

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207318Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management Review

Application Type NDA

Application Number 207318

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Established Name Pimavanserin

(Proposed) Trade Name Nuplazid

Applicant ACADIA Pharmaceuticals Inc

Therapeutic Class Selective inverse agonism of the serotonin 5-HT2A receptor

Formulation(s) 17 mg coated tablet

Dosing Regimen 2 tablets, 34 mg orally once a day

Proposed Indication(s) Psychosis associated with Parkinson's Disease

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for pimavanserin (Nuplazid) is necessary to ensure the benefits outweigh the risks. Acadia submitted a New Drug Application (NDA 207318) to the Division of Psychiatry Products (DPP) for pimavanserin with the proposed indication for the treatment of psychosis associated with Parkinson's Disease. The Sponsor did not submit a proposed REMS or risk management plan with this application.

The safety issues of pulmonary phospholipidosis, inflammation and lung fibrosis that were found in preclinical studies as well as high incidence of death in the clinical program have been discussed internally at length in terms of need for a REMS. The pulmonary manifestations have not been found to warrant a REMS due to the potential for reversibility and high safety margin with dose. The higher incidence of death in the clinical program is concerning but is consistent with other antipsychotics used in similar populations. The lack of unifying mechanism makes this risk difficult to mitigate via a REMS. Though pimavanserin was found to be statistically significant in efficacy, the Agency has not yet determined if the efficacy has enough clinical relevance to outweigh risks that were evaluated. In addition, in light of the use of other off label, but effective, treatment, the higher rate of death and SAEs in pimavanserin treated patients are particularly concerning. An Advisory Committee meeting will assist with the evaluation of this NDA and the Agency has yet to determine if pimavanserin will be approved.

1 Introduction

This review by DRISK evaluates whether a REMS for pimavanserin (Nuplazid) is necessary to ensure the benefits outweigh the risks. Acadia submitted a New Drug Application (NDA 207318) to the DPP for pimavanserin with the proposed indication for the treatment of psychosis associated with Parkinson's Disease. The Sponsor did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Pimavanserin, a new molecular entity, is selective serotonin inverse agonist proposed for treatment of psychosis associated with Parkinson's Disease (PDP). Pimavanserin was granted breakthrough therapy and is on a priority review clock. It is proposed for oral administration as one dose of two 17 mg tablets (34 mg) daily. The precise mechanism of action of pimavanserin is unknown. The Sponsor reports that results of *in vitro* studies suggest that the principal mechanism of action is through selective inverse agonism of the serotonin 5-hydroxytryptamine (5-HT_{2A}) receptor. If approved, this will be a chronic therapy for PDP, and most often used in an outpatient setting or long term care facility.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for [Application/Number] relevant to this review:

- April 9, 2013: Type C meeting; DPP agrees to file NDA based on one strongly positive study with supportive data from other trials
- August 13, 2014: Pimavanserin granted breakthrough status
- September 1, 2015: NDA 207318 submitted to FDA. During preliminary review of the application prior to filing, the risk of pulmonary fibrosis with pimavanserin was identified
- September 29, 2015: Filing Meeting where a potential risk of is pulmonary fibrosis in humans due to findings in rat studies is discussed with the review team
- November 13, 2015: 74 day letter sent to Sponsor; Sponsor is informed “...we are concerned that pimavanserin may be used off-label in populations where the potential risk of pulmonary fibrosis is not outweighed by a commensurate clinical benefit. These populations would include patients with autism, schizophrenia and bipolar disorder.”
- November 23, 2015: Midcycle meeting
- December 3, 2015: Post Midcycle meeting
- January 13, 2016: Office of Food Additives in the Center for Food Safety and Applied Nutrition (CFSAN) consult review on rat pulmonary data shows that the findings are not consistent with pulmonary fibrosis
- February 24, 2016: Wrap-Up meeting
- March 15, 2016: Late Cycle meeting
- March 29, 2016: Advisory Committee meeting. The committee voted to approve pimavanserin 12 to 2.

