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For further information regarding Indication, **Boxed WARNING** and other Important Safety Information for NUPLAZID, please click here: Prescribing Information.

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NUPLAZID® (pimavanserin) Drug-Drug Interactions

This letter is being provided based on your specific request for information on the drug-drug interactions with NUPLAZID. Acadia Pharmaceuticals Inc. is unable to provide a comprehensive list of specific medications within the drug classes presented below. As new products are continually emerging in the US market, Acadia cannot ensure the accuracy of such a listing. For more information regarding the concomitant medications within the drug classes listed, please refer to the FDA-approved labeling or manufacturer.

Relevant Labeling Information[1]

- Concomitant use of drugs that prolong the QT interval may add to the QT effects of NUPLAZID and increase the risk of cardiac arrhythmia. Avoid the use of NUPLAZID in combination with other drugs known to prolong QT interval (e.g., Class 1A antiarrhythmics, Class 3 antiarrhythmics, certain antipsychotics or antibiotics).
- Concomitant use of NUPLAZID with a strong CYP3A4 inhibitor increases pimavanserin exposure. If NUPLAZID is used with a strong CYP3A4 inhibitor, reduce the dosage of NUPLAZID.
- Concomitant use of NUPLAZID with strong or moderate CYP3A4 inducers reduces pimavanserin exposure. Avoid concomitant use of strong or moderate CYP3A4 inducers with NUPLAZID.
- Based on pharmacokinetic studies, no dosage adjustment of carbidopa/levodopa is required when administered concomitantly with NUPLAZID.

Summary

- The recommended dose of NUPLAZID when coadministered with strong **CYP3A4 inhibitors** is 10 mg, taken orally as one tablet once daily (QD).[1] An *in-vivo* pharmacokinetic (PK) analysis showed pimavanserin had a 1.5-fold increase in C_{max} and a 3-fold increase in area under the curve (AUC) when co-administered with ketoconazole, a strong CYP3A4 inhibitor. In addition, plasma elimination half-life of pimavanserin increased from 58.2 hours to 89.2 hours.[2]
- Avoid concomitant use of strong or moderate **CYP3A4 inducers** with NUPLAZID.[1] In a clinical study, concomitant use of NUPLAZID with a strong CYP3A4 inducer reduced pimavanserin C_{max} and AUC by 71% and 91%, respectively.[3] In a simulation with a moderate CYP3A4 inducer (efavirenz), models predicted pimavanserin $C_{max,ss}$ and AUC_{tau} at steady state decreased by approximately 60% and 70%, respectively.

Background

Pimavanserin is predominantly metabolized by cytochrome P450 enzymes, specifically CYP3A4 and CYP3A5.[1] The potential for pimavanserin to be involved in PK drug-drug interactions in humans was assessed via *in vitro* metabolism and transporter studies. Four drug-drug interaction studies have been conducted with pimavanserin: 1) Study 023 evaluated the effect of concomitant administration of a strong CYP3A inhibitor, ketoconazole, on pimavanserin PK;

2) Study 040 evaluated the effects of rifampin on the single-dose PK of pimavanserin; (3) Study 024 evaluated the effect of pimavanserin on the PK of levodopa when carbidopa/levodopa was administered concomitantly; 4) Study 029 evaluated the effects of pimavanserin and its major metabolite AC-279 on the PK of midazolam and its metabolites.[2-5]

QT-Interval Prolongation

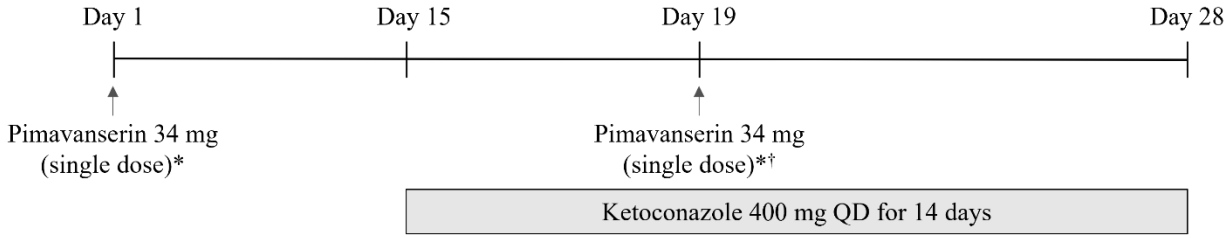
Concomitant use of drugs that prolong the QT interval may add to the QT effects of NUPLAZID and increase the risk of cardiac arrhythmia.[1] In the 6-week, placebo-controlled effectiveness studies, mean increases in QTc interval of ~5-8 msec were observed in patients receiving once-daily doses of NUPLAZID 34 mg. Avoid the use of NUPLAZID in combination with other drugs known to prolong the QT interval (e.g. class 1A antiarrhythmics: quinidine, procainamide, disopyramide; class 3 antiarrhythmics: amiodarone, sotalol; antipsychotics: ziprasidone, chlorpromazine, thioridazine; Antibiotics: gatifloxacin, moxifloxacin).[1]

