Drug Monograph

Drug/Drug Class:	**Nuplazid® (pimavanserin tartrate) tablet/ Atypical Antipsychotics (Selective Serotonin Inverse Agonists)**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Nuplazid® is available in a coated tablet that contains 17 mg pimavanserin tartrate respectively. Manufacturer: Acadia Pharmaceuticals Inc., San Diego, CA 92130
Summary of Findings:	Nuplazid® was evaluated in a randomized, double-blind, placebo-controlled, 6-week clinical trial that assessed its efficacy in 199 patients with Parkinson's disease psychosis. Nuplazid® significantly decreased the frequency and/or severity of hallucinations and delusions by 37% compared with placebo (14%) without affecting motor symptoms when measured by the Scale for the Assessment of Positive Symptoms adapted for Parkinson's Disease (SAPS-PD).
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☒ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☒ Appropriate Indications ☐ Non-Preferred Agent

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [3]

Psychosis doesn't just affect individuals with psychiatric disorders such as schizophrenia. It also affects other illnesses, including Parkinson's disease. Over five million people worldwide have Parkinson's disease, struggling with symptoms such as shaking, stiffness, slowness of movement and instability. Research has shown that psychosis may affect 1 in 5 Parkinson's patients, with as many as 2 out of 3 patients experiencing minor symptoms. Patients primarily experience visual hallucinations with around 10 to 20% of patients experiencing auditory hallucinations.

Dosage Form(s) [1]

Nuplazid® is available in a coated tablet that contains 17 mg pimavanserin tartrate.

Manufacturer [1]

Acadia Pharmaceuticals Inc., San Diego, CA 92130

Indication(s) [1]

Nuplazid® is indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

Clinical Efficacy [1,2] (mechanism of action/pharmacology, comparative efficacy)

Nuplazid® is an atypical antipsychotic. While its mechanism of action is unknown, it is thought that it may be mediated through inverse agonist and antagonist activity at serotonin 5-HT(2A) and serotonin 5-HT(2C) receptors without affecting dopamine.

Pharmacokinetics:

	Nuplazid®
Protein binding	95%
Metabolism	Liver, via CYP3A4/5 (major) to active metabolite
Excretion	Feces, 1.53% unchanged drug Urine, 0.55% unchanged drug; < 1% active metabolite
Half-life	57 hours, parent drug 200 hours, active metabolite
Volume of distribution	2173L

Treament with Nuplazid® improved the frequency and/or severity of hallucinations and delusions compared with placebo in patients with Parkinson's disease psychosis.

STUDY DESIGN	Randomized, double-blind, placebo-controlled, multicenter, 6 week phase 3 study (n=199).
INCLUSION CRITERIA	Adults (40 years or older) with Parkinson's disease psychosis
EXCLUSION CRITERIA	Patients receiving antipsychotic agents.
TREATMENT REGIMEN	Patients were randomized to receive Nuplazid 40 mg orally once daily or placebo.
RESULTS	Nuplazid significantly decreased the frequency and/or severity of hallucinations and delusions after 6 weeks compared with placebo, as measured by the SAPS-PD (-5.79 vs -2.73). Significantly more patients in the Nuplazid group experienced at least a 20% reduction in SAPS-PD scores compared with placebo (63% vs 47%). Patients had an approximate mean SAPS-PD score of 15 at study entry and experienced a 37% improvement with Nuplzaid and a 14% improvement with placebo without affecting motor symptoms.
SAFETY	Adverse events leading to discontinuation of study drug occurred in 10 patients in the Nuplazid arm and 2 patients in the placebo arm.

Contraindications [(1)]

- None

Warnings and Precautions [(1)]

- Risk of death is increased in elderly patients with dementia-related psychosis
- QT prolongation has been reported; avoid use in patients with known QT prolongation, history of cardiac arrhythmias, congenital QT prolongation, or if increased risk of torsade de pointes or sudden death exists, including those with symptomatic bradycardia, hypokalemia, or hypomagnesemia.
- Avoid concomitant use with other drugs known to prolong the QT interval, including Class 1A antiarrhythmics, Class 3 antiarrhythmics, certain antipsychotics (eg. ziprasidone, chlorpromazine), and certain antibiotics (eg. gatifloxacin, moxifloxacin).

Adverse Effects [(1)]

Most common, ≥ 2 %	**Nuplazid® (n=202)**	**Placebo (n=231)**

Nausea	7%	4%
Peripheral edema	7%	2%
Confusional state	6%	3%
Hallucination	5%	3%
Constipation	4%	3%
Gait disturbance	2%	<1%

Drug Interactions [(1)]

- Class 1A antiarrhythmics: quinidine, procainamide, disopyramide
- Class 3 antiarrhythmics: amiodarone, sotalol
- Antipsychotics: ziprasidone, chlorpromazine, thioridazine
- Antibiotics: gatifloxacin, moxifloxacin
- CYP3A4 inhibitors, strong: ketoconazole, itraconazole, clarithromycin, indinavir
- CYP3A4 inducers, strong: rifampin, carbamazepine, phenytoin, St. John's wort

Dosage and Administration [(1)]

The FDA recommended dose is 34 mg (2-17mg tablets) orally once daily, without titration, and administered with or without food. Dosage adjustments may be necessary when used concomitantly with strong CYP3A inhibitors or inducers.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	Dose	COST/ MONTH
Pimavanserin	Nuplazid	Acadia	17 mg tab	2 tablets daily	$1,950*

* Wholesale Acquisition Cost

Conclusion

Nuplazid® is an oral atypical antipsychotic that is the first of a new class of drugs, selective serotonin inverse agonists (SSIA), that specifically target serotonin receptors without affecting dopamine. Nuplazid® is the only FDA-approved treatment for hallucinations and delusions associated with Parkinsons' disease psychosis. In a phase 3, randomized, double blind, placebo-controlled study, results showed that Nuplazid® significantly decreased the frequency and/or severity of hallucinations and delusions after 6 weeks compared with placebo, as measured by the SAPS-PD (-5.79 vs -2.73). This occurred without affecting motor symptoms. Also, more patients in the Nuplazid® group experienced at least a 20% reduction in SAPS-PD scores compared with placebo (63% vs 47%). Nuplazid® is generally well tolerated with the most common adverse effects being nausea, peripheral edema, and confusion. It can prolong the QT interval and concomitant use of other agents that prolong the QT interval should be avoided. The drug should not be used in elderly patients with dementia-related psychosis.

Recommendation

The Division recommends adding this drug to the current Atypical Antipsychotics Clinical Edit.

References

1. Product Information: Nuplazid™, pimavanserin tablets. Acadia Pharmaceuticals Inc, San Diego, CA, 04/2016
2. Cummins J, Isaacson S, Mills R et al: Pimavanserin for patients with Parkinson's disease psychosis: a randomized, placebo-controlled phase 3 trial. Lancet 2014; 83 (9916): 533-540.
3. Tartakovsky, Margarita. "What you need to know about psychosis in parkinson's disease." Retrieved 11/22/2016 from www.psychcentral.com

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