DSH PSYCHOTROPIC MEDICATION Operational Procedures

LUMATEPERONE PROTOCOL:

I. Indications:

A. At least one of the following clinical indications is present and documented in the chart:

1. DSM diagnosis of schizophrenia, schizoaffective disorder or other acute and/or chronic psychoses. Antipsychotic efficacy appears to be modest, with an effect size in pivotal trials of 0.3.

2. DSM diagnosis of intolerance of dopamine antagonism resulting in acute adverse motor effects not able to be managed with dose reduction, switch to alternate agents, or amantadine. Lumateperone is a potent antagonist at 5HT-2A receptors but only a weak antagonist at dopamine receptors and a modest modulator of glutamate.

3. DSM diagnosis of a major depressive episode with current psychotic features. Mood effects in major depressive disorder remain somewhat uncertain; however, benefits have been demonstrated in bipolar depression.

4. Severe persistent agitation, aggressive, self-injurious, stereotypic, or impulsive behaviors with evidence that a behavioral treatment, as part of a formal treatment program, was adequately implemented and found to be ineffective. Lumateperone may be less effective for aggressive behaviors than other antipsychotics.

II. Contraindications:

A. Hypersensitivity to lumateperone or any of the components of its formulation. May cause type I allergic responses, including angioedema and anaphylaxis.

B. Moderate to severe hepatic disease. Avoid combined use with valproic acid.

C. Concurrent treatment with strong cytochrome P450 3A4 inducers (e.g., carbamazepine, phenobarbital, or rifampin) or inhibitors (e.g., ketoconazole).

III. Precautions (risk/benefit analysis supports use):

A. Cerebrovascular disease and conditions that would predispose individuals to hypotension (e.g., dehydration, hypovolemia and treatment with antihypertensive medications).

B. Severe cardiovascular disease, history of QT prolongation or personal/family history of dyslipidemia.

C. Liver disease, history of hepatitis or treatment with potentially hepatotoxic drugs. Avoid concurrent use with valproic acid.

D. History of active (or, poorly controlled) seizure disorder requiring anticonvulsant treatment or use of other drugs known to lower seizure threshold without neurological consultation.

E. Poorly controlled diabetes mellitus or history of diabetic ketoacidosis.

F. Pregnancy or breast feeding.

G. Elderly neurocognitively disordered individuals with psychosis.

H. History of leukopenia or severe neutropenia. Risk is low; however, the U.S. Food and Drug Administration has mandated a class warning for the second-generation antipsychotics.

IV. The following initial workup should be completed:

A. There is informed consent or alternate legal authorization.

B. There is chart documentation of:

1. Weight/BMI.

2. Waist circumference.

C. Initial work up includes:

1. Electrolytes and liver function tests within 30 days.

2. Fasting blood sugar or hemoglobin A1C and lipid panel within 30 days.

3. AIMS rating within one year.

4. Neurology consultation (for individuals with history of an active or poorly controlled seizure disorder).

5. ECG within one year.

6. Vital signs within 30 days.

V. Monitoring:

A. Monthly monitoring includes weight and waist circumference.

B. Semi-annual monitoring includes:

1. Hepatic functions, if known liver disease

2. Basic metabolic panel, fasting blood sugar or hemoglobin A1C, lipid panel, and hepatic functions, as well as an ECG if used concurrently with other medications known to prolong the QT interval per their package insert.

C. Annual monitoring includes:

1. Serum prolactin level. Prolactin measurement should be obtained sooner if prolactin-related symptoms, such as menstrual cycle changes, galactorrhea, gynecomastia and/or hirsutism, occur. Prolactin elevation due to lumateperone treatment is very unlikely.

   Medical consultation and consideration of brain imaging with focus on the pituitary/sella turcica should be considered if symptoms persist despite interventions such as changing to a less robust dopamine antagonist medication or partial dopamine agonist medication, lowering the dose of the medication, or treating with a dopamine agonist medication.

   Prolactin-related adverse effects become increasingly likely at serum concentrations exceeding 50 ng/mL. [Please see the appendix chapter of this policy regarding hyperprolactinemia.]

   Persisting prolactin level above 100 ng/mL, despite the aforementioned cited interventions, results in medical consultation and consideration of obtaining brain imaging with focus on the pituitary/sella turcica.

2. Breast examination in men and women (including a note regarding presence or absence of galactorrhea or gynecomastia). Medical consultation and consideration of brain imaging with focus on the pituitary/sella turcica if galactorrhea or gynecomastia persist despite the interventions cited above.

3. Waist circumference.

4. ECG.

5. AIMS rating. Done quarterly if positive until twice negative.

6. Fasting serum glucose is 100 mg/dL or higher or elevated Hgb A1c results in glucose tolerance test or 2-hour postprandial glucose measurement and medical consultation.

7. Nutritional consultation and appropriate dietary and exercise interventions if any of the following weight gain indicators occurs:

   a. Weight % increase of 5% in one month, 7.5% in three months, or 10% in six months.

   b. Waist circumference increase from below 35in. to > 35in. for females and from below 40in. to > 40in. for males

c. BMI increase from normal to overweight (less than 25 to higher than 25) or from overweight to obese (25-29.9 to 30 or higher).

8. Abnormal or rising triglyceride and cholesterol levels result in medical consultation and appropriate interventions.

VI. Dose initiation and titration:

A. Initial and maintenance dose is 42 mg QD with food. There is no dose titration. Doses higher than 42 mg per day should not be used. Nevertheless, use of higher doses for more than 15 days requires an MRC or TRC consultation.

B. Dosage accounts for drug-drug interactions:

1. Use is contraindicated with strong cytochrome P450 3A4 inducers (e.g., carbamazepine, phenobarbital, or rifampin).

2. Lumateperone is contraindicated with strong cytochrome P450 3A4 inhibitors (e.g., ketoconazole). It also is contraindicated in combination with valproic acid.

C. Pulse and blood pressure are monitored prior to dose administration as clinically indicated (e.g., during titration or at doses above maximum) for one week after starting or increasing dose. Signs of orthostatic hypotension are documented if individual can verbalize.

Pulse and blood pressure are recorded first in the seated position after three minutes and then in the standing position after two minutes. If individual cannot stand up, he/she is monitored closely until the dose is stable if he/she is known to try to get up and not follow recommendations.

If any recorded item lies outside following parameters, the measure is repeated after 15 minutes. If the item is then within the parameter, lumateperone may be given. If still outside the parameter, the physician is called to assess before dose administration.

The parameters are:

1. Systolic blood pressure <90 mm or >150 mm.

2. Diastolic blood pressure <60 mm or >100 mm.

3. Drop >20 mm in systolic or diastolic pressure between sitting and standing.

4. Pulse >120/min or <60/min.

VII. Possible adverse reactions:

A. Type I allergic reactions, including angioedema or anaphylaxis.

B. Sedation or fatigue.

C. Insomnia.

D. Agitation and anxiety.

E. Dyspepsia and other upper gastrointestinal symptoms.

References:

American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. (2004). Consensus development conference on antipsychotic drugs and obesity and diabetes. *Obes Res*, 12, 362-368.

Intra-cellular Therapies, I. (2019). Caplyta (lumateperone) package insert. Towson, Maryland.