Drug-Drug Interaction Studies

CYP3A Inhibitors

Study 023 evaluated the potential effect of multiple doses of ketoconazole, a strong CYP3A inhibitor, on the PK of pimavanserin in an open-label, two-period, single-sequence study in healthy male and female participants.[2] Twenty participants (14 males and 6 females) were enrolled in this study, and nineteen completed the study. The PK of pimavanserin by treatment with either pimavanserin alone or pimavanserin with ketoconazole (as per **Figure 1**), were assessed using non-compartmental analysis.

Figure 1. Dosing Schedule for Pimavanserin and Ketoconazole in Study 023[2]



**Administered under fasting conditions.*
†Administered 60 minutes after the fifth ketoconazole dose (on Day 19).
Abbreviation: QD=once daily.

The study showed that pimavanserin had a 1.5-fold increase in C_{max} and a 3-fold increase in AUC when co-administered with the strong CYP3A4 inhibitor. These results are consistent with *in vitro* data demonstrating a major role for CYP3A4 in pimavanserin metabolism. The plasma elimination half-life of pimavanserin increased from 58.2 hours to 89.2 hours.[2]

Population PK modeling and simulation show that steady-state exposure ($C_{max,ss}$ and AUC_{tau}) for 10 mg pimavanserin with ketoconazole is similar to exposure for 34 mg pimavanserin alone.[1] The recommended dose of NUPLAZID when coadministered with strong CYP3A4 inhibitors is 10 mg taken orally as one tablet QD.[1] Examples of strong CYP3A4 inhibitors include itraconazole, ketoconazole, clarithromycin, and indinavir.[6]

CYP3A Inducers

Study 040 was a Phase 1, open-label, sequential study to evaluate the effect of multiple-dose administration of rifampin, a strong CYP3A4 inducer, on the single-dose PK of pimavanserin in 36 healthy participants (33 males, 3 females). Participants received single doses of pimavanserin 34 mg on Days 1 and 22 and were given rifampin 600 mg QD on Days 15–36.[3]

The study showed that the single-dose PK profile of pimavanserin was significantly altered following coadministration with rifampin on Day 22. Pretreatment with rifampin markedly reduced pimavanserin plasma concentrations. Pimavanserin exposure parameters were reduced by 91% (to 9% of pre-rifampin values) for both $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$, and by 71% (to 29% of pre-rifampin values) for C_{max}, compared to pre-rifampin plasma concentrations. The apparent systemic clearance increased from 28.06 L/h to 302.8 L/h (approximately 10-fold). The apparent terminal half-life was decreased from 55.52 to 15.49 hours (approximately 4-fold).[3]

On the basis of physiologically based PK (PBPK) modelling, concomitant use of moderate CYP3A4 inducers is predicted to reduce pimavanserin exposure, although not as much as with strong CYP3A4 inducers. The model predicted pimavanserin $C_{max,ss}$ and AUC_{tau} at steady state decreased by approximately 60% and 70%, respectively. Avoid concomitant use of strong or moderate CYP3A4 inducers with NUPLAZID.[1] Examples of strong CYP3A4 inducers include carbamazepine, St. John's wort, phenytoin, and rifampin. Examples of moderate CYP3A4 inducers include bosentan, efavirenz, etravirine, and phenobarbital.[6]

Concomitant Carbidopa/levodopa

Study 024 was conducted to assess the PK of levodopa when carbidopa/levodopa was taken with pimavanserin.[4] This was an open-label, two-period, single-sequence study in healthy male and female participants. Oral pimavanserin 34 mg was administered QD to participants from Days 4 to 17 alone and then in combination with morning doses of immediate-release carbidopa/levodopa on Days 15 through 17. Immediate-release carbidopa/levodopa, containing 25 mg of carbidopa and 100 mg of levodopa, was administered orally three times daily, 8 hours apart, on Days 1 to 3 (alone) and on Days 15 to 17 (with pimavanserin).

