Pimavanserin (NUPLAZID)

Criteria for Use

December 2016; revised May 2018, August 2019

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**
The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive pimavanserin.*

☐ The patient has a diagnosis of dementia-related psychosis due to Alzheimer's disease, Lewy Body Dementia or other dementia not secondary to Parkinson disease.

☐ The patient has known QTc prolongation, history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, or the presence of congenital prolongation of the QT interval, or is taking other medications known to prolong the QT interval.

☐ The patient is taking another antipsychotic (see *Issues for Consideration*).

☐ The patient is taking a moderate or strong CYP3A4 inducer.

Inclusion Criteria

☐ The patient meets the National Institute of Neurological Disorders and the National Institute of Mental Health Work Group's diagnostic criteria for Parkinson Disease Psychosis (PDP)[1]:

- Presence of at least one of the following PDP symptoms: illusions, false sense of presence, hallucinations or delusions
- Primary diagnosis of Parkinson disease (PD)
- The symptoms of PDP occur after the onset of PD
- The duration of PDP symptoms are recurrent or continuous for 1 month
- Symptoms are not better accounted for by another cause such as dementia with Lewy bodies, psychiatric disorder such as schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features or a general medical condition including delirium.

☐ The prescriber is a psychiatrists, neurologist or geriatric medicine specialist.

[1]Ravina B, Marder K, Fernandez HH, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. Movement Disorders 2007;22(8):1061-8.

Renewal Criteria

- Assess pimavanserin's effectiveness within 3 months after initiation through either in-person or telephone interview with the patient and/or caregiver. Discontinue if ineffective.

Dosage and Administration

- The recommended dose of pimavanserin is 34 mg, taken orally once daily, without titration.
- Pimavanserin can be taken with or without food.
- Coadministration with Strong CYP3A4 Inhibitors: the recommended dose of when coadministered with strong CYP3A4 inhibitors (e.g., ketoconazole) is 10 mg, taken orally as one tablet once daily.

Issues for Consideration

- Pimavanserin is an atypical antipsychotic indicated for the treatment of hallucinations and delusions associated with Parkinson disease psychosis.
- There is no clear first-line pharmacologic choice for the treatment of Parkinson disease psychosis. Frequently tried alternative treatments for Parkinson disease psychosis are low doses of quetiapine or clozapine. Five small, low quality trials have found quetiapine's efficacy equivalent to placebo. Two trials of moderate size and quality have found clozapine to be more effective that placebo. Clozapine's requirement for weekly ANC monitoring and dispensing may be burdensome in this patient population. See the pimavanserin monograph for additional discussion.
- Box Warning: Increased mortality in elderly patients with dementia-related psychosis. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Pimavanserin is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis.
- Mortality rates were greater with pimavanserin in clinical trials reported to FDA prior to pimavanserin's approval.[2] There were 57 deaths among the 1575 persons enrolled in clinical trials: 48/901 (5.3%) within 30 days of the last dose of pimavanserin and 1/210 (0.5%) within 30 days of the last dose of placebo. Among persons exposed to pimavanserin for >6 months 51/459 (11.1%) died. The likelihood of death >60 days after initiation was 3 times greater with pimavanserin in the Phase 3 trial: 4 in the pimavanserin group and 1 in the placebo group (OR 2.94; 0.28, 148). Deaths were attributed to myocardial infarction, septic shock, sepsis, respiratory distress in the pimavanserin group, and cardiorespiratory arrest (placebo). All deaths were considered unlikely or not related to treatment.
- Post marketing pimavanserin adverse drug event (ADE) reporting to FDA included 712 patient deaths among 5735 reported ADEs (12.4%).[3]
- The FDA reviewed all postmarketing reports of deaths and serious adverse events reported with the use of pimavanserin and has determined that there was no evident pattern to suggest a drug effect.[4]
- Use in combination with another antipsychotic is associated with increased mortality rate and serious adverse events comparted to pimavanserin alone.[5] It is recommended to discontinue current antipsychotics before starting pimavanserin. The Institute for Safe Medication Practices noted that 318 out of 2236 pimavanserin adverse event cases reported to FDA between April 2016 and March 2017 were taking another antipsychotic. Patients' using pimavanserin and another antipsychotic had worse outcomes compared to those taking pimavanserin; mortality 13% vs. 11% and hospitalizations 15% vs. 11%.[6]
- Pimavanserin prolongs the QT interval. The use of pimavanserin should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval including Class 1A antiarrhythmics or Class 3 antiarrhythmics, certain antipsychotic medications, and certain antibiotics. Pimavanserin should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval.
- Pimavanserin failed to demonstrate efficacy as an augmentation treatment for schizophrenia.[7]

[2] FDA Medical Review, NDA 207-318 Nuplazid® (pimavanserin). April 9, 2015.

[3] FDA ADERS Public Dashboard

[4] https://www.fda.gov/Drugs/DrugSafety/ucm621160.htm. Accessed November 26, 2018.

[5] Ballard C, Isaacson S, Mills R, et al. Impact of current antipsychotic medications on comparative mortality and adverse events in people with Parkinson disease psychosis. JAMDA 2015;16:898.e1-e7.

[6] Institute for Safe Medication Practices, Quarterly Watch, November 1, 2017. www.ismp.org/QuaterlyWatch/ accessed May 22, 2016.

[7] Meltzer HY, Elkis H, Vanover K, Weiner DM, van Kammen DP, Peters P, Hacksell U. Pimavanserin, a selective serotonin (5-HT)2A-inverse agonist, enhances the efficacy and safety of risperidone, 2mg/day, but does not enhance efficacy of haloperidol, 2mg/day: comparison with reference dose risperidone, 6mg/day. Schizophr Res. 2012 Nov;141(2-3):144-52.

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