Brand Name: Nuplazid

Generic Name: pimavanserin

Manufacturer[1]: Acadia Pharmaceuticals, Inc.[1]

Drug Class[2]: atypical antipsychotic[3]

Uses:

Labeled Uses[1,2,3,4]: Parkinson's disease-Psychotic disorder/Parkinson's disease psychosis

Unlabeled Uses[2,3,4]: None

Mechanism of Action:

The antipsychotic effect of pimavanserin is not fully understood, but may be mediated through inverse agonist and antagonist activity at serotonin 5-HT(2A) and to a lesser extent serotonin 5-HT(2C) receptors.[2,3] This decreases the increased serotonin levels at these receptors that can lead to hallucinations and delusions.

Pharmacokinetics[2,3,4]:

Absorption:

T_{max}	6 hours
V_d	2173 L
t ½	57 hours
Clearance	Not reported
Protein Binding	95%
Bioavailability	Not reported

Metabolism:

Pimavanserin is metabolized by the liver, predominantly by CYP3A4 and CYP3A5, with lesser contribution from CYP2J2, CYP2D6, and various other CYP and FMO enzymes.[3] Formation of the active metabolite AC-279 occurs primarily by CYP3A4.[2,4]

Elimination:

Pimavanserin is excreted 0.55% unchanged (<1% changed) by the kidney. It is excreted 1.53% in the feces.[2,3]

Efficacy:

Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A, Dhall R, Ballard C. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet. 2014;383:533–40.

Study Design: Multi-center, double-blind, randomized, placebo-controlled, parallel-group design study

Description of Study: *Methods:* Patients were randomly allocated in a 1:1 ratio for treatment with either 40 mg of pimavanserin (n=105) or placebo (n=94). Patients were required to meet established diagnostic criteria for Parkinson's disease psychosis, including idiopathic Parkinson's disease lasting at least one year, and have psychotic symptoms that developed after Parkinson's disease diagnosis that were present for at least one month, occurred at least weekly in the month before screening, and were severe enough to warrant treatment with antipsychotics. The primary outcome was change in total Parkinson's disease-adapted scale for assessment of positive symptoms (SAPS-PD) score from baseline to day 43. Secondary outcomes

included change in clinical global impression-severity (CGI-S) and improvement (CGI-I) scale scores. *Outcome Results:* The safety analysis noted that there was no evidence of motor impairment in either group. Patients receiving pimavanserin had a mean change of 37% improvement from baseline compared to 14% for placebo (p=0.0006). Adverse included nausea, peripheral edema, urinary tract infection, fall, confusional state, headache, and hallucination (including visual). Serious adverse events were reported in 11 and 4 patients taking pimavanserin and placebo respectively. Pimavanserin showed a mean 7.2 ms increase in QTcB interval from baseline.

Limitations: The manufacturer of pimavanserin, Acadia, designed, funded, led statistical analysis, and employed authors to write the study. Therefore, there is potential bias due to conflict of interest. The subjects were assessed by live video conference, which could have been confusing to patients with the disease state being studied. Only adverse effects that were reported in more than 5% of patients were reported. The study is relatively short-term, lasting only 6 weeks.

Conclusion: Pimavanserin shows tolerability and efficacy when used to treat Parkinson's disease psychosis. Pimavanserin also showed benefit when compared to placebo on the 20 item SAPS-hallucinations plus delusions scale. More studies are needed to determine long-term effects of pimavanserin.

Meltzer H., Mills R., Revell S., Williams H., Johnson A., Bahr D., et al. (2010) Pimavanserin, a serotonin(2A) receptor inverse agonist, for the treatment of Parkinson's disease psychosis. Neuropsychopharmacology 35: 881–892.

