Drug Use Research & Management Program
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New Drug Evaluation: **pimavanserin** tablet, oral

Date of Review: January 2017
Generic Name: pimavanserin
PDL Class: Antipsychotics, Second Generation

End Date of Literature Search: September 28, 2016
Brand Name (Manufacturer): Nuplazid™ (Acadia Pharmaceuticals)
AMCP Dossier Received: yes

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

Research Questions:

- What is the evidence for efficacy of pimavanserin for the treatment of hallucinations and delusions associated with Parkinson's disease (PD) psychosis and how does it compare to current therapy?
- Is pimavanserin safe for the treatment of PD psychosis?
- Are there subpopulations of adults (i.e. age, gender, ethnicity, disease duration or severity) for whom pimavanserin is more effective or associated with more harms?

Conclusions:

- There is low quality evidence based on one 6-week randomized controlled trial (RCT) that pimavanserin is associated with statistical improvement in the Scale for the Assessment of Positive Symptoms in Parkinson's disease (SAPS-PD), a new clinical instrument designed and modified during phase 2 and 3 clinical trials to assess reduction in hallucinations and delusions in patients with PD. In patients with weekly hallucinations or delusions lasting at least a month, 14% of patients in the pimavanserin group (vs. 1% in the placebo group) had a complete response (defined as a SAPS-PD score of 0) at the end of treatment (NNT=8).[1]
- There is insufficient evidence comparing pimavanserin to other therapies for the treatment of PD psychosis or to evaluate efficacy in subpopulations.
- There is insufficient evidence for the treatment of psychosis associated with other conditions (e.g., schizophrenia) or for PD symptoms other than hallucinations and delusions (e.g., tremor, rigidity, etc.).
- Pimavanserin FDA labeling has a boxed warning for increased mortality in elderly patients with dementia-related psychosis. In clinical trials in patients with PD psychosis, pimavanserin use was associated with a numerically greater number of serious adverse events and death.[1] There is insufficient evidence to evaluate long term safety of pimavanserin for the treatment of PD psychosis and long-term data are needed to determine the significance of harms observed in short-term phase 3 trials.

Recommendations:

- A safety edit to restrict use to populations that may benefit from this drug without undue harms is proposed in **Appendix 3**.

Background:

Parkinson's disease (PD) is a progressive disease characterized by loss of dopaminergic neurons in the substantia nigra, the motor center of the brain.[2,3] Exact etiology of PD is unclear, but it has been associated with defects in the parkin gene, tau gene or alpha-synuclein proteins which can cause nerve damage characteristic of PD and lead to common neuromuscular signs of PD.[3] Diagnosis is typically based on clinical signs and symptoms including symptoms of bradykinesia, muscular rigidity, resting tremor and postural instability.[2] Loss of dopaminergic neurons in other parts of the brain can also lead to non-motor symptoms including decreased autonomic function, fatigue, sleep disturbances, mood disorders, and erectile dysfunction.[2] Long-term complications of PD include dementia, psychosis, hallucinations and delusions. Up to 40-50% of patients with PD experience thinking, behavioral problems or psychosis.[1] Generally, presence of hallucinations indicates a worsening prognosis over time.[4,5] In a small study (n=48), 81% of patients with minor "benign" hallucinations had progressive symptoms characterized by delusions or loss of insight within 3 years.[6] Presence of psychosis symptoms has also been positively associated with nursing home admission.[4,7]

Currently there are no FDA-approved therapies for treatment of PD psychosis. Guidelines from the American Academy of Neurology for psychosis in PD recommend off-label use of clozapine or quetiapine.[8] The guidelines note that clozapine is probably an effective treatment as it demonstrated superior improvement in psychosis symptoms compared to placebo in at least 1 RCT.[8] However, because clozapine is associated with serious adverse effects and requires frequent monitoring, it may not be an optimal treatment for many patients. Guidelines also recommend quetiapine as a treatment option.[8] However, while quetiapine is generally well tolerated, it has not demonstrated consistent efficacy compared to placebo for reduction of symptoms associated with PD psychosis.[9]

