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Drug Class Update with New Drug Evaluation: Antipsychotics

Date of Review: August 2020

Date of Last Review: March 2019
Dates of Literature Search: 01/01/2019 - 03/12/2020
Brand Name (Manufacturer): Caplyta® (Intra-Cellular Therapeutics, Inc)
Dossier Received: yes

Generic Name: Lumateperone

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Evidence for the comparative effectiveness of first-generation antipsychotics (FGAs), second-generation antipsychotics (SGAs), and parenteral antipsychotic products was last reviewed by the Oregon Pharmacy & Therapeutic Committee (P&T) in March 2019. This review examines recently published comparative evidence of FGA, SGA, and parenteral antipsychotics, as well as to the efficacy and safety of lumateperone, a SGA which received Food and Drug Administration (FDA) approval in 2019.

Research Questions:
1. Is there new comparative evidence of meaningful difference in clinical efficacy or effectiveness between oral FGAs or SGAs, or between oral antipsychotic agents and parenteral antipsychotic agents (first- or second-generation) for schizophrenia, bipolar mania, or major depressive disorder?
2. Is there new comparative evidence of meaningful difference in harms between oral antipsychotic agents (first- or second-generation) or compared to parenteral antipsychotic agents?
3. Is there new comparative evidence of meaningful difference in effectiveness or harms in certain subpopulations based on demographic characteristics (age, gender, or comorbidities), treatment history (treatment naive or treatment resistant), or concomitant medications?
4. What is the evidence for efficacy and safety with lumateperone?

Conclusions:
- No systematic reviews were included in this class update.
- A 2019 guideline by the American Academy of Neurology on Tourette syndrome (TS) and chronic tic disorders included recommendations for antipsychotic drugs (APD) for tics when the benefit outweighs the risk (level C).[1,2] Haloperidol, risperidone, aripiprazole, and tiapride are *probably* more likely than placebo to reduce tic severity, while pimozide, ziprasidone, and metoclopramide *possibly* reduce tic severity when compared to placebo.[1,2] Insufficient evidence of comparative efficacy between these medications is available.[1,2]

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- There is low quality evidence that lumateperone 42 mg once daily may reduce Positive and Negative Syndrome Scale (PANSS) score from baseline compared to placebo in two similarly designed trials [least squares mean (LSM) -13.4 vs. -7.4, p=0.017[3] and LSM -14.5 vs. -10.3, p=0.02[4]] after 4 weeks, though not after 6 weeks in a third trial (LSM -14.6 vs. -15.1, 95% confidence interval (CI) -2.9 to 3.8[5]), in patients with schizophrenia who are not treatment-naïve or treatment-resistant. Patients and endpoints were extremely similar across the three studies. Evidence is limited by attrition bias, reporting bias, funding bias, and inconsistency of efficacy results and dose-response with lack of benefit in at least one trial with every dosage strength studied.[3-5]
- There is no evidence that other doses of lumateperone (14 mg, 28 mg, 84 mg) are superior to placebo in reducing PANSS score over 4-6 weeks due to lack of statistical significance when studied.[3-5]
- There is insufficient evidence to determine if lumateperone offers superior efficacy or safety compared to any other APD for schizophrenia.[3-5]
- There is no new evidence assessing safety and harms between various APD products. Warnings were added to the clozapine labeling that untreated constipation can lead to serious bowel problems.[6]

Recommendations:
- No further review or research needed at this time.
- No changes to the preferred drug list (PDL) are recommended for oral or parenteral antipsychotics based on efficacy or safety data.
- After evaluate costs in executive session, recommend making aripiprazole tablets and ziprasidone capsules preferred.

Summary of Prior Reviews and Current Policy
In the Oregon Health Plan, APDs are exempt from traditional PDL and PA requirements. However, clinical PA criteria that address safety concerns or medically inappropriate use may be implemented. Currently, safety edits are implemented for low dose quetiapine to prevent off-label use, and for pimavanserin to promote safe use in patients with Parkinson's disease psychosis. The PA criteria for these safety edits are outlined in **Appendix 5**. Injectable formulations of aripiprazole, chlorpromazine, fluphenazine, haloperidol, paliperidone palmitate, and risperidone are on the PDL. Oral APDs on the PDL include chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, thioridazine, thiothixene, trifluoperazine, asenapine, cariprazine, clozapine, lurasidone, olanzapine, quetiapine, and risperidone. Most APD use in the Oregon Medicaid population is for oral SGAs, including aripiprazole, quetiapine, risperidone, and olanzapine. Approximately 4% of APD claims are for parenteral formulations. Paliperidone and aripiprazole are the most frequently prescribed injectable APDs in this class. The APDs included on the Oregon PDL are presented in **Appendix 1**.

Previous reviews have found insufficient evidence of clinically meaningful differences between antipsychotic agents in efficacy, effectiveness, or harms between antipsychotic agents for schizophrenia, bipolar mania, or major depressive disorder (MDD). There is insufficient evidence from randomized controlled trials or high quality systematic reviews to determine if new formulations of long-acting injectable aripiprazole and paliperidone offer improved safety or efficacy over other formulations of aripiprazole and paliperidone, or to other APDs.

Background:
Antipsychotic medications are typically categorized as FGAs and SGAs. **Appendix 1** lists the oral and parenteral FGAs and SGAs which are currently available. Antipsychotic medications are indicated for a variety of conditions including schizophrenia and schizoaffective disorder, bipolar disorder (acute and maintenance treatment), adjunct treatment for depression, autism, and Tourette's syndrome.[7] They are often used off-label for other mental health conditions including borderline personality disorder, agitation, aggression, and nausea or vomiting.[7]

Schizophrenia is characterized by presence of delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior and negative symptoms. Diagnosis based on the Diagnostic and Statistical Manual of Mental Health Disorders (DSM-5) criteria requires presence of at least 2 of these symptoms (one must be either delusions, hallucinations or disorganized speech) for longer than 6 months. Symptoms are commonly categorized as positive symptoms (delusions and hallucinations) or negative symptoms (blunted affect, alogia, asociality, anhedonia, and avolition).[8] Onset of schizophrenia occurs most commonly in early adulthood and can have a significant impact on quality of life. Approximately 20% of patients remain relapse-free after a first psychotic episode.[9] However, the majority of patients experience relapse or continued symptoms which can decrease quality of life and create social or occupational difficulties. Factors associated with worse prognosis and disease course include presence of negative symptoms, longer duration of untreated psychosis, and slow or early disease onset at less than 18 years of age.[9] Schizophrenia has been associated with increased risk of mortality, and is often also associated with increased cannabis use, substance abuse, and higher rates of depression.[9] Treatment indicated for schizophrenia includes both FGAs and SGAs. First-generation antipsychotics are generally associated with higher incidence of extrapyramidal side effects whereas SGAs may have increased risk for long-term cardiovascular adverse effects.[9] Non-pharmacological therapy including psychological counseling, skills training, psychoeducation, or cognitive therapy is also often combined with pharmacological therapy.[9] Initial medication selection is often dependent on effectiveness and risks for adverse effects.