3 Medical Condition(s) and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Parkinson's Disease (PD) is a progressive neurodegenerative disorder caused by the degeneration of dopaminergic neurons in the substantia nigra of the brain. The characteristics of PD include bradykinesia, rigidity, tremor, and postural instability. One percent of Americans older than 60 years of age have PD with age of onset 96% of patients being greater than 50 years old. PD can be associated with psychiatric symptoms including psychosis such as hallucinations and delusions.¹ The psychosis seen in these patients was previously thought to be an effect of PD dopaminergic therapy.² However, this

¹ Gazewood, J. et al. Parkinson Disease: An Update. AAFP 2013;87:267-273

etiology is now more believed to be a result of multiple factors including treatment as well as underlying neurodegenerative processes.^{3 4} Still, overall the incidence with drug treatment increases rapidly with the duration of anti-Parkinson drug-treatment and PDP is currently viewed as relatively common in the course of Parkinson's disease.

PDP has significant negative effect on patient quality of life as well as caregiver burden. Psychosis is considered a symptom at the end stage of the disease with two year survival in extended-care facilities and longer with home-based care.⁵

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are no antipsychotics approved for treatment of psychosis or agitation in elderly demented patients and therefore nothing specific to PDP. Though not approved for this indication, clozapine, an atypical antipsychotic, Dr. Andreason's review of the literature confirms that it is used off label with favorable results on psychosis with little effect on motor symptoms.^{6,7} Another possible treatment, quetiapine (also an atypical antipsychotic), can be considered but efficacy has not been demonstrated.⁷

4 Benefit Assessment

There was only one full Phase III study (ACP-103-020) that was statistically positive and served as the main efficacy trial for the pimavanserin NDA. Prior to NDA submission, the Agency and Sponsor agreed that this would be acceptable. This study evaluated 40 mg pimavanserin versus placebo in 199 subjects with PDP and was completed at 54 centers in North America. A modified Scale for the Assessment of Positive Symptoms (SAPS-PD) was used to measure effectiveness. This scale included nine items and was modified from a PD scale for positive symptoms to reflect only the psychosis related symptoms. Highly statistically significant improvement over placebo was demonstrated on the primary and secondary measures of psychosis over the 6-week treatment period. The pimavanserin 40 mg group demonstrated a 5.79-point improvement on the SAPS-PD compared to a 2.73-point improvement for the placebo group, a treatment difference of 3.06 points ($p=0.001$). However, Dr. Andreason, the primary clinical reviewer, notes that this particular scale has not been previously used and actual clinical results are difficult to interpret.⁶ Clinical benefits were also observed in exploratory efficacy measures such as nighttime sleep, daytime wakefulness, and caregiver burden.

² Moskowitz C, Moses H 3rd, Klawans HL. Levodopa-induced psychosis: a kindling phenomenon. *Am J Psychiatry*. 1978;135(6):669-675.

³ Huot et al. The serotonergic system in motor and non-motor manifestations of Parkinson's disease. *Exp Brain Res*. 2013;230(4):463-476.

⁴ Kummer et al. Neuropsychiatry of Parkinson's disease. *Arq Neuropsiquiatr*. 2009;67(3B):930-939.

⁵ Factor, S. A., P. J. Feustel, J. H. Friedman, C. L. Comella, C. G. Goetz, R. Kurlan, M. Parsa, R. Pfeiffer, and P. S. Group, 2003, Longitudinal outcome of Parkinson's disease patients with psychosis: *Neurology*, v. 60, p. 1756-61.

⁶ Friedman, J. et al. Low Dose Clozapine for the Treatment of Drug-Induced Psychosis in Parkinson's Disease *NEJM*; 340:757-763.

⁷ Andreason, Paul. Primary Review of Pimavanserin April 13, 2016.

The overall magnitude of effect was measured by the Clinical Global Impression scale (CGI). This scale is designed in National Institutes of Mental Health trials to offer an assessment of the healthcare provider's view of a patient's global functioning before and after an intervention. Although pimavanserin is overall determined to be efficacious, using this scale, the improvements in PDP are described as minimal.⁶

In his review, Dr. Andreason describes the complicating issue that clozapine is a recommended treatment and widely used, though it is not approved for the PDP indication. As a result, approving pimavanserin may mislead the PDP community to think that it is a better treatment, though no comparative studies were done.

5 Risk Assessment

There are two major safety concerns with pimavanserin that have been discussed at length between the review division and DRISK. One of these, pulmonary phospholipidosis with resultant inflammation and fibrotic lung tissue development, was observed in preclinical animal studies. The other was the serious adverse event (SAE) of death seen in the clinical program.