In 2016, the FDA approved pimavanserin as the first treatment for hallucinations and delusions associated with Parkinson's disease. Pimavanserin acts as a selective inverse agonist and antagonist at serotonin 5-HT_{2A} and 5-HT_{2C} receptors.[10] In patients with PD, these receptors are located in high concentrations in the visual and auditory areas of the brain and are thought to be linked with psychosis symptoms.[11] Theoretically, selective blockade of these receptors will decrease psychosis symptoms without causing any adverse motor effects associated with dopamine blockade. This is especially important in PD because many antipsychotics, including clozapine and quetiapine, have dopamine antagonist effects and have the potential to worsen motor symptoms of Parkinson's disease. Ongoing trials are also examining pimavanserin for psychosis related to Alzheimer's disease and as adjuvant therapy in addition to other antipsychotics in schizophrenia.[12]

Pimavanserin achieved accelerated approval as a breakthrough therapy for PD psychosis primarily on the results from one phase 3 trial of 199 patients with PD and persistent hallucinations or delusions severe enough to warrant antipsychotic therapy.[11] Data from additional phase 2 studies, unpublished phase 3 trials, and open-label extension studies were used to assess safety. During these trials approximately 278 patients were exposed pimavanserin for more than 12 months and 141 for more than 24 months.[1] In the single published phase 3 trial, patients were randomized to pimavanserin 34 mg daily or placebo and followed for 6 weeks.[11] In this trial, symptom improvement was assessed using a newly developed tool called the Scale for the Assessment of Positive Symptoms in Parkinson's disease (SAPS-PD).[11] There is currently no universally used scale to assess symptoms in PD,[8] and the tools used to assess hallucinations and delusions in PD psychosis have evolved over the course of these clinical trials. Initial phase 3 trials utilized the Scale for the Assessment of Positive Symptoms sections for hallucinations and delusions (SAPS-HD) to assess symptom improvement. Due to lack of improvement with use of this scale in these trials, the assessment tool was further modified to the Scale for the Assessment of Positive Symptoms in Parkinson's disease (SAPS-PD).[11] The SAPS-PD is a 9-item questionnaire which specifically assesses the frequency or severity of the most common types of hallucinations or delusions; namely, auditory hallucinations, voices conversing, somatic or tactile hallucinations, visual hallucinations, persecutory delusions, delusions of jealousy, and delusions of reference.[13] The SAPS-PD also includes a

global assessment for hallucinations and delusions.[13] Each item is rated on a 0 to 5 scale with a total assessment range of 0 to 45.[13] Prior to this trial, the SAPS-PD score had not been prospectively evaluated in a trial. In order to establish consistent efficacy compared to other assessment scales, the Clinical Global Impression-Improvement scales for improvement (CGI-I) and severity (CGI-S) were also evaluated as exploratory outcomes.[11] Upon retrospective comparison of the SAPS-PD and CGI-I scales in a population of phase 3 patients with PD, a 1 point change in the CGI-I scale, was associated with a 2.33 reduction in SAPS-PD score.[13] CGI-I scores evaluate symptom improvement on a 1-7 scale with a change of 1 corresponding to a minimally improved change in symptoms.[14] Complete improvement in symptoms (defined as a SAPS-PD score of 0 at the end of treatment) was also assessed in a post-hoc analysis by FDA. Activities of daily living and adverse motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) sections 2 and 3. Using these scales, individual items related to motor function and daily activities are rated on a 0-4 scale with higher scores indicating mores severe disease. Exact assessment of disease severity has not been established, but some studies suggest that mild disease corresponds to scores of less than 12 or 16 for daily activities or less than 32 for motor function.[15,16] Similarly, severe disease corresponds to scores greater than 29 or 32 for daily activities and 58 for motor function.[15,16]

Pimavanserin is the first drug FDA approved for the treatment of hallucinations and delusions associated with PD. This document examines the efficacy and safety supporting use of pimavanserin in PD psychosis and makes recommendations for PDL status and PA criteria.