Bipolar disorder is characterized by episodes of mania and episodes of depression or hypomania and is estimated to occur in approximately 2% of the world population.[10] Initial diagnosis is most common in patients less than 25 years of age.[10] It is classified as bipolar I disorder (characterized by at least one manic episode) or bipolar II disorder (primarily characterized by history of depressive and hypomanic episodes, but without manic episodes).[10] It can be further classified as rapid cycling with at least 4 episodes of mania, hypomania or depression per year, mania with mixed features, or mania with psychotic features (including hallucinations or delusions).[10] Frequently bipolar disorder is associated with other mental health conditions including anxiety disorder, ADHD and substance use disorders.[10] First-line treatment for bipolar disorder is medication therapy including APDs or mood stabilizers such as lithium, divalproex, quetiapine, or lamotrigine.[10] Goals of treatment include resolution of acute symptoms and long-term prevention of recurrent mania or depressive episodes.[11] Typically, if acute symptoms do not resolve with treatment, the patient is switched to an alternative medication or an additional medication is added.[10] Other treatments include electroconvulsive therapy (ECT), psychoeducational therapy, cognitive behavioral therapy and social therapy. The American Psychiatric Association and the National Institute for Health and Clinical Excellence (NICE) recommends ECT as an option for patients with life-threatening suicidality, psychosis or refusal to eat.[10] ECT may also be considered with severe or treatment-resistant bipolar depression and as a first-line option for pregnant women with severe depression.[10]

Symptom improvement and disease severity for schizophrenia can be evaluated using a variety of rating scales. The Clinical Global Impression Scale (CGI) evaluates disease severity and improvement using a 7-point analogue scale with lower scores indicating less severe symptoms and a change of 1 point corresponding to a minimum clinically important difference (MCID).[8,11] The Positive and Negative Syndrome Scale (PANSS) evaluates 30 items in patients with schizophrenia each scored on a 7-point scale with lower scores indicating less severe symptoms (range 30-210). This scale can also be sub-divided to assess general psychopathology, positive symptoms, or negative symptoms. Response to treatment is typically defined as greater than 20% improvement in the PANSS score, though this definition can vary among trials.[9,12] There is no established MCID for the PANSS, though improvements of 4-8 points have been correlated to increases in employment and improvements of 10 points have been correlated with reduced hospitalization. Negative symptoms of schizophrenia may also be assessed using the Scale for Assessment of Negative Symptoms (SANS) score which assesses negative symptoms including alogia, affective blunting, avolition-apathy, anhedonia-asociality, and attention impairment. Each item is assessed on a 0-5 point scale with higher scores indicating more severe symptoms (range 0-125). The Brief Psychiatric Rating Scale (BPRS) assesses schizophrenia symptom severity via assessment of 16-18 items (each assessed on a 7-point scale with a total score of 0 to 126). Similarly, quality of life and functional improvement may be assessed using a variety of metrics. The Global Assessment Scale of

Functioning (GAF) scale is commonly used for patients with schizophrenia and assesses functional improvement on a 0 to 100 scale. Clinically important improvements in function have been correlated to changes of at least 10 points.[9]

For patients with bipolar disorder, symptom improvement is commonly evaluated using the 11-item Young Mania Rating Scale (YMRS). Using this scale, changes of at least 6 points have been correlated with clinically significant improvements.[11,13] Symptom improvement and severity for patients with bipolar disorder may also be evaluated using the CGI scale (range 1-7 with a MCID of 1 point).[11]

Most APD use is for SGAs, with over 25,000 patients with claims for them each quarter. Approximately 1500 and 1200 patients have prescriptions for FGAs and parenteral antipsychotics filled quarterly.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
After review, 33 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses),[14-31] wrong study design of included trials (e.g., observational),[32-38] comparator (e.g., no control or placebo-controlled),[39,40] or outcome studied (e.g., non-clinical).[41-46]

New Guidelines:
High Quality Guidelines:
Tourette Syndrome and Chronic Tic Disorders: American Academy of Neurology
The American Academy of Neurology published a 2019 guideline of recommendations on the management of tics in people with TS and chronic tic disorders.[1]
The authors included a systematic review and evidence quality assessment to answer the following questions:

- In children and adults with TS or a chronic tic disorder, when should clinicians and patients pursue treatment for tics?
- In children and adults with TS or a chronic tic disorder who require treatment for tics, how should clinicians and patients choose between evidence-based treatment options and determine the sequence or combinations of these treatments?

These guidelines include 46 recommendations related to the assessment and management of TS and chronic tic disorders. A systematic literature review with evidence quality and risk of bias grading was conducted. The research team excluded those with conflicts of interest (COI) from decision making and the chairperson was free of all COI. Due to the paucity of data in some areas related to this condition, there was a need for extensive expert opinion where data were lacking. Four different premises were used in the development of the recommendations based upon availability of evidence and usage of expert opinion in

the absence of direct data. These include: (1) evidence-based conclusions from systematic review, (2) generally accepted principles of care, (3) strong evidence from related conditions, and (4) deductive inferences from other premises.[1] When an evidence-based premise is used, the panel used A (must), B (should), and C (may) as recommendation designations based on the quality and magnitude of the evidence available.[1,2] All medication treatment recommendations were based on evidence and not premises 2 through 4 above. The details of the literature evaluation are published separately from the guidelines.[1,2]

Recommendations included in the guideline were:

- Clinicians may prescribe antipsychotics for tics when the benefit outweighs the risk (C).[1]
- Appropriate counseling and monitoring for side effects, including weight gain, metabolic changes, and extrapyramidal movements, must be done (A), and the lowest effective dose used (B).[1]
- Pimozide and ziprasidone and medications added to other QT prolonging agents must have a baseline electrocardiogram (A).[1]
- When medications are discontinued they should be tapered over weeks to months to avoid dyskinesias (B).[1] This recommendation is based on the assessment that haloperidol, risperidone, aripiprazole, and tiapride are probably more likely than placebo to reduce tic severity, while pimozide, ziprasidone, and metoclopramide possibly reduce tic severity when compared to placebo.[1]
- Insufficient evidence of comparative efficacy between these medications is available.[1]

After review, one guideline was excluded due to poor quality.[47]

New Formulations or Indications:
There were no new formulations or indications.