5.1 ANIMAL DATA: PULMONARY PHOSPHOLIPIDOSIS, INFLAMMATION AND LUNG FIBROSIS

Pimavanserin is a cationic amphiphilic drug (CAD). Exposure to CADs is known to result in phospholipidosis (PLD), the excessive accumulation of phospholipids in cells. Many known marketed drugs are CADs and cause PLD in animals and humans (fluoxetine, chloroquine, amiodarone). Usually PLD is reversible after cessation of drug treatment, however high or prolonged exposures to PLD may lead to dose-limiting functional and structural tissue damage, including damage to the lung. Amiodarone is one of the more well-known CADs to cause PLD in animals and humans. Additionally, amiodarone causes pulmonary fibrosis, which unlike PLD is irreversible and leads to morbidity and mortality.

Dr. Avila, the primary toxicology reviewer, describes that in the preclinical studies, pimavanserin induced widespread systemic PLD was seen in mice, rats, and monkeys. In rat studies, chronic inflammation and lung fibrosis secondary to this inflammation was also observed. This is particularly concerning because it alludes to the pulmonary fibrosis caused by amiodarone, which is irreversible and leads to morbidity and mortality. After a thorough review of the toxicology data, the lung fibrosis seen with pimavanserin was determined to be secondary to chronic inflammation, a minor component of the cellular response and not part of a direct process as occurs with human pulmonary fibrosis with other CADs. Dr. Avila describes this in her review as well as cites a consult review with Office of Food Additives in the Center for Food Safety and Applied Nutrition (CFSAN) where there are subject matter experts at reviewing this type of animal data. The toxicologists concluded that the chronic inflammation and fibrosis is both dose and duration dependent. In addition, the PLD, chronic inflammation and secondary lung fibrosis are likely clinically relevant but nonetheless not suggestive of the irreversible pulmonary fibrosis seen with other CADs such as amiodarone. Dr. Avila suggests patients should be carefully monitored but the current safety margin of five-fold for the PLD and other lung findings is acceptable.^{8 910}

5.2 SERIOUS ADVERSE EVENT (SAE): DEATH

Extensive internal discussion between DRISK and DPP took place regarding the SAE of death seen in pimavanserin treated patients. In his review, Dr. Andreason describes that the SAE of death in the PDP population is a common event. The presence of psychosis in patients with PD increases this risk. Dr. Andreason has evaluated that the observed deaths and other serious adverse events reported in the clinical program do not have an apparent unifying mechanism; in addition, causes are not different than what one may expect in this population of patients.

Overall a greater proportion of deaths occurred in pimavanserin-treated subjects (48/901, 5.3%) compared to those who received placebo (1/210, 0.5%). In long term open-label treatment there were 51/459 (11.1%) deaths in patients treated with pimavanserin. Causes of death include cardiopulmonary arrest, myocardial infarction, septic shock, septicemia and respiratory distress. Dr. Andreason also discusses that all SAEs in general follow the same pattern as the specific SAE of death. The observed risk of SAEs is higher in the pimavanserin treated patients for serious adverse events at 2.38 (95% CI 1.00 to 5.73, $p=0.05$) for 34 mg vs. placebo. SAEs occurred in 16/202 (7.9%) subjects taking pimavanserin 34mg versus 8/231 (3.5%) in patients treated with placebo. Dr. Andreason notes that this disproportional difference is consistent with what is observed with the use of conventional and new generation antipsychotics in the demented elderly population. The lack of unifying mechanism makes this a difficult SAE to mitigate. Clozapine and other atypical antipsychotics contain a boxed warning for increased mortality in elderly patients.

5.3 SAFETY CONCLUSIONS

Overall, the safety margin with the pulmonary inflammation and fibrosis is acceptable and likely can be monitored and reversed if seen in patients. In terms of the increased rate of death in the treated population, Dr. Andreason notes that the increased mortality risk observed in the clinical program lacks premonitory signs and mitigating the risks is not possible.⁶

6 Expected Postmarket Use

As described, PD patients are generally older and patients with PD that also have psychosis are oftentimes nearing end of life. Neurologists, psychiatrists and generalists all take care of PD patients and

⁸ Avila, Amy. Primary Pharmacology/Toxicology Review Draft February 2, 2016.