Study Design: Multi-center, double-blind, randomized, placebo-controlled, parallel-group study

Description of Study: *Methods:* Patients were enrolled in a 1:1 ratio to receive either pimavanserin (n=29) or placebo (n=31). The duration of the study was 4 weeks, followed by a 4-week follow-up period. Patients received pimavanserin, starting at 20 mg on day 1, with possible increases to 40 or 60 mg on days 8 and 15, respectively. The modified Hoehn and Yahr (UPDRS Part V) staging of PD was completed at screening. The primary measures used to assess motor symptoms were the Unified Parkinson's Disease Rating Scale (UPDRS) Parts II and III. Safety assessments were also evaluated. *Outcome Results:* The mean final dose of pimavanserin administered was 44.8 mg. At day 28, a small nonsignificant improvement in the combined UPDRS parts II and III score in both treatment groups was observed. No statistically significant differences were observed in treatment effect (p=0.74, 95% CI: -4.18-5.80). There was statistically significant improvement in the global rating of hallucinations in the pimavanserin group (p=0.02). There was no significant difference in the incidence of adverse events in the placebo and pimavanserin groups. In the pimavanserin group, the most common adverse events ($\geq$10% of patients) were somnolence, edema, and increases in BUN. Motor function adverse events occurred infrequently in both groups, were mild, and did not lead to drug discontinuation. There were no trends or clinically meaningful changes in laboratory studies, vital signs, ECG measurements, or neurological measurements.

Limitations: This sample size of this study was small, which could have led to type II error. The dose escalation was performed quickly; however, it takes between 10 and 14 days to reach steady state with pimavanserin.

Conclusion: Further studies need to be performed to assess safety of pimavanserin. Risk of type II error cannot be ruled out. Mild efficacy was shown in the study. No head-to-head trials exist between pimavanserin and other drug options; therefore, further investigation into efficacy comparisons should be performed. Adverse effects from this study need to be further investigated within a larger population in order to form a conclusion about pimavanserin's safety profile.

Vanover KE, Robbins-Weilert D, Wilbraham DG, Mant TG, van Kammen DP, Davis RE, Weiner DM (2007) Pharmacokinetics, tolerability, and safety of ACP-103 following single or multiple oral dose administration in healthy volunteers. J Clin Pharmacol 47:704–714

Study Design: Two single-center, randomized, double-blind, placebo controlled, escalating dose studies

Description of Study: *Methods:* The first study was a single-dose study in which different groups of 5 subjects each received either placebo or 1 of 5 dose levels of pimavanserin (ACP-103) as a single oral (25, 50 mg) or nasogastric dose (100, 200, 300 mg). Doses were escalated using a declining multiple, and were administered after a 10-hour fast. The second study was a multiple-dose study in which 3 different groups of 8 subjects each received either placebo or 1 of 3 dose levels of ACP-103 (50, 100, 150 mg) once daily for 14 days. The initial dose of the multiple dose study was based on predicted plasma level at steady state not to exceed exposure observed in the single-dose study. Safety data were monitored throughout both studies. *Outcome Results:* No clinically meaningful changes or trends were observed in clinical laboratory data and vital signs with administration of increasing single doses of ACP-103. Clinical laboratory data and vital signs were similar between treatment and placebo subjects. One subject receiving 200 mg ACP-103, experienced extreme bradycardia close to time of syncope with approximately a 2 to 8 second pause, which then returned to normal values. Another subject, receiving 300 mg ACP-103, experienced vasovagal symptoms associated with a 2.9-second pause, which then returned to normal values. There were no clinically relevant changes in individual 12-lead ECG findings or mean ECG parameters between the treatment and placebo subjects. There were no changes in behavior, coordination, or gait observed in any subject. There were no tremors observed during the scheduled neurological examinations. There were no clinically meaningful changes or trends observed in mean or median laboratory values from baseline to end of study for any of the treatment groups. In the second study, there were no adverse events reported or clinically meaningful changes for vital sign abnormalities, oral temperatures, or physical examination results. Lead-II monitoring was normal, except for 1 subject who received oral doses of 150 mg ACP-103. The subject showed asystole for approximately 15 seconds during a vasovagal episode, which then returned to normal. A total of 27 events (26 in ACP-103-treated subjects and 1 placebo subject) of ECG intervals outside of normal limits were observed during the study. Two subjects receiving ACP-103 experienced mild tremors, which were recorded as adverse events.

Limitations: The sample size of the study was very small, which could have attributed to fewer adverse effects being present. The study only enrolled male participants, which is not a realistic sample for the disease population.

Conclusion: Pimavanserin seems to be well tolerated at single oral/nasogastric doses of 20 to 300 mg. Further research should be performed to determine safety in regard to QTc prolongation and safety in the female population. Further studies should also focus on finding the most efficacious dose with the minimal amount of adverse effects.