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Clozapine	Clozaril®	1/28/2020	Warnings	Untreated constipation can lead to serious bowel problems. Evaluate bowel function and avoid concomitant use of agents such as anticholinergics which may cause gastrointestinal hypomotility.[6]

Randomized Controlled Trials:
A total of 54 citations were manually reviewed from the initial literature search and were excluded because of wrong study design (e.g., observational),[48-74] comparator (e.g., no control or placebo-controlled),[75-87] or outcome studied (e.g., non-clinical).[88-101]

NEW DRUG EVALUATION:
See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Lumateperone is a SGA antipsychotic indicated for the treatment of adult patients with schizophrenia at a dose of 42 mg once daily, without titration.[102] The exact mechanism of action is unclear. Lumateperone exhibits high affinity for serotonin 5-HT_{2A} receptors and moderate affinity for dopamine D_2 receptors.[102] Additionally, it has moderate affinity for serotonin transporters, dopamine D_1 and D_4 receptors, and adrenergic $alpha_{1A}$ and $alpha_{1B}$ receptors.[102] It has low affinity for muscarinic and histaminergic receptors.[102] Lumateperone has been studied in 3 applicable clinical trials, 2 of which are detailed in Table 4, while the remaining 1 failed to meet the primary endpoint and remains unpublished.[5]

Lumateperone tosylate was evaluated in a randomized, double-blind, placebo- and active- controlled, phase 2, multicenter trial conducted in the US (NCT 01499563).[3] Patients were randomized 1:1:1:1 to placebo, lumateperone tosylate 60 mg once daily (equivalent to lumateperone 42 mg), lumateperone tosylate 120 mg once daily (equivalent to lumateperone 84 mg), and risperidone 4 mg once daily.[3] There was a washout period of up to 7 days prior to randomization, followed by the assigned treatment for 28 days while the patient was inpatient.[3] Following this, patients were discontinued from study medication and stabilized on non-study APDs for 5 days and then discharged with follow-up 2 weeks after the last study dose for a safety assessment.[3] Included patients were 18-55 years of age with a DSM-Clinical Trials Version (DSM-CTV) diagnosis of schizophrenia and were experiencing an acute exacerbation of psychosis that began within the previous 4 weeks (defined as having a score of at least 40 using the 18-item Brief Psychiatric Rate Scale, with a score of at least 4 (range 1-7) on at least 2 positive symptom items of that scale).[3] Participants were required to have shown response to previous APD therapy.[3] Additional criteria are listed in Table 4. Patients were assessed at baseline and weekly using the PANSS by remote central raters who were trained to demonstrate high interrater reliability and who were blinded to study design, treatment, and time point of assessment.[3] Calgary Depression Scale for Schizophrenia (CDSS) was used to assess for depression while numerous other indicators and tools were used for the safety assessment; these were used by site-based raters after standardized training across study locations was conducted.[3]

The resulting study population was primarily male (82.6%) and African-American (78.1%), with a mean age 40.1 years.[3] The mean number of years since diagnosis ranged from 15.2 to 17.0 between treatment arms, while the mean baseline PANSS ranged from 84.6 to 88.1.[3] The primary efficacy endpoint, conducted on the modified intent-to-treat (mITT) population (those with a valid baseline and minimum of one post-dose assessment), was the change from baseline to day 28 of PANSS score versus placebo.[3] Statistical improvement from baseline when compared to placebo [LSM -7.4 $\pm$ standard error of the mean (SEM) 1.68] were lumateperone tosylate 60 mg (LSM -13.2 $\pm$ SEM 1.69; p=0.017), lumateperone tosylate 120 mg (LSM -8.3 $\pm$ SEM 1.68; p=0.708), and risperidone 4 mg (LSM -13.4 $\pm$ SEM 1.72; p=0.013).[3] The investigators could not explain why the lumateperone tosylate 120 mg dose did not show benefit when lumateperone tosylate 60 mg demonstrated a statistically significant benefit versus placebo, though higher rates of somnolence and sedation may have introduced detection bias by affecting behavior and masking therapeutic effects during centralized assessment. A sensitivity analysis was performed using the last observation carried forward, adjusted for baseline PANSS score, which again showed statistical significance only for lumateperone tosylate 60 mg [LS mean -12.3; SEM $\pm$ 1.7; p=0.011; effect size (ES)=0.41] and risperidone 4 mg (LS mean -12.6; SEM $\pm$ 1.7; p=0.008; ES=0.43), while lumateperone tosylate 120 mg was not statistically significantly different compared to placebo (LS mean -7.7; SEM $\pm$ 1.6; p=0.558; ES=0.09).[3] An a priori responder analysis of patients who had a reduction of at least 30% of the total PANSS score indicated 40.8% of patients taking lumateperone tosylate 60 mg (LSM 18.3%, 95% CI 3.9 to 32.6; p=0.014), 25.0% of patients taking lumateperone tosylate 120 mg (LSM 2.5%, 95% CI -10.7 to 15.7; p=0.711), and 40.0% of patients taking risperidone 4 mg (LSM 17.5%, 95% CI 3.1 to 31.9; p=0.019) were responders when compared to 22.5% for placebo.[3] Additionally, there were secondary a priori subgroup analyses of patients with negative symptoms and/or depression at baseline based on their PANSS or CDSS (Table 4).[3] The PANSS depression subgroup showed a statistically significant mean change of -31.7 (± 7.31 SEM; p=0.018) for lumateperone tosylate 60 mg versus placebo (mean change -12.4 ± 3.89 SEM).[3] The other study

groups were non-significant for this sub-group analysis, and no group was statistically different from placebo from analysis of the PANSS negative subscale subgroup.[3]

A second, similarly designed placebo-controlled study (NCT2282761) evaluated lumateperone 42 mg and lumateperone 28 mg once daily.[4] Inclusion and exclusion were essentially the same, with the exclusion for use of injectable antipsychotics within 1.5 treatment cycles (administration interval for each medication), rather than 1 treatment cycle.[4] Baseline demographics were primarily male (77.1%), African-American (66.4%), and with a mean age of 42.4 years [standard deviation (SD) 10.2 years].[4] The baseline mean PANSS was 89.8 (SD 10.5) and time since schizophrenia diagnosis of 17.0 years (SD 10.5 years).[4] The mean PANSS change from baseline using a mixed-effect model repeated measures was -15.6 for lumateperone 42 mg (LS mean difference from placebo -4.2, 95% CI -7.8 to -0.6; ES -0.3, p=0.02) and -13.7 for lumateperone 28 mg (LS mean difference from placebo -2.6, 95% CI -6.2 to 1.1; ES -0.18, p=0.16), compared to -12.4 for placebo.[4]

A third, unpublished, double-blind RCT (NCT02469155) compared lumateperone 42 mg, lumateperone 14 mg, and risperidone 4 mg (each dosed once daily) to placebo after 6 weeks of inpatient treatment (n=696).[5] The demographic, baseline, and inclusion/exclusion criteria for this trial were similar to the previous two.[5] There were 31 (12.2%) patients in the ITT group with major protocol violations, usually due to a positive substance abuse drug screen during the treatment period or concomitant use of psychotropic medication other than lorazepam, benztropine, or propranolol.[5] An FDA reviewer noted that this was not expected to greatly affect the efficacy endpoint analysis.[5] The primary endpoint of change in total PANSS score from baseline to end of treatment at 6 weeks resulted in no difference compared to placebo for lumateperone 14 mg (LSM -15.0 $\pm$ SEM 1.3; placebo subtracted difference 0.1, 95% CI -3.4 to 3.5) and lumateperone 42 mg (LSM -14.6 $\pm$ SEM 1.2; placebo subtracted difference 0.5, 95% CI -2.9 to 3.8), though risperidone 4 mg did differentiate from placebo (LSM -20.5 $\pm$ SEM 1.3; placebo subtracted difference -5.4, 95% CI -8.9 to -1.9).[5] Study discontinuation due to lack of efficacy were highest in the placebo (6.9%), lumateperone 14 mg (7.5%), and lumateperone 42 mg (6.3%) groups compared to risperidone 4 mg (4.6%).[5] Completion of the medication treatment period was as follows: lumateperone 14 mg (67.8%), lumateperone 42 mg (74.7%), risperidone 4 mg (62.6%) and placebo (78.7%). Overall study completion, after conversion to non-study APDs and outpatient follow-up 2 weeks after final study dose, resulted in additional attrition.[5] Notably, this study was the longest and the largest of the three studies, which increases concern that the primary endpoint was not achieved.

