Pharmacokinetics and Drug-Drug Interaction of Ocedurenone (KBP-5074) in Healthy Subjects

Ping Wang, Jinrong Liu, Judy Tan, Jay Zhang, Fred Yang

KBP BIOSCIENCES PTE. LTD.
• Disclosures:
  • Ping Wang, Jinrong Liu, Judy Tan, Jay Zhang, Fred Yang are employees of KBP Biosciences
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ABSTRACT

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BACKGROUND:

Ocedurenone, a novel non-steroidal mineralocorticoid receptor antagonist (MRA), is currently under development, for the treatment of uncontrolled hypertension in patients with chronic kidney disease (CKD).

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OBJECTIVES:

To determine the pharmacokinetic drug-drug interactions of Ocedurenone with CYP3A inhibitor itraconazole and inducer rifampin in healthy subjects.

METHOD:

This is a Phase 1, open-label, parallel, 2-arm, crossover study to investigate the effect of coadministration of a strong CYP3A4 inhibitor and CYP3A4 inducer on the plasma PK of a single dose of Ocedurenone in healthy male and female subjects. 24 subjects 18 to 60 years of age with a BMI of 18.0 to 32.0 kg/m² were enrolled. Serial blood samples are collected from pre-dose through 240 hours post-dose for analysis of plasma concentrations of Ocedurenone.

RESULTS:

The strong CYP3A4 inhibitor itraconazole and CYP3A4 inducer rifampin have statistically significant effects on the pharmacokinetics of Ocedurenone. Its C₀ and AUC₀→∞ are increased to 110% and 175%, respectively, when itraconazole is co-administered. The median t₁/₂ is slightly reduced from 4 hr to 2 hr, and the geometric mean t₁/₂ is increased from 60.3 to 125 hr. When rifampin is co-administered, Ocedurenone C₀ and AUC₀→∞ are significantly reduced to approximately 72% and 16%. Median t₁/₂ is unchanged (4 hr), and the geometric mean t₁/₂ is increased to 10.9 hr. CONCLUSION: This clinical DDI study indicates that a strong CYP3A4 inhibitor (itraconazole) has a weak effect on Ocedurenone pharmacokinetic properties, with less than 2-fold change in C₀ and AUC₀→∞ whereas a strong CYP3A4 inducer (rifampin) has strong effect on pharmacokinetic properties of Ocedurenone, with about 5-fold decrease in AUC and t₁/₂.

Ocedurenone was well tolerated when administered as a single 0.5-mg dose alone or in combination with itraconazole or rifampin.

For additional information please contact: Jay Zhang PhD
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REFERENCES


Table 1. Summary of Ocedurenone Pharmacokinetic Parameters Following Single Oral Dose of 0.5 mg in the Presence and Absence of Itraconazole and Rifampin Co-administration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preceded Ocedurenone Alone</th>
<th>Ocedurenone+Itraconazole</th>
<th>Ocedurenone+Rifampin</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀→∞ (ng/mL)</td>
<td>640±21.4</td>
<td>1090±16.7</td>
<td>104±16.8</td>
</tr>
<tr>
<td>AUC₀→∞ (ng/mL)</td>
<td>690±23.8</td>
<td>1410±20.0</td>
<td>109±16.5</td>
</tr>
<tr>
<td>C₀ (ng/mL)</td>
<td>9.1±1.2</td>
<td>10.1±2.3</td>
<td>6.5±1.1</td>
</tr>
<tr>
<td>t₁/₂ (hr)</td>
<td>4.2±0.6</td>
<td>2.1±0.8</td>
<td>4.1±0.4</td>
</tr>
<tr>
<td>Vz/F (L)</td>
<td>63±20.4</td>
<td>125±13.8</td>
<td>10.9±13.9</td>
</tr>
<tr>
<td>CL/F (L/hr)</td>
<td>0.72±0.3</td>
<td>0.35±0.2</td>
<td>4.6±1.6</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>63±15.1</td>
<td>58±17.8</td>
<td>72±9.7</td>
</tr>
</tbody>
</table>

CONCLUSION:

- Ocedurenone is well tolerated when administered as a single 0.5-mg dose, in the presence and absence of itraconazole and rifampin.
- Co-administration of a strong CYP3A4 inhibitor itraconazole significantly increased the Ocedurenone plasma exposures, AUC₀→∞ and C₀ increased to approximately 110% to 175%, while t₁/₂ increased from 60 to 125 hr.
- Co-administration of rifampin significantly decreased Ocedurenone plasma exposures, with AUC₀→∞ and C₀ decreased to 16% and C₀ decreased to approximately 72%.

Figure 3. Arithmetic Mean (±SD) Plasma Concentrations of Ocedurenone Following

Single Oral Dose Administration of Ocedurenone 0.5 mg Alone (Day 1, Pooled) and in Combination with Itraconazole (Day 18, Cohort 1) and in Combination with Rifampin (Day 21, Cohort 2)