See **Appendix 2** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning 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:
Pimavanserin was approved primarily on the basis of a single phase 3 clinical trial.[11] The primary outcome in this trial was change in SAPS-PD score at 6 weeks. This study also examined efficacy using the CGI scales for improvement and severity of symptoms and the UPDRS scales for daily activity level and motor function. Because the SAPS-PD scoring tool has not been previously validated and this trial only demonstrated a modest improvement in the SAPS-PD score, the FDA also looked at post-hoc analyses of patients who achieved complete resolution of their symptoms.[1]

Patients involved in this trial were a mean 72 years of age and had symptoms of PD psychosis lasting at least 1 month.[11] Only patients with frequent symptoms (occurring at least weekly) and symptoms severe enough to necessitate medical treatment were included in the trial.[11] Baseline SAPS-PD score was 14.7 (standard deviation [SD] 5.55) for placebo group and 15.9 (SD 6.12) for pimavanserin.[11] Patients were excluded if they had psychosis due to other disorders, dementia, baseline cognitive dysfunction, uncontrolled serious mental illness or were taking concurrent medications including antipsychotics, anticholinergics or QT-prolonging medications.[11] Approximately 18% had previously been on an antipsychotic within 21 days of trial enrollment.[11] Because dopaminergic treatments for PD may also exacerbate psychosis symptoms, patients were required to be on a stable medication regimen for their disease.[11] The study was also designed with a 2 week run-in period before randomization in order to elicit a placebo response. Prior trials had demonstrated a significant placebo response, limiting investigator's ability to detect significant differences between groups.[17] During the 2 week run-in period, patients received non-pharmacological psychosocial therapy consisting of daily interactions between the patient and their caregiver.[11] The therapy was intended to provide baseline standard of care prior to the treatment phase and to help the patient and caregiver manage psychosis symptoms.[17] Patients who responded to psychosocial therapy (assessed based on SAPS-PD score) were also excluded from the trial.[11] The exact number of patients excluded due to response to non-pharmacological therapy was not reported, but overall 36.6% (n=115) of patients screened were excluded from the study, and 16.9% (n=53) failed to meet baseline inclusion criteria for symptom severity (SAPS-PD score ≥3 out of 5 in at least one global symptom and one specific symptom, or a neuropsychiatric inventory score >4 for hallucination and/or delusion items).[11] Continuation of the non-pharmacological psychosocial therapy was not required during the 6-week treatment period, but the caregiver was involved in

all follow-up visits.[17] Inclusion of this run-in period may limit applicability to real-world populations and highlights that non-pharmacological psychosocial therapy many improve symptoms in some patients.

Overall, the phase 3 study used for FDA approval had moderate risk of bias. The study was a randomized, double blinded, placebo-controlled trial. Methods to randomize patients appeared adequate, but differences in baseline characteristics were still present, notably in gender (42% female in placebo vs. 33% in the pimavanserin group), time since first PD psychosis symptoms (5.5 months longer in placebo group), and stereotactic surgery (11% in pimavanserin vs. 3% in placebo).[11] The clinical implications of these differences are unclear. With greater time since diagnosis of PD psychosis, patients randomized to placebo may have had more progressive disease resulting in a more conservative estimate of the treatment effect. All patients and assessors were blinded to treatment assignment. However, the subjective assessment of symptom improvement increases risk of bias. Because adverse events were more common in the pimavanserin group, risk of unblinding and knowledge of treatment assignment is higher. Attrition was relatively low compared to other studies conducted in populations with PD psychosis with 15.2% of patients in the pimavanserin group versus 7.4% in the placebo group who withdrew from the study.[11] Multiple sensitivity analyses conducted using last-observation-carried-forward, worst-observation-carried-forward and mixed model repeated measures analysis all resulted in similar effect size, indicating low attrition bias. Protocol violations were noted in 6 patients (5 in the pimavanserin group) who took quetiapine or clozapine during the trial which may bias results in favor of the treatment group.[17] Risk of reporting bias was high. This study was funded by Acadia Pharmaceuticals who was involved in trial design, governance, statistical analysis and publication. In addition, 2 prior unpublished phase 3 studies (NCT00477672, NCT00658567) using alternate assessment methods for symptom improvement (primarily SAPS-HD) did not demonstrate statistical significance compared to placebo.[12]