These studies suffered from risk of internal biases and applicability concerns (Table 4). These include risk of reporting bias related to funding of research, possible publication bias, and inconsistency in results between studies and between doses. The presence of an active control group (risperidone) was used in two studies, but without a priori analysis for between group comparisons, the comparative efficacy increases uncertainty in these results. The short duration of these studies and use in only the inpatient setting limit real world applicability. Additionally, the significant attrition with these inpatients studies leaves questions and concerns about outpatient medication adherence.

Clinical Safety:

Lumateperone carries many of the same warnings and precautions of other SGAs. Elderly patients with dementia-related psychosis are at increased risk of death, including fatal stroke, as well as overall incidence of stroke and transient ischemic attacks.[102] Other class-wide warnings include risk of neuroleptic malignant syndrome and tardive dyskinesia.[102] Second-generation antipsychotic use can result in metabolic changes such as hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain; these adverse reactions have been reported in patients using lumateperone.[102] Leukopenia, neutropenia, agranulocytosis, orthostatic hypotension, syncope, falls, seizures, body temperature dysregulation, and dysphagia are additional class-based precautions.[102] Lumateperone is contraindicated in those with history of hypersensitivity to the agent, and reactions may present as pruritis, rash, and urticaria.[102]

The Lieberman et al. Phase 2 trial did not have any serious adverse events associated with lumateperone tosylate over 4 weeks, though serious worsening of schizophrenia and psychosis did occur in one risperidone and one placebo participant.[3] Two patients discontinued lumateperone tosylate secondary to an adverse events (dry mouth and worsening schizophrenia), while there were 3 associated with risperidone use (elevated creatine phosphokinase and 2 cases of akathisia).[3] Rates of akathisia were similar to placebo for both doses of lumateperone, while risperidone had the highest rates of akathisia (placebo 2.3%; lumateperone tosylate 60 mg 1.2%; lumateperone tosylate 120 mg 2.4%; risperidone 4 mg 7.3%).[3] Mean weight change from baseline was increased in all active treatment groups [placebo 0.83 kg (95% CI 0.00-1.67); lumateperone tosylate 60 mg, 2.01 kg (95% CI 1.27-2.75 kg); lumateperone tosylate 120 mg, 1.93 kg (95% CI 1.13-2.73 kg); risperidone 4 mg, 3.01 kg (2.13-3.90 kg)].[5]

In the Correll et al. study, there were 2 patients with severe treatment emergent adverse event (TEAE) resulting in discontinuation, one in the lumateperone 42 mg group with orthostatic hypotension and one in the lumateperone 28 mg group with convulsions who had preexisting risk factors and a relevant medical history regarding seizures.[4] Additional discontinuations occurred in 2 patients in the lumateperone 42 mg group due to headache, and one in the placebo group due to presumed worsening of schizophrenia.[4] There was no association with suicidal ideation (lumateperone 42 mg 1.4%; lumateperone 28 mg 1.4%; placebo 1.4%) or suicidal behavior (0% all groups) as measured by the Columbia Suicide Severity Rating Scale.[4] Akathisia was seen in similar rates among the three study groups (lumateperone 42 mg 4%; lumateperone 28 mg 1.3%; placebo 2.7%).[4] Weight gain of greater than or equal to 7% with a shift from an overweight to obese BMI increased with dose (lumateperone 42 mg 8.4%; lumateperone 28 mg 4.3%; placebo 3.8%), though the median change in weight was similar among all groups (lumateperone 42 mg 0.9 kg; lumateperone 28 mg 0.6 kg; placebo 0.7 kg).[4]

One patient in the unpublished study withdrew after a serious adverse event of agitation secondary to worsening psychosis from the lumateperone 42 mg arm.[5] Somnolence, fatigue, and sedation were the most common TEAEs (lumateperone 42 mg 23.6%; lumateperone 14 mg 17.2%; risperidone 4 mg 26%; placebo 9.8%).[5] Common TEAEs from all 3 studies included creatine phosphokinase increases, dry mouth, fatigue, somnolence/sedation, dizziness, increased transaminases, nausea, vomiting, and decreased appetite.[5] Long-term safety data are lacking in light of study durations of only 4-6 weeks. As with other SGAs, long-term data related to metabolic risk factors and weight gain are vital.

Table 2: Pooled Adverse Events from 4- to 6-week duration Schizophrenia trials[102]

Adverse event	Lumateperone 42 mg (%) (n=406)	Placebo (%) (n=412)
Somnolence/Sedation	24	10
Nausea	9	5
Dry mouth	6	2
Dizziness	5	3
Increased creatine phosphokinase	4	1
Fatigue	3	1
Vomiting	3	2
Increased hepatic transaminases	2	1
Decreased appetite	2	1

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Reduction of symptoms of psychosis
2) Improved quality of life or function
3) Reduction of positive or negative or depression symptoms
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Change in PANSS from baseline

Table 3 Pharmacology and Pharmacokinetic Properties.[102]

Parameter	
Mechanism of Action	Unknown, likely mediated via antagonism of central serotonin 5-HT_{2A} receptors and postsynaptic antagonism of central dopamine D_2 receptors.
Oral Bioavailability	4.4%, High-fat meal increases C_{max} by 33% and AUC by 9%
Distribution and Protein Binding	Volume of distribution 4.1 L/kg Protein binding 97.4% (when tested at 70-fold higher than therapeutic concentrations)
Elimination	Clearance of 27.9 L/hr; 58% urine, 29% feces, less than 1% unchanged in urine
Half-Life	18 hr
Metabolism	Extensive metabolism via multiple enzymes with more than 20 metabolites. Enzymes include: uridine 5'-diphospho-glucuronsultransferases 1A1, 1A4, 2B15; aldoketoreductase 1C1, 1B10, 1C4; cytochrome P450 3A4, 2C8, 1A2.

