bottling at a 3rd party facility. Unintentional consumption of sildenafil may pose serious health risks to consumers with underlying medical issues, it may interact with nitrates found in some prescription drugs (such as nitroglycerin) lowering blood pressure to dangerous levels. Consumers with diabetes, high blood pressure, or heart disease often take nitrates. Unintended intake of trazodone may result in adverse health consequences such as somnolence/sedation, dizziness, constipation, and blurred vision. These adverse events may be more concerning in elderly patients due to a subsequent increased risk for falls and driving impairment. To date, AvKARE has not received any reports of adverse events related to this recall.

Safety-related Labeling Changes

Epidiolex (cannabidiol): Additions to the drug interactions section:
7.2 Effect of EPIDIOLEX on Other Drugs *(Additions underlined)*
<u>UGT1A9, UGT2B7, CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2C19 Substrates</u>
Cannabidiol is a weak inhibitor of CYP1A2 *[see Clinical Pharmacology (12.3)]*. Increases in exposure of sensitive CYP1A2 substrates (e.g., caffeine, theophylline, or tizanidine) may be observed when co- administered with cannabidiol. Because of potential inhibition of enzyme activity, consider a reduction in dosage of substrates of

UGT1A9, UGT2B7, CYP1A2, CYP2C8, and CYP2C9, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with EPIDIOLEX. Because of the potential for both induction and inhibition of enzyme activity, consider adjusting dosage of substrates of CYP2B6, as clinically appropriate.
Concomitant use of EPIDIOLEX and stiripentol causes an elevation in exposure to stiripentol *[see Clinical Pharmacology (12.3)]*. The mechanism of this interaction has not been determined. The clinical relevance of this effect is unknown, but patients should be monitored for stiripentol-related adverse drug reactions.

Victoza (liraglutide recombinant): Additions to the warnings and precautions section:
5.4 Hypoglycemia (Additions underlined)
Adult patients receiving VICTOZA in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. In pediatric patients 10 years of age and older, the risk of hypoglycemia was higher with VICTOZA regardless of insulin and/or metformin use. [see Adverse Reactions (6.1), Drug Interactions (7.2)].
The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin. Inform patients using these concomitant medications and pediatric patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

Austedo (deutrabenazine): Revisions to the warnings and persecutions section:
5.3 QTc Prolongation *(Additions and/or revisions underlined)*
AUSTEDO may prolong the QT interval, but the degree of QT prolongation is not clinically significant when AUSTEDO is administered within the recommended dosage range *[see Clinical Pharmacology (12.2)]*.

News Briefs

The following information was shared with the committee members:

Statin Use Appears Not to Be Tied to Suicidality, Anxiety Disorders, or Seizures

Healio (11/3, Gramigna) reports, "Statin use did not appear associated with suicidality, anxiety disorders or seizures," investigators concluded after examining Swedish registry data on "1,149,384 individuals who were dispensed statins and aged 15 years or older between 2006 and 2013." The findings of the "total-population cohort study" were published in the November issue of The Lancet Psychiatry.

Systematic Review Looks at Safety, Efficacy of SNRIs for Treatment of Back Pain, OA

HealthDay (1/21) reports, "Serotonin-[norepinephrine] reuptake inhibitors (SNRIs) have a small and not clinically important effect on back pain, but may have a clinically important effect for osteoarthritis [OA]," investigators concluded after conducting a 33-trial, 5,318-participant systematic review and meta-analysis. The

findings were published online in The BMJ. Healio (1/21, Laday) also covers the study.

Monoclonal Antibody Treatment Appears Successful at Preventing SARS-CoV-2 Infection in Nursing Home Staff and Residents Based on Study's Preliminary Results

The New York Times (1/21, Kolata) reports researchers found that Eli Lilly's monoclonal antibody treatment bamlanivimab reduced SARS-Cov-2 infections among nursing home residents by 80%, "according to preliminary results of a study conducted in partnership with the" NIH. The FDA has already granted an emergency use authorization for the treatment for "symptomatic patients early in the course of their infection," but the preliminary results of the new study suggests the treatment "could stop infections before they started." The AP (1/21, Murphy) reports, "The study involved more than 1,000 residents and staff at nursing homes and other long-term care locations." Other sources covering the story include: Bloomberg (1/21, Griffin), and the Wall Street Journal (1/21, Loftus, Subscription Publication).

Clozapine May Be More Effective Than Olanzapine Or Haloperidol At Reducing Aggression In Patients With Schizophrenia And Conduct Disorder, Small Study Indicates

Psychiatric News (1/25) reports, "Clozapine is more effective than olanzapine or haloperidol at reducing aggression in patients with schizophrenia and conduct disorder," investigators concluded after examining "data from 99 hospitalized schizophrenia patients aged 18 to 60" who took part in a "12-week, double-blind clinical trial" in which patients were randomized "to receive clozapine, olanzapine, or haloperidol to see which drug was associated with the greatest reduction in aggression." The findings were published online Jan. 21 in the American Journal of Psychiatry.

Open Forum

The committee discussed using aripiprazole for the management of hyperprolactinemia caused by antipsychotic use.

Next Meeting Date

The next meeting is scheduled for April 29, 2020.

Adjourn

There being no further business, the meeting was adjourned at 2:43 p.m.

Approved: *David Moron*

David Moron, MD, Interim Chairman

Minutes Prepared by:

Jean Baemayr, PharmD

Appendix

- Appendix A – Lumateperone (Caplyta®) monograph

Appendix A

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 -FDA & literature supported non-FDA

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%. Cmax reached approximately 1 (fasting) to 2 h (food) post dosing. Ingestion of high fat meal lowers mean Cmax 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).

Contraindications

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
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
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
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 Characteristics	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)

Demographic Characteristics	Lumateperone 42 mg (n = 150)	Lumateperone 28 mg (n = 150)	Placebo (n = 149)	Total (n = 449)
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
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

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 Adult/ped (10 to 17 yo) with bipolar depression (monotherapy) Adjunctive tx with lithium or valproate in adults with bipolar depression	Adjunctive tx of MDD SCZ	SCZ acute tx of manic or mixed epis. in bipolar I in adults 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.

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