Pimavanserin demonstrated a mean 3.06 point reduction in SAPS-PD score compared to placebo at 6 weeks (95% CI -4.91 to -1.20; p-value 0.0014).[11] Total scores on the SAPS-PD scale can range from 0 to 45. A statistical difference between groups was apparent at week 4 and continued until treatment discontinuation.[1] Similar trends in symptom improvement were observed in CGI-I (RD -0.67, 95% CI -1.06 to -0.27; p=0.0011) and CGI-S (RD -0.58, 95% CI -0.92 to -0.25; p=0.0007), though these are not clinically meaningful reductions.[11] In a post-hoc analysis conducted by the FDA of patients who completed 6 weeks of treatment (n=173), 14% of patients in the pimavanserin group (vs 1% in placebo group) had a complete response (defined as a SAPS-PD score of 0) at the end of treatment.[1] However, this analysis did not account for patients who discontinued the trial before completion of 6 weeks (15.2% in pimavanserin vs. 7.4% in placebo groups). Subgroup analyses based on age, gender, and race were similar to results in the overall population.[1]

However, despite the fact that this trial demonstrates statistically significant changes in the SAPS-PD score, questions remain about the efficacy of pimavanserin. Further information is necessary to establish a minimal clinically important difference with SAPS-PD and establish definite correlations with symptom improvement. Data from previous clinical trials suggest that a change of 2.33 points correlates with a clinically significant difference of 1 point in the CGI-I scoring tool.[13] However, review by the FDA suggests that a 5 to 7 point change may be a more accurate assessment of clinical improvement.[17] In this trial, SAPS-PD demonstrated a moderate correlation with CGI-I (Spearman's Rank correlation coefficient [R] 0.6, 95% CI 0.5 to 0.7) and CGI-S (R 0.5, 95% CI 0.4 to 0.6) but no correlation with sleep or psychosis (R<0.2).[11] A lack of correlation with psychosis indicates that SAPS-PD may not be an adequate surrogate marker for overall psychosis symptoms. Because it focuses on specific types of hallucinations and delusions, the SAPS-PD may give more weight to auditory hallucinations and does not evaluate other psychotic symptoms.[17]

Pimavanserin represents a drug with a unique mechanism of action which demonstrates benefit in patients with PD psychosis. Prior to its approval, patients with PD psychosis had few options for treatment. Current standard of care utilize off-label clozapine or quetiapine which either have stringent monitoring parameters or limited efficacy. Pimavanserin use in patients with moderate symptoms of PD psychosis has shown statistical improvement, but its efficacy in patients with

severe psychosis and with treatment durations longer than 6 weeks is still unknown. Further studies designed and powered to examine long-term symptom improvement, clinically relevant outcomes of disease progression or admission to nursing homes, and comparisons to other off-label treatments for PD psychosis would help define pimavanserin's place in therapy.

Clinical Safety:

Safety analyses included patients from multiple controlled trials. Early discontinuation due to adverse events was also more common in patients taking pimavanserin (n=16/202, 8%) compared to placebo (n=10/231, 4%).[10] Rates of most common adverse reactions occurring during clinical trials are listed in Table 1. Serious adverse events occurred more frequently in the pimavanserin group (n=16/202, 8%) compared to placebo (n=8/231, 3.5%).[1] However, serious adverse events were varied with no unifying pathological mechanism and were unlikely to be related to the study drug.[1] In an unpublished open-label extension study of patients previously enrolled in an RCT with pimavanserin (n=459), most common adverse events were falls (26.4%), UTI (16.6%), and hallucinations (13.5%).[18] Median length of follow-up for the extension study was 439 days.[18]

Table 1. Frequency of common adverse effects associated with pimavanserin[10]

	Pimavanserin (n=202)	Placebo (n=231)
Peripheral edema	7%	2%
Nausea	7%	4%
Confusional state	6%	3%
Hallucination (visual, auditory, tactile and somatic)	5%	3%
Constipation	4%	3%
Gait disturbances	2%	<1%