Abbreviations: AUC = area under the curve; C_{max} = maximum concentration; hr = hour; L = liter; kg = kilogram

Table 4. Comparative Evidence Table: lumateperone

Ref./ Study Design	Drug Regimens*/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Lieberman JA, et al.[3] MC, DB, RCT phase II NCT 1499563	1. Placebo 2. Lumateperone tosylate 60 mg (equiv to 42 mg) 3. Lumateperone tosylate 120 mg (equiv to 84 mg) 4. Risperidone 4 mg	Demographics: Male: 82.6% Age: mean 40.1y Black: 78.1% Baseline PANSS: 91.2 Key Inclusion Criteria: 1. Age 18-55 years 2. Diagnosis of schizophrenia by DSM-CTV 3. Acute exacerbation of psychosis (≥40 on	Rand: N=335 1. 85 2. 84 3. 83 4. 82 mITT: N=311 1. 80 2. 76 3. 80 4. 75	Primary Endpoint: Change from baseline to day 28 on PANSS score vs placebo LSM (± SEM) 1. -7.4 ± 1.68 2. -13.4 ± 1.69 (p=0.017) 3. -8.3 ± 1.68 (p=0.708) 4. -13.4 ± 1.72 (p=0.013) CI not reported	NA	Serious AE: 1. 1 2. 0 3. 0 4. 1 AE causing discontinuation: 1. 0 2 or 3.† 2 4. 3 Weight gain (kg)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Inclusion qualifications verified by both study investigators and independent psychiatrists or clinical psychologists as a doublecheck against subjectivity in scales used. Randomization via automated telephone or web-based system with allocation concealment using unique randomized number for a numbered kit containing visually matched capsules. Groups were well matched. Performance Bias: (low) All are taking visually matched capsules to maintain blinding.

	Daily dose in the AM x 4 weeks inpatient therapy then transitioned and stabilized on standard APD for 5 days and discharged Safety visit 2 weeks post-final study dose	Brief Psychiatric Rating Scale) 4.Episode starting within 4 wks of screening 5. Not treatment-resistant OR treatment-naïve <u>Key Exclusion Criteria</u>: 1. Presence of: dementia, delirium, mental retardation, epilepsy, drug-induced psychosis, brain trauma, schizoaffective d/o, bipolar d/o, acute mania, major depression w/ psychotic features, imminent danger to self or others, suicidal ideation/behavior, unstable living environment, use of depot antipsychotic within 1 treatment cycle, use of any antipsychotic in screening period, use of agents with 5-HT2A receptor interaction 2. Cardiovascular, renal, hepatic, endocrine, neurological dz or significant lab abnormalities 3. SA/dependence 4. Unable to be safely discontinued from current antipsychotic/psychotropic regimen	<u>Safety:</u> N=334 (received 1+ dose study drug <u>Inpatient Attrition</u>: 1. 19 (22%) 2. 17 (20%) 3. 14 (17%) 4. 15 (18%) <u>Completed study safety visit</u>: 1. 61 (72%) 2. 60 (71%) 3. 64 (76%) 4. 63 (77%)	<u>Secondary Endpoints</u>: Responder Analysis: PANSS decrease $\geq$ 30% 1. 18 (22.5%) 2. 31 (40.8%) 3. 20 (25%) 4. 30 (40%) 1 vs. 2: RD 18.3%, 95% CI 3.9 to 32.6; p=0.014 1 vs. 3: RD 2.5%, 95% CI -10.7 to 15.7; p=0.711 1 vs. 4: RD 17.5%, 95% CI 3.1 to 31.9; p=0.019 Subgroup analysis of patients through day 28 group with negative symptoms at baseline PANSS Negative subscale subgroup Mean (± SEM) from baseline (p vs. placebo) 1. -1.3 ± 0.92 2. -3.0 ± 0.88 (p=0.206) 3. -1.1 ± 0.93 (p=0.865) 4. -1.2 ± 0.80 (p=0.893) Subgroup analysis of per protocol patients through day 28 group depression at baseline Total PANSS depression subgroup Mean (± SEM) from baseline (p vs placebo) 1. -12.4 ± 3.89 2. -31.7 ± 7.31 (p=0.018) 3. -14.2 ± 3.51 (p=0.736) 4. -20.6 ± 3.89 (p=0.152) CDSS depression subgroup Mean (± SEM) from baseline (p vs placebo) 1. -5.4 ± 1.00 2. -7.7 ± 0.42 (p=0.044) 3. -5.6 ± 0.74 (p=0.839) 4. -7.2 ± 1.31 (p=0.271)	18.3%/5 NA 17.5%/6 NA	Median, Mean (SD) 1. 0.8, 0.8 (2.3) 2. 1.0, 2.0 (3.10) 3. 1.1, 1.9 (3.35) 4. 2.5, 3.0 (3.69) Sedation 1. 11 (12.9%) 2. 14 (16.7%) 3. 27 (32.5%) 4. 17 (20.7%)	NA NA	<u>Detection Bias</u>: (low) Remote raters with training for interrater reliability and blinding to study design, treatment, and time point of assessment. Validated PANSS and CDSS used for assessment. <u>Attrition Bias</u>: (high) High overall attrition rate (19% at 28 days while inpatient and 26% by final safety visit). Last observation carried forward used for missing data. Approximately 2-fold higher attrition in placebo patients from "lack of efficacy" than other groups <u>Reporting Bias</u>: (high) Secondary endpoints difficult ascertain as a priori vs. post hoc between published study, FDA review document, and clinicaltrials.gov listing. <u>Other Bias:</u> (high) Funding provided by drug company and several authors had financial conflicts of interest. **Applicability**: <u>Patient</u>: Racial distribution not representative of normal disease distribution, though it more closely aligns to Oregon Medicaid population. Exclusion of treatment-naïve patients, treatment-resistant patients, and patients with other mental health conditions as well as exclusive inpatient use limits applicability. <u>Intervention</u>: Salt formulation used: 60 mg salt = 42 mg, 120 mg salt = 84 mg, with lack of dose response as 120 mg salt did not meet primary endpoint. <u>Comparator</u>: Placebo appropriate to establish efficacy, direct comparisons with risperidone group is more informative to clinical practice. <u>Outcomes</u>: Validated scales used to assess schizophrenia symptoms, longer duration of response needed to assess long term reduction in symptoms and safety. Quality of life data needed. <u>Setting</u>: 8 sites in US. Limited applicability to the outpatient setting.

