Pharmacokinetics (PK) and Safety Evaluation of Palonosetron (PALO) Administered as a 15-minute Infusion Versus a 30-second Infusion in Healthy Subjects

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ABSTRACT

Palonosetron (Aloxi®) is a novel serotonin (5-HT3) receptor antagonist that has been shown to effectively prevent both acute and delayed chemotherapy-induced nausea and vomiting. A standard procedure at many clinics is to administer a premixed IV solution of a 5-HT3 receptor antagonist and dexamethasone over approximately 15 minutes. The PK and safety of 0.25 mg PALO administered as a 15-minute infusion (Treatment A) was compared to a 30-second infusion (Treatment B) currently FDA approved in 15 healthy subjects (15 males and 3 females) were enrolled in an open, randomized, two-way crossover study. On days 1 and 15, subjects received Treatment A or B in a randomly assigned order. Serial plasma samples were obtained predose-168 hr postdose and assayed for PALO by LC/MS/MS. Safety was evaluated by clinical assessments of adverse events (AEs), vital signs, ECGs, and laboratory results. Eleven subjects completed both treatments. Mean (CJV) of Cmax was 91 (94%) and 1300 (99%) for treatment A and B, respectively, and AUC0-¥ was 20700 (25%) and 20700 (21%) respectively. The ratio of geometric means (90% CI) of Treatment A to B for Cmax was 0.24 (4.4%-98.9%), and for AUC0-¥, 0.29% (1.0%-187.3%). Mean (CJV) of fold, Vdss and T1/2 for Treatments A and B were 2.4 (20%) and 329 (21%) ml/min, 611 (24%) and 354 (37.0%) and 3.7 (39.3) hr for treatment A and B respectively. Cmax (77.1), Vdss (265), and T1/2 (379) were not significantly different for the treatments. PK was well tolerated, with no significant change in vital signs, ECGs, and no clinically important drug-related adverse events. The alternative administration schedule of 30 seconds was as safe and well-tolerated, with a predictable PK profile that resulted in equivalent AUC0-¥ and lower Cmax compared to a 30-second infusion.

METHODS (Continued)

RESULTS (Continued)

Table 1. Subject Disposition by Sequence

<table>
<thead>
<tr>
<th>Subject</th>
<th>Disposition</th>
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<tr>
<td>15 subjects enrolled and 11 subjects (9 males and 2 females) completed the study</td>
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<td>15 subjects experienced etravusation during the 15-minute infusion and withdrew from the study, replacements were enrolled</td>
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<td>One replacement subject discontinued study participation (personal reasons) and received only a 0.25 mg dose of palonosetron via 15-min infusion</td>
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Table 3. Summary of Pharmacokinetic Parameters for Palonosetron

Pharmacokinetics

- Mean C0–1h values were predictably lower for the 15-minute infusion than for the 30-second infusion, and mean CL/F, Vdss and T1/2 were not significantly different for the two treatments.

Table 3. Summary of Pharmacokinetic Parameters for Palonosetron

Figure 1. Mean Plasma Concentration of Palonosetron Following 15-minute (T1) and 30-second (T2) IV infusions. In Healthy Subjects Over 4 hours and 12 hours

Table 3. Summary of All Treatment-Emergent Adverse Events

CONCLUSIONS

- Palonosetron was safe and well tolerated when administered to healthy subjects both as an IV infusion over 15 minutes and over 30 seconds.
- Infusion of palonosetron over 15 minutes resulted in equivalent AUC0–¥ and CL/F compared to a 30-second IV infusion.
- Plasma elimination half-life, total body clearance, and volume of distribution at steady state were not significantly altered.
- The safety and PK profile of palonosetron, either infused over 15 minutes or 30 seconds, was consistent with previous clinical trials in healthy subjects and patients.
- The safety and pharmacokinetic results of this study in healthy volunteers indicate that a 15-minute IV infusion of 0.25 mg palonosetron can be used clinically as an alternative to the 30-second infusion.

REFERENCES