⁹ Francke, Sabine and Mog, Steven. CFSAN Memo to Amy Avila January 13, 2016.

¹⁰ Draft labeling for pimavanserin as of 4/15/16, Section 13 Nonclinical Toxicology

would be expected to prescribe pimavanserin. In many cases, patients would be expected to be in long term care facilities. However, in discussion the review team has explained that psychiatric medications are frequently used off label in attempts to treat other psychiatric illnesses such as schizophrenia and autism. As a result, child psychiatrists and developmental pediatricians may also prescribe pimavanserin.

7 Discussion of Need for a REMS

During review, there was discussion about the potential risk of pulmonary fibrosis and how this risk may manifest if pimavanserin was prescribed to patients chronically for psychosis related to other psychiatric conditions. This was particularly concerning when considering patients afflicted with diseases that affect younger patients who have long life expectancy. However, during the review it was determined that the type of inflammation and resultant fibrosis seen is not what has been seen with other CADs (e.g. amiodarone) and was more accurately classified as phospholipidosis with resulting inflammation and lung fibrosis.

The PLD, inflammation and lung fibrosis findings are only in animal data at this point. These findings are thought to be reversible since they are not consistent with the pulmonary fibrosis associated with CADs such as amiodarone. In addition, there is a significant safety margin with the animal data corresponding to the human dose. Though PLD, inflammation and lung fibrosis is concerning in PDP patients, these patients generally have limited life expectancy at this point in their disease and may benefit from the symptomatic relief in spite of the side effects. Furthermore, since these AEs take some time to develop, these side effects may not manifest in these patients that have a limited life expectancy, as is the case in this stage of their disease.

At this point in the review cycle, the Advisory Committee has not met and definitive recommendations on approval of the drug have not been made. In addition, only limited internal labeling discussions have taken place. While it is clear that, if approved, this data will be included in the label, it is unclear at this point where it will be included. Some areas under consideration for inclusion of the pulmonary inflammation and lung fibrosis from animal data would be Warnings and Precautions and Nonclinical Toxicology. Labeling should suffice in informing providers about this risk so that they monitor patients as needed for respiratory changes.

Overall, the review team has determined that the risk of PLD, inflammation, and pulmonary fibrosis observed in animal studies does not warrant the need for REMS at this time to ensure the benefit outweighs the risk. If approved, the information will be included in labeling and the sponsor may be required to conduct a postmarketing study to further characterize this potential risk in the postmarketing setting.

The increased risk of death in elderly patients with dementia-related psychosis is seen in other drugs approved for psychiatric conditions that have associated symptomatic psychosis. As mentioned, clozapine and all approved atypical antipsychotic labeling contains a Box Warning for increased mortality in elderly patients with dementia-related psychosis. Therefore, it is expected that prescribers

who manage psychosis will have some knowledge of this risk in elderly patients. This risk is a difficult one to characterize in elderly patients that suffer from dementia-related psychosis as they commonly have many comorbidities. Patients with Parkinsons Disease have these same characteristics making this same risk similarly difficult to characterize and therefore difficult to mitigate. There are no specific signs, symptoms or diseases that patients or providers can be educated about to decrease the risk. Providers and patients must consider this as the decision to use these medications are made, but cannot apply a specific intervention to minimize the risk. None of the atypical antipsychotics have a REMS to mitigate this well known risk. DRISK and DPP agree that this risk cannot be mitigated with a REMS. At this time, the review team is discussing similar labeling to address this risk for pimavanserin as is seen for atypical antipsychotics. However, since this product will be indicated for PDP, who are often elderly, this risk will be addressed at the AC meeting and is considered by Dr. Andreason to be an approvability issue.

8 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for pimavanserin beyond routine measures.

9 Conclusion & Recommendations

In conclusion, risk mitigation measures beyond professional labeling are not warranted for pimavanserin if approved. In general, healthcare providers who treat PDP are monitoring their patients for many comorbidities including respiratory problems. Also, due to the labeling of increased risk of death when treating patients with dementia-related psychosis associated with atypical antipsychotics, providers have knowledge that commonly used medical treatments in elderly psychotic patients has increased risk. Labeling for pimvanserin will clarify and reinforce the risks specific to this treatment.

Should DPP have any concerns or questions, or feel that a REMS is warranted for this product, or if new safety information becomes available, please send a consult to DRISK.

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