2. Correll et al.[4] MC, DB, RCT, phase 3 NCT 2282761	1. Lumateperone 42 mg 2. Lumateperone 28 mg 3. Placebo Daily dose in the AM x 4 weeks inpatient therapy Then transitioned and stabilized on standard APD for 5 days and discharged Safety visit 2 weeks post-final study dose	Demographics: Male: 77.1% Age: mean 42.4y (SD ± 10.2) Black: 66.4% Baseline PANSS: 89.8 (SD ± 10.3) Key Inclusion Criteria: 1. 18-60 years 2. Diagnosis of schizophrenia by DSM-CTV 3. Acute exacerbation of psychosis (≥40 on Brief Psychiatric Rating Scale with ≥4 (range 1-7) on at least 2 positive symptoms) 4. Episode starting within 4 wks of screening 5. Mod-severe dz severity (CGI-S score≥4) 6. Moderate-extreme schizophrenia (PANSS score ≥70) 7. Not treatment-resistant OR treatment-naïve Key Exclusion Criteria: 1. Presence of: dementia, delirium, mental retardation, epilepsy, drug-induced psychosis, brain trauma, schizoaffective d/o, bipolar d/o, acute mania, major depression w/ psychotic features, imminent danger to self or others, suicidal ideation/behavior, unstable living	N=449 Rand: 1. 150 2. 150 3. 150 mITT: 1. 148 2. 146 3. 141 Safety: 1. 150 2. 150 3. 149 Attrition: 1. 14.7% 2. 20.0% 3. 26.0%	Primary Endpoint (MMRM): Change from baseline to day 28 on PANSS score vs placebo LSM (± SEM) 1. -14.5 ± 1.3 2. -12.9 ± 1.3 3. -10.3 ± 1.3 1 vs. 3: -4.2; 95% CI -7.8 to -0.6 (p=0.02) 2 vs. 3: -2.6; 95% CI -6.2 to 1.1 (p=0.16) Secondary Endpoints: CGI-S score: LSM (± SEM) 1. -0.8 ± 0.07 2. -0.8 ± 0.08 3. -0.5 ± 0.08 1 vs. 3: -0.3; 95% CI -0.5 to -0.1 (p=0.003) 2 vs. 3: -0.2; 95% CI -0.5 to 0.0) (p=0.003)	NA NA	Serious AE 1. 0 2. 1 3. 1 AE causing discontinuation: 1. 2 2. 2 3. 1 Death 1. 0 2. 0 3. 1 (13 days after discontinuing study) Weight gain (kg) Mean (range) 1. 0.9 (-36 to 11) 2. 0.6 (-12 to 13) 3. 0.7 (-12 to 16) Sedation/ Somnolence 1. 45 (30.0%) 2. 31 (20.6%) 3. 14 (9.4%)	NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Central randomization via automated telephone or web-based system. Unique randomization number assigned to each patient with dispensing of identical capsules from patient kit by pharmacist or staff member. Performance Bias: (low) Investigators, study staff at clinical site, patients, primary study team, and sponsor blinded to study treatment. Visually matched capsule dispensed by pharmacy or designated staff member. Detection Bias: (low) Primary and some secondary efficacy endpoints measured via videoconference by trained central raters, blinded to treatment and study visit. Additional secondary and safety endpoints assessed by trained raters at individual study sites. Validated PANSS and CDSS used for assessment. Attrition Bias: (high) Significant attrition overall (18.7% by end of inpatient treatment and 20.2% through final safety visit). Higher rate from withdrawal of consent and lack of efficacy, indicating possible unblinding in placebo group (placebo 22.1%, lumateperone 42 mg 10.7%, lumateperone 28 mg 12.7%). Missing data not imputed based on assumption that data is missing at random, which may be inappropriate given differential attrition between placebo and active groups. Reporting Bias: (high) Funding provided by drug company who contributed to all aspects of study from design to publication decision. Several authors had financial conflicts of interest. **Applicability**: Patient: Racial distribution not representative of normal disease distribution, though it more closely aligns to Oregon Medicaid population. Exclusion of treatment-naïve patients, treatment-resistant patients, and patients with other

		environment, use of depot antipsychotic within 1.5 treatment cycle, use of any antipsychotic in screening period, use of agents with 5-HT2A receptor interaction 2. Cardiovascular, renal, hepatic, endocrine, neurological dz or significant lab abnormalities 3. SA/dependence 4. Unable to be safely discontinued from current antipsychotic/ psychotropic regimen						mental health conditions as well as exclusive inpatient use limits applicability. Intervention: Highest dose in this study (42 mg) is only FDA approved dose. Comparator: Placebo appropriate to establish efficacy, active comparator would be more informative to clinical practice. Outcomes: Validated scales used to assess schizophrenia symptoms, longer duration of response needed to assess long term reduction in symptoms and safety. Quality of life data needed. Setting: 12 sites in US. Limited applicability to the outpatient setting.

Abbreviations: Adverse event = AE; ARR = absolute risk reduction; CDSS = Calgary depression scale for schizophrenia; CGI-S = Clinical Global Impression-Severity of Illness; CI = confidence interval; CPK = creatine phosphokinase; DB = double blind; d/o = disorder; DSM-CTV = Diagnostic and Statistical Manual of Mental Disorders-clinical trials version; dz = disease; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human Immunodeficiency virus; hx = history; ITT = intention to treat; LAE = liver associated enzymes; LSM = least squares of the mean; kg = kilograms; MC = multicenter; mITT = modified intention to treat; MMRM = mixed-effect model repeated measures; N = number of subjects; NA = not applicable; NMS = neuroleptic malignant syndrome; NNH = number needed to harm; NNT = number needed to treat; PANSS = positive and negative syndrome scale ; PP = per protocol; PSQI = Pittsburg Sleep Quality Index; Rand = Randomized ; RD = rate difference; RCT = randomized controlled trial; SA = substance abuse; SD = standard deviation; SEM = standard error of the mean; tx = treatment; US = Unites States, y = years

* Lumateperone tosylate 40 mg = lumateperone 28 mg; Lumateperone tosylate 60 mg = lumateperone 42 mg; Lumateperone tosylate 120 mg = lumateperone 84 mg

† Treatment assignment unclear

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Appendix 1: Current Preferred Drug List

1st Generation oral antipsychotics

Generic	Brand	Route	Formulation	PDL
chlorpromazine HCl	CHLORPROMAZINE HCL	ORAL	ORAL CONC	Y
fluphenazine HCl	FLUPHENAZINE HCL	ORAL	ELIXIR	Y
fluphenazine HCl	FLUPHENAZINE HCL	ORAL	ORAL CONC	Y
fluphenazine HCl	FLUPHENAZINE HCL	ORAL	TABLET	Y
fluphenazine HCl	PROLIXIN	ORAL	TABLET	Y
haloperidol	HALOPERIDOL	ORAL	TABLET	Y
haloperidol lactate	HALOPERIDOL LACTATE	ORAL	ORAL CONC	Y
loxapine succinate	LOXAPINE	ORAL	CAPSULE	Y
perphenazine	PERPHENAZINE	ORAL	TABLET	Y
thioridazine HCl	THIORIDAZINE HCL	ORAL	ORAL CONC	Y
thioridazine HCl	THIORIDAZINE HCL	ORAL	TABLET	Y
thiothixene	THIOTHIXENE	ORAL	CAPSULE	Y
thiothixene HCl	THIOTHIXENE HCL	ORAL	ORAL CONC	Y

trifluoperazine HCl	STELAZINE	ORAL	TABLET	Y
trifluoperazine HCl	TRIFLUOPERAZINE HCL	ORAL	TABLET	Y
chlorpromazine HCl	CHLORPROMAZINE HCL	ORAL	TABLET	V
chlorpromazine HCl	THORAZINE	ORAL	TABLET	V
loxapine	ADASUVE	INHALATION	AER POW BA	V
pimozide	PIMOZIDE	ORAL	TABLET	V