Contraindications[1,2,3,4]:

None

Precautions:

Black box Warning: risk of death is increased in elderly patients with dementia-related psychosis[1,2,3,4]

QT Prolongation: may cause QT prolongation and should be avoided in patients with cardiac disease or other risk factors for QT prolongation, torsade de pointes, and/or other sudden cardiac death[3] Avoid use with other drugs known to cause QT interval prolongation, such as Class 1A antiarrhythmics, Class 3 antiarrhythmics, certain antipsychotics, and certain antibiotics[2].

Renal Impairment[3]: not recommended for use in patients with CrCl less than 30 mL/min because the drug has not been evaluated in this population; no dosage adjustment is require in mild-to-moderate renal impairment

Hepatic Impairment[3]: not recommended for use in patients with mild, moderate, or severe hepatic impairment because the drug has not been evaluated in this population

Orthostatic Hypotension[4]: use with caution in patients at risk for this condition

CNS Depression[4]: may cause CNS depression; patients should be cautioned about performing tasks that require mental alertness

Pregnancy and Lactation[1,2,3,4]: use during pregnancy and lactation are not recommended due to lack of evaluation in this population

Adverse Effects:

Occurring in >1% to <10% of patients[2,3,4]:

Cardiovascular: Peripheral edema (7%)

Central nervous system: Confusion (6%), hallucinations (5%), abnormal gait (2%)

Gastrointestinal: Nausea (7%), constipation (4%)

Drug Interactions[1,2,3,4]:

Drugs that increase the risk of QT interval prolongation should not be used concurrently with pimavanserin:

Mesoridazine, thioridazine, posaconazole, piperaquine, dronedarone, cisapride, amifampridine, terfenadine, sparfloxacine, ketoconazole, fluconazole, pimozide, ziprasidone, bepridil, saquinavir, amisulpride, indapamide, ivabradine, mifepristone, vinflunine

Concomitant use of pimavanserin and CYP3A4 inhibitors may result in increased pimavanserin exposure:

Nefazodone, azole antifungal agents, antiviral agents, macrolide antibiotics, aprepitant, conivaptan, fosaprepitant, fusidic acid, idelalisib, ivacaftor, netupitant, palbociclib

Concomitant use of strong CYP3A4 inducers may reduce the efficacy of pimavanserin, monitor for reduced efficacy:

Rifampin, dexamethasone, phenytoin, anticonvulsants, rifabutin, St. John's Wort

Dosing/Administration[1,2,3,4]:

Adult dosing:

No titration needed

Take without regard to meals

Usual dose: 34 mg (two 17 mg tablets) once daily

With strong CYP3A4 inhibitors: 17 mg (one 17 mg tablet) once daily

With strong CYP3A4 inducers: 34 mg once daily; monitor for reduced efficacy (dose increase may be required)

Elderly:

No dosage adjustment

Pediatrics:

Not studied in this population, use not recommended

Renal impairment:

CrCl $\geq$ 30 mL/min: no dosage adjustment

CrCl < 30 mL/min: use not recommended

Hepatic impairment:

Not recommended

Use in Special Circumstances[2]:

There is no antidote to pimavanserin. In case of overdose, consider activated charcoal if the overdose is recent, patient is not vomiting, and airway is obtainable. If life-threatening cardiac arrhythmia occurs, perform intubation.

Conclusion:

Pimavanserin is the only FDA indicated treatment for Parkinson 's disease Psychosis. Side effects and adverse events seem to be minimal; however, there is great potential for multiple drug interactions and caution should be used when prescribing this medication. pimavansrin can be used without adjustment in those with CrCl >30 mL/min. Pimavanserin shows moderate efficacy and should be studied further in comparison to other therapeutic options. Due to the high cost of pimavanserin, other therapeutic options may be more preferable if efficacy proves to be similar. Other therapeutic options include quetiapine and clozapine; however, efficacy and safety profiles should be taken into consideration when selecting a medication for this indication. Because of its breakthrough therapy designation, pimavanserin requires further research to prove efficacy and safety in long-term studies.

Recommended References:

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Prepared by: Brianna Stalnaker, Doctor of Pharmacy Candidate