Other adverse events of interest included musculoskeletal effects, QTc-interval prolongation, and mortality in elderly patients with dementia-related psychosis. Because many antipsychotics also have undesired musculoskeletal effects, phase 3 trials specifically examined occurrence of musculoskeletal adverse effects. No differences were observed between placebo and treatment groups (evaluated by UPDRS score).[1] However, development of motor symptoms with long-term treatment greater than 6 weeks remains uncertain. Because motor symptoms typically progress in PD, establishing a causal relationship between long-term motor symptoms and pimavanserin would be challenging. QTc interval was also prolonged in patients taking pimavanserin (mean 5-8 milliseconds) compared to placebo.[1,11] Patients with prolonged QTc interval or those taking concomitant medications known to prolong the QT interval were excluded from the study.[11] Death was more frequent in the pimavanserin group compared to placebo (4 patients vs. 1 patient, respectively), though the number of deaths were too small to be statistically significant.[1] Overall, numbers of patients experiencing these events were small, and cause of death did not have any clear pathology.[1] In all cases, investigators thought cause of death was unlikely or not related to treatment.[1] However, because of the disproportionate increase in serious adverse events and death without an underlying pathological cause, a boxed warning for increased risk of death in elderly patients with dementia related psychosis was included in the labeling. In addition, in animal trials, respiratory distress associated with an increase in phospholipids was observed in animal trials at doses 5-10 times the recommended human dose.[1] No evidence of respiratory problems was observed in clinical trials, but this warning was included in the FDA labeling.[1] No post-marketing risk evaluation is recommended for this drug, but further monitoring of adverse events should be conducted to evaluate long-term safety outcomes in the elderly population. Recommendations from the FDA for Phase 4 post-marketing trials include a randomized withdrawal trial, further evaluation of lung tissue from animals, and drug-drug interaction studies to evaluate effects of CYP3A4 inducers.[1]

Pharmacology and Pharmacokinetic Properties:[10]

Parameter	
Mechanism of Action	Selective inverse agonist and antagonist at serotonin 5-HT_{2A} and 5-HT_{2C} receptors
Absorption	T_{max}: median 6 (range 4-24) hours No significant effect of food on absorption
Distribution and Protein Binding	Mean volume of distribution was 2173 L (SD: 307 L) ~95% dose-dependent protein binding
Metabolism	Metabolism via CYP3A enzymes and to a lesser extent via CYP2J2 and CYP2D6; active metabolite
Half-Life	57 hours, active metabolite of 200 hours
Elimination	Less than 1% eliminate unchanged in the urine, 1.53% eliminated in feces

Abbreviations: SD = standard deviation; T_{max}= time to maximum concentration

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Improvement or resolution of psychosis symptoms
2) Improvement in quality of life or activities of daily living
3) Mortality
4) Nursing home admission

Primary Study Endpoint:

1) Improvement in symptoms measured by change in SAPS-PD Score

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
Cummings et al, 2014.[11] Nuplazid FDA Medical Review[17] DB, MC, PC, RCT 2 week run-in period with placebo and psychosocial therapy designed to exclude patients who respond to non-medical therapy	1. Pimavanserin 34 mg daily 2. Placebo Duration: 6 weeks (plus a 2 week run-in period)	Demographics • Mean age: 72 years • BMI: 26.3 kg/m2 • MMSE: 26.3 • Mean UPDRS-II (ADL): 19 • Mean UPDRS-III (motor): 33 • Prior antipsychotic use: 18% • Time since first PDP symptoms: 1. 30.9 months 2. 36.4 months • Female: 1. 33% 2. 42% • Stereotactic surgery 1. 11% 2. 3% Key Inclusion Criteria • Age >40 years • Idiopathic PD >1 year • Diagnosis of PDP (symptoms developing after PD diagnosis) • Severe hallucinations or delusions occurring weekly for duration >1 month requiring medical treatment Key Exclusion Criteria • Psychosis due to other causes or occurring within 6 months of stereotactic surgery • Concurrent dementia, delirium, or uncontrolled mental illness • Non-stable anti-parkinsonian medication regimens • Stroke, MI within 6 months, CHF, prolonged QT or other significant lab abnormalities • Concurrent antipsychotics, anticholinergics, or QT prolonging medications	ITT 1. 105 2. 95 PP 1. 95 2. 90 Attrition 1. 16 2. 7	Primary Endpoint Mean change in SAPS-PD Score (SE) 1. -5.79 (0.66) 2. -2.73 (0.67) RD: -3.06 (95% CI -4.91 to -1.20; p=0.0014) Secondary Endpoints Change in CGI-I Score 1. 2.78 (0.14) 2. 3.45 (0.14) RD: -0.67 (95% CI -1.06 to -0.27; p=0.0011) Change in CGI-S Score 1. -1.02 (0.12) 2. -0.44 (0.12) RD: -0.58 (95% CI -0.92 to -0.25; p=0.0007)	NA NA NA	SAE 1. 11 (11%) 2. 4 (4%) Mortality 1. 2 (2%) 2. 1 (1%) DC due to ADE 1. 10 (9.5%) 2. 2 (2%) p-values NR for safety outcomes	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Randomized via preprogramed kit randomization schedule in a block size of 4. Allocation concealment NR. P values NR for baseline characteristics; unable to determine statistical significances. Differences >5% between groups revealed more females in placebo (33 vs 42%) and more stereotactic surgery in pimavanserin group (11 vs 3%). Mean time since first PDP symptoms was greater in placebo (5.5 months). Differences may lead to a more conservative estimate of treatment effect. Performance Bias: LOW. Patients blinded with use of matching placebo. Outcome assessors (central assessor, site assessors, and caregivers) were blinded. Detection Bias: LOW. Subjective outcomes increases risk of bias, but all assessors were blinded. SAPS-PD assessed by a centralized, independent, blinded interviewer via videoconference. Attrition Bias: LOW. Attrition higher in treatment group (15.2% vs 7.4%). Analysis done with MMRM, LOCF, & WOCF in both PP & ITT populations with similar results. Crossovers & adherence were NR. 6 patients (5 taking pimavanserin) took quetiapine or clozapine during the trial which may bias results in favor of pimavanserin.[17] Reporting Bias: HIGH. Funded by Acadia Pharmaceuticals who were involved in trial design, governance, statistical analysis and publication. 2 unpublished phase 3 trials were identified. **Applicability**: Patient: Narrow inclusion criteria limit applicability in patients with comorbid conditions and in patients with infrequent symptoms (16.9% of patients did not meet baseline symptom criteria). Intervention: Run-in period excluded patients with response to non-pharmacological therapy. Efficacy/safety beyond 6 weeks is unclear. Comparator: Placebo is appropriate to establish efficacy. Outcomes: Multiple scales used to assess symptom improvement. SAPS-PD is not validated and the minimum important difference is unclear. SAPS-PD focuses on the most common symptoms and may not correlate to a general improvement in psychosis symptoms. Setting: 52 hospitals and research centers in the US and Canada.

Abbreviations [alphabetical order]: ADE = adverse drug event; ADL = activities of daily living; ARR = absolute risk reduction; BMI = body mass index; CI = confidence interval; CGI-I = clinical global impression improvement; CGI-S = clinical global impression severity; DB = double-blind; DC = discontinuation; FDA = food and drug administration; ITT = intention to treat; LOCF = last observation carried forward; mITT = modified intention to treat; MMRM = mixed model repeated measures analysis; MMSE = mini-mental status examination; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo-controlled; PDP = Parkinson's disease psychosis; PP = per protocol, RCT = randomized control trial; SAE = serious adverse events; SAPS-PD = Parkinson's disease-adapted scale for assessment of positive symptoms; SE = standard error; UPDRS = unified Parkinson's disease rating scale; WOCF = worst observation carried forward.