2nd Generation oral antipsychotics

Generic	Brand	Route	Formulation	PDL
asenapine maleate	SAPHRIS	SUBLINGUAL	TAB SUBL	Y
cariprazine HCl	VRAYLAR	ORAL	CAP DS PK	Y
cariprazine HCl	VRAYLAR	ORAL	CAPSULE	Y
clozapine	CLOZAPINE	ORAL	TABLET	Y
clozapine	CLOZARIL	ORAL	TABLET	Y
lurasidone HCl	LATUDA	ORAL	TABLET	Y
olanzapine	OLANZAPINE	ORAL	TABLET	Y
olanzapine	ZYPREXA	ORAL	TABLET	Y
quetiapine fumarate	QUETIAPINE FUMARATE	ORAL	TABLET	Y
quetiapine fumarate	SEROQUEL	ORAL	TABLET	Y
risperidone	RISPERDAL	ORAL	SOLUTION	Y
risperidone	RISPERIDONE	ORAL	SOLUTION	Y
risperidone	RISPERDAL	ORAL	TABLET	Y
risperidone	RISPERIDONE	ORAL	TABLET	Y
aripiprazole	ARIPIPRAZOLE	ORAL	SOLUTION	V
aripiprazole	ARIPIPRAZOLE ODT	ORAL	TAB RAPDIS	V
aripiprazole	ABILIFY MYCITE	ORAL	TAB SENSPT	V
aripiprazole	ABILIFY	ORAL	TABLET	V
aripiprazole	ARIPIPRAZOLE	ORAL	TABLET	V
asenapine	SECUADO	TRANSDERM	PATCH TD24	V
brexpiprazole	REXULTI	ORAL	TABLET	V
clozapine	VERSACLOZ	ORAL	ORAL SUSP	V
clozapine	CLOZAPINE ODT	ORAL	TAB RAPDIS	V
clozapine	FAZACLO	ORAL	TAB RAPDIS	V
olanzapine	OLANZAPINE ODT	ORAL	TAB RAPDIS	V

olanzapine	ZYPREXA ZYDIS	ORAL	TAB RAPDIS	V
paliperidone	INVEGA	ORAL	TAB ER 24	V
paliperidone	PALIPERIDONE ER	ORAL	TAB ER 24	V
pimavanserin tartrate	NUPLAZID	ORAL	CAPSULE	V
pimavanserin tartrate	NUPLAZID	ORAL	TABLET	V
quetiapine fumarate	QUETIAPINE FUMARATE ER	ORAL	TAB ER 24H	V
quetiapine fumarate	SEROQUEL XR	ORAL	TAB ER 24H	V
quetiapine fumarate	SEROQUEL XR	ORAL	TAB24HDSPK	V
risperidone	RISPERIDONE ODT	ORAL	TAB RAPDIS	V
ziprasidone HCl	GEODON	ORAL	CAPSULE	V
ziprasidone HCl	ZIPRASIDONE HCL	ORAL	CAPSULE	V

Parenteral antipsychotics

Generic	Brand	Route	Form	PDL
aripiprazole	ABILIFY MAINTENA	INTRAMUSC	SUSER VIAL	Y
aripiprazole	ABILIFY MAINTENA	INTRAMUSC	SUSER VIAL	Y
aripiprazole	ABILIFY MAINTENA	INTRAMUSC	SUSER SYR	Y
aripiprazole	ABILIFY MAINTENA	INTRAMUSC	SUSER SYR	Y
aripiprazole lauroxil	ARISTADA	INTRAMUSC	SUSER SYR	Y
aripiprazole lauroxil	ARISTADA	INTRAMUSC	SUSER SYR	Y
aripiprazole lauroxil	ARISTADA	INTRAMUSC	SUSER SYR	Y
aripiprazole lauroxil	ARISTADA	INTRAMUSC	SUSER SYR	Y
aripiprazole lauroxil,submicr.	ARISTADA INITIO	INTRAMUSC	SUSER SYR	Y
chlorpromazine HCl	CHLORPROMAZINE HCL	INJECTION	AMPUL	Y
chlorpromazine HCl	THORAZINE	INJECTION	AMPUL	Y
fluphenazine decanoate	FLUPHENAZINE DECANOATE	INJECTION	VIAL	Y
fluphenazine HCl	FLUPHENAZINE HCL	INJECTION	VIAL	Y
haloperidol decanoate	HALDOL DECANOATE 50	INTRAMUSC	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	INTRAMUSC	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	INTRAMUSC	VIAL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	INTRAMUSC	VIAL	Y
haloperidol decanoate	HALDOL DECANOATE 100	INTRAMUSC	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	INTRAMUSC	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE 100	INTRAMUSC	AMPUL	Y
haloperidol lactate	HALDOL	INJECTION	AMPUL	Y
haloperidol lactate	HALOPERIDOL LACTATE	INJECTION	AMPUL	Y

haloperidol lactate	HALOPERIDOL LACTATE	INJECTION	VIAL	Y
haloperidol lactate	HALOPERIDOL LACTATE	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA SUSTENNA	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA SUSTENNA	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA SUSTENNA	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA SUSTENNA	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA SUSTENNA	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA TRINZA	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA TRINZA	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA TRINZA	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA TRINZA	INTRAMUSC	SYRINGE	Y
risperidone	PERSERIS	SUB-Q	SUSER SYKT	Y
risperidone	PERSERIS	SUB-Q	SUSER SYKT	Y
risperidone microspheres	RISPERDAL CONSTA	INTRAMUSC	VIAL	Y
risperidone microspheres	RISPERDAL CONSTA	INTRAMUSC	VIAL	Y
risperidone microspheres	RISPERDAL CONSTA	INTRAMUSC	VIAL	Y
risperidone microspheres	RISPERDAL CONSTA	INTRAMUSC	VIAL	Y
trifluoperazine HCl	STELAZINE	INTRAMUSC	VIAL	Y
olanzapine	OLANZAPINE	INTRAMUSC	VIAL	V
olanzapine	ZYPREXA	INTRAMUSC	VIAL	V
olanzapine pamoate	ZYPREXA RELPREVV	INTRAMUSC	VIAL	V
olanzapine pamoate	ZYPREXA RELPREVV	INTRAMUSC	VIAL	V
olanzapine pamoate	ZYPREXA RELPREVV	INTRAMUSC	VIAL	V
ziprasidone mesylate	GEODON	INTRAMUSC	VIAL	V
ziprasidone mesylate	ZIPRASIDONE MESYLATE	INTRAMUSC	VIAL	V