Twenty participants were enrolled in the study, 12 males and 8 females, and the PK analysis set was comprised of 11 males and 7 females. The PK of levodopa after the morning dose on Day 3 (carbidopa/levodopa alone) and Day 17 (carbidopa/levodopa with steady-state pimavanserin) were assessed using non-compartmental analysis.[4]

Levodopa $C_{max\text{-}ss}$ and AUC_{τ} increased by approximately 7.5% and 3.4%, respectively, after co-administration with pimavanserin at steady state.[4] Based on PK studies, no dosage adjustment of carbidopa/levodopa is required when administered concomitantly with NUPLAZID.[1]

CYP3A Substrates

Study 029 was a Phase 1, open-label, single-sequence, single group, multiple dose, drug interaction study in healthy adult participants to determine the extent to which pimavanserin and its significant circulating active metabolite, AC-279, affect the PK of midazolam and its metabolites (1'-OH midazolam and 4-OH midazolam), a probe drug for CYP3A4/5.[5] The dosing schedule for midazolam and pimavanserin is shown in **Table 1**.

Table 1. Dosing Schedule for Midazolam and Pimavanserin in Study 029[5]

	Day 1	Day 3	Day 4–19	Day 20	Day 21–39	Day 40
Midazolam*	✓	✓		✓		✓
Pimavanserin 34 mg		✓†	✓	✓†	✓	✓†

**Midazolam 2 mg syrup given orally after a fast of ≥10 hours.*
†Pimavanserin administered 30 minutes prior to midazolam dose.

The effect of pimavanserin and AC-279 at steady state on midazolam single-dose PK parameters (AUC_t, AUC_∞, and C_{max}) were evaluated at each of Days 20 and 40, respectively, in comparison with Day 1. The effect of pimavanserin and AC-279 on midazolam single-dose PK parameters was also evaluated after a single dose of pimavanserin at Day 3 in comparison with Day 1.[5]

The study enrolled 24 participants ranging from 21 to 49 years of age, 21 (87.5%) of whom were male, and 16 (66.7%) of whom were Black or African American. The Day 3 versus Day 1 analysis of the geometric means showed that pimavanserin increased the plasma C_{max} of midazolam by 7.52% and increased $AUC_{0-\infty}$ and AUC_{0-24h} by 3.15 and 2.64%, respectively. As the 90% confidence intervals (CIs) for the ratio of the geometric means were within the 80–125% range, it was concluded that pimavanserin was not a clinically significant CYP3A4 inhibitor.[5]

The geometric means on Day 20 showed a decrease in the plasma C_{max} of midazolam of 4.51% and a comparable decrease in $AUC_{0-\infty}$ and AUC_{0-24h} of 4.73 and 5.91% respectively. The 90% CIs for the ratio of the geometric means fell within the 80–125% range for all parameters. On Day 40, the C_{max} for midazolam increased by 5.63% whereas the $AUC_{0-\infty}$ and AUC_{0-24h} decreased by 13.95% and 16.05%, respectively. Although the lower 90% CIs of the geometric mean ratios were slightly wider than 80–125% for both parameters it was concluded that pimavanserin was unlikely to be a clinically significant CYP3A4 inducer.[5]

Exposure (C_{max} and AUC) to midazolam, which is participant to substantial intestinal and hepatic first-pass metabolism, principally by CYP3A4, was not significantly affected by coadministration with NUPLAZID, indicating that pimavanserin is neither an inhibitor nor an inducer of CYP3A4/5.[5]

References

1. NUPLAZID® (pimavanserin) [package insert]. San Diego, CA. Acadia Pharmaceuticals Inc. **[Link]**
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3. Acadia Pharmaceuticals Inc. Data on File. Clinical Study Report ACP-103-040. 2017.
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6. FDA. Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers. **[Link]**.