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Date: January 2017

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL	Carveout
ORAL	TABLET	CLOZAPINE	CLOZAPINE	Y	Y
ORAL	TABLET	CLOZARIL	CLOZAPINE	Y	Y
ORAL	TABLET	OLANZAPINE	OLANZAPINE	Y	Y
ORAL	TABLET	ZYPREXA	OLANZAPINE	Y	Y
ORAL	TABLET	QUETIAPINE FUMARATE	QUETIAPINE FUMARATE	Y	Y
ORAL	TABLET	SEROQUEL	QUETIAPINE FUMARATE	Y	Y
ORAL	TABLET	RISPERDAL	RISPERIDONE	Y	Y
ORAL	TABLET	RISPERIDONE	RISPERIDONE	Y	Y
ORAL	SOLUTION	RISPERDAL	RISPERIDONE	Y	Y
ORAL	SOLUTION	RISPERIDONE	RISPERIDONE	Y	Y
ORAL	TABLET	ARIPIPRAZOLE	ARIPIPRAZOLE	V	Y
ORAL	TABLET	ABILIFY	ARIPIPRAZOLE	V	Y
ORAL	SOLUTION	ARIPIPRAZOLE	ARIPIPRAZOLE	V	Y
ORAL	TAB RAPDIS	ARIPIPRAZOLE ODT	ARIPIPRAZOLE	V	Y
SUBLINGUAL	TAB SUBL	SAPHRIS	ASENAPINE MALEATE	V	Y
ORAL	TABLET	REXULTI	BREXPIPRAZOLE	V	Y
ORAL	CAP DS PK	VRAYLAR	CARIPRAZINE HCL	V	Y
ORAL	CAPSULE	VRAYLAR	CARIPRAZINE HCL	V	Y
ORAL	TAB RAPDIS	CLOZAPINE ODT	CLOZAPINE	V	Y
ORAL	TAB RAPDIS	FAZACLO	CLOZAPINE	V	Y
ORAL	ORAL SUSP	VERSACLOZ	CLOZAPINE	V	Y
ORAL	TABLET	FANAPT	ILOPERIDONE	V	Y
ORAL	TABLET	LATUDA	LURASIDONE HCL	V	Y
ORAL	TAB RAPDIS	OLANZAPINE ODT	OLANZAPINE	V	Y
ORAL	TAB RAPDIS	ZYPREXA ZYDIS	OLANZAPINE	V	Y
ORAL	TAB ER 24	PALIPERIDONE ER	PALIPERIDONE	V	Y
ORAL	TAB ER 24	INVEGA	PALIPERIDONE	V	Y
ORAL	TABLET	NUPLAZID	PIMAVANSERIN	V	Y
ORAL	TAB ER 24H	SEROQUEL XR	QUETIAPINE FUMARATE	V	Y
ORAL	TAB RAPDIS	RISPERDAL M-TAB	RISPERIDONE	V	Y
ORAL	TAB RAPDIS	RISPERIDONE ODT	RISPERIDONE	V	Y
ORAL	CAPSULE	GEODON	ZIPRASIDONE HCL	V	Y
ORAL	CAPSULE	ZIPRASIDONE HCL	ZIPRASIDONE HCL	V	Y

Appendix 2: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NUPLAZID safely and effectively. See full prescribing information for NUPLAZID.

NUPLAZID™ (pimavanserin) tablets, for oral use
Initial U.S. Approval: 2016

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.**
- **NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis. (5.1)**

INDICATIONS AND USAGE

NUPLAZID is an atypical antipsychotic indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. (1)

DOSAGE AND ADMINISTRATION

- Recommended dose is 34 mg, taken orally as two 17 mg tablets once daily, without titration. (2)
- Can be taken with or without food. (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 17 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- QT Interval Prolongation: Increases in QT interval; avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (≥5% and twice the rate of placebo): peripheral edema and confusional state. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ACADIA Pharmaceuticals Inc. at 1-844-422-2342 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A4 Inhibitors (e.g., ketoconazole): Reduce NUPLAZID dose by one-half. (2.2, 7.1)
- Strong CYP3A4 Inducers: Monitor for reduced efficacy. Increase in NUPLAZID dosage may be needed. (2.2, 7.1)

USE IN SPECIFIC POPULATIONS

- Renal Impairment: No dosage adjustment for NUPLAZID is needed in patients with mild to moderate renal impairment. Use of NUPLAZID is not recommended in patients with severe renal impairment. (8.6)
- Hepatic Impairment: Use of NUPLAZID is not recommended in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2016

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

Approval Criteria		
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: *01/2017*
Implementation: *TBD*