Appendix 2: Abstracts of Comparative Clinical Trials

None

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 10, 2014

Search performed March 13, 2020

1	Chlorpromazine/ae, tu, th [Adverse Effects, Therapeutic Use, Therapy]	5346
2	Fluphenazine/ae, tu [Adverse Effects, Therapeutic Use]	1218
3	Haloperidol/ae, tu [Adverse Effects, Therapeutic Use]	5212
4	Loxapine/ae, tu [Adverse Effects, Therapeutic Use]	189
5	Perphenazine/ae, tu [Adverse Effects, Therapeutic Use]	591
6	Thioridazine/ae, tu [Adverse Effects, Therapeutic Use]	1132
7	Thiothixene/ae, tu [Adverse Effects, Therapeutic Use]	259
8	Trifluoperazine/ae, tu [Adverse Effects, Therapeutic Use]	612
9	Pimozide/ae, tu [Adverse Effects, Therapeutic Use]	496
10	asenapine.mp.	407
11	cariprazine.mp.	197
12	Clozapine/ae, tu [Adverse Effects, Therapeutic Use]	5217
13	Lurasidone Hydrochloride/ae, tu [Adverse Effects, Therapeutic Use]	90
14	Olanzapine/ae, tu [Adverse Effects, Therapeutic Use]	152
15	Quetiapine Fumarate/ae, tu [Adverse Effects, Therapeutic Use]	359
16	Risperidone/ae, tu [Adverse Effects, Therapeutic Use]	4664
17	Aripiprazole/ae, tu [Adverse Effects, Therapeutic Use]	442
18	brexpiprazole.mp.	189
19	Paliperidone Palmitate/ae, tu [Adverse Effects, Therapeutic Use]	202
20	pimavanserin.mp.	170
21	ziprasidone.mp.	1997
22	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	25047
23	limit 22 to yr="2019 -Current"	498
24	limit 23 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	85
25	limit 24 to humans	84
26	limit 25 to English language	82
27	Lumateperone.mp.	13
28	limit 27 to (English language and humans)	6
29	26 or 28	88

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CAPLYTA® safely and effectively. See full prescribing information for CAPLYTA.

CAPLYTA (lumateperone) capsules, for oral use
Initial U.S. Approval: 2019

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete 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. (5.1)

----------INDICATIONS AND USAGE----------
CAPLYTA is an atypical antipsychotic indicated for the treatment of schizophrenia in adults. (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage of CAPLYTA is 42 mg once daily. (2.1)
- Administer CAPLYTA with food. (2.1)
- Dose titration is not required. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 42 mg (3)

----------CONTRAINDICATIONS----------
Known hypersensitivity to lumateperone or any components of CAPLYTA. (4)

----------WARNINGS AND PRECAUTIONS----------
- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke and transient ischemic attack). (5.2)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring. (5.3)
- *Tardive Dyskinesia:* Discontinue treatment if clinically appropriate. (5.4)
- *Metabolic Changes:* Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. (5.5)
- *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. (5.6)
- *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. (5.7)
- *Seizures:* Use cautiously in patients with a history of seizure or with conditions that lower seizure threshold. (5.9)
- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery. (5.10)

----------ADVERSE REACTIONS----------
Most common adverse reactions in clinical trials (incidence ≥ 5% and greater than twice placebo) were somnolence/sedation and dry mouth. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Intra-Cellular Therapies, Inc. at 1-888-611-4824 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- CYP3A4 inducers: Avoid concomitant use. (2.2, 7.1)
- Moderate or strong CYP3A4 inhibitors: Avoid concomitant use. (2.2, 7.1)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)
- Lactation: Breastfeeding not recommended. (8.2)
- Moderate or severe hepatic impairment: Avoid use. (2.3, 8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2019

Appendix 5: Key Inclusion Criteria

Population	**Adults with schizophrenia**
Intervention	Antipsychotic medications
Comparator	Placebo, active control
Outcomes	Clinical effectiveness, safety
Timing	n/a
Setting	Inpatient or outpatient

Appendix 6: Prior Authorization Criteria

Low Dose Quetiapine

Goal(s):
- To promote and ensure use of quetiapine that is supported by the medical literature.
- To discourage off-label use for insomnia.
- Promote the use of non-pharmacologic alternatives for chronic insomnia.

Initiative:
- Low dose quetiapine (Seroquel® and Seroquel XR®)

Length of Authorization:
- Up to 12 months (criteria-specific)

Requires PA:
- Quetiapine (HSN = 14015) doses ≤50 mg/day
- Auto PA approvals for :
  - Patients with a claim for a second generation antipsychotic in the last 6 months
  - Patients with prior claims evidence of schizophrenia or bipolar disorder
  - Prescriptions identified as being written by a mental health provider

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/
- Zolpidem is available for short-term use (15 doses/30 days) without PA.

Table 1. Adult (age ≥18 years) FDA-approved Indications for Quetiapine

Bipolar Disorder	
Major Depressive Disorder (MDD)	Adjunctive therapy with antidepressants for MDD
Schizophrenia	
Bipolar Mania	
Bipolar Depression	

Table 2. Pediatric FDA-approved indications

Schizophrenia	Adolescents (13-17 years)	
Bipolar Mania	Children and Adolescents (10 to 17 years)	Monotherapy

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Do not proceed and deny if diagnosis is not listed in Table 1 or Table 2 above (medical appropriateness)	
2. Is the prescription for quetiapine less than or equal to 50 mg/day? (verify days' supply is accurate)	**Yes**: Go to #3	**No:** Trouble-shoot claim processing with the pharmacy.
3. Is planned duration of therapy longer than 90 days?	**Yes:** Go to #4	**No:** Approve for titration up to maintenance dose (60 days).
4. Is reason for dose ≤50 mg/day due to any of the following: • low dose needed due to debilitation from a medical condition or age; • unable to tolerate higher doses; • stable on current dose; or • impaired drug clearance? • any diagnosis in table 1 or 2 above?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny for medical appropriateness. Note: may approve up to 6 months to allow taper.

P&T/DUR Review: *8/2020 (SF); 3/19 (DM); 9/18; 11/17; 9/15; 9/10; 5/10*
Implementation: *1/1/18; 10/15; 1/1/11*

Pimavanserin (Nuplazid™) Safety Edit

Goals:

- Promote safe use of pimavanserin in patients with psychosis associated with Parkinson's disease.

Length of Authorization:

- Up to 6 months

Requires PA:

- Pimavanserin

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the treatment for hallucinations and/or delusions associated with Parkinson's disease?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Are the symptoms likely related to a change in the patient's anti-Parkinson's medication regimen?	**Yes:** Go to #4 Consider slowly withdrawing medication which may have triggered psychosis.	**No:** Go to #5
4. Has withdrawal or reduction of the triggering medication resolved symptoms?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #5
5. Is the patient on a concomitant first- or second-generation antipsychotic drug?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #6
6. Has the patient been recently evaluated for a prolonged QTc interval?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh; Deny; medical appropriateness

P&T Review: *8/2020 (SF); 3/19 (DM); 9/18; 3/18; 01/17*
Implementation: *4/1/17*