Co-administration of Doravirine With an Aluminum/Magnesium-Containing Antacid or Pantoprazole, a Proton-Pump Inhibitor, Does Not Have a Clinically Meaningful Effect on Doravirine Pharmacokinetics

INTRODUCTION

- Doravirine (MK-4319) is a novel, potent, once-daily, non-nucleoside reverse transcriptase inhibitor (NNRTI) in Phase 3 development for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in combination with other antiretroviral therapies.
- Doravirine is metabolized primarily via cytochrome P450 3A (CYP3A). It is not a metabolic inducer or inhibitor and is unlikely to cause significant drug-drug interactions.
- Doravirine is poorly soluble but highly permeable, and it is rapidly absorbed with peak concentrations attained 1-2 h post-dose.
- Many patients with HIV-1 infection are treated with antacids or acid-reducing agents to alleviate gastrointestinal discomfort.
- Antacids containing aluminum and magnesium are known to help reduce acid indigestion, heartburn, upset stomach, and bloating; the alkaline ions decrease the activity of gastric secrete and directly neutralize hydrochloric acids.
- Pantoprazole is a proton-pump inhibitor (PPI) indicated to treat conditions where reduction in gastric acid secretion is required.

METHODS

- Study Design
  - This was a double-blind, placebo-controlled, parallel-group study in healthy males and females 18-60 years of age. Study design is presented in Figure 1.
- The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines; all subjects provided written informed consent.

RESULTS

- Treatment compliance was high, with 95% of subjects completing the study.
- No treatment-emergent adverse events (AEs) were reported as severe in intensity or potentially related to study treatments.
- Doravirine plasma concentration, nM

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Doravirine alone</th>
<th>Doravirine co-administered with pantoprazole</th>
<th>GM (95% CI)</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-inf</td>
<td>43.9 (26.5, 75.7)</td>
<td>43.7 (25.7, 75.6)</td>
<td>1.01 (0.82, 1.21)</td>
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<tr>
<td>Cmax</td>
<td>1840 (1400, 2290)</td>
<td>1830 (1400, 2440)</td>
<td>0.99 (0.76, 1.3)</td>
<td></td>
</tr>
<tr>
<td>C24</td>
<td>868 (736, 949)</td>
<td>880 (745, 945)</td>
<td>1.03 (0.94, 1.12)</td>
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</tr>
<tr>
<td>t1/2</td>
<td>1.9 (1.6, 2.3)</td>
<td>1.8 (1.6, 2.1)</td>
<td>1.0 (0.89, 1.1)</td>
<td></td>
</tr>
<tr>
<td>Vz/F</td>
<td>3.99 (3.10, 5.18)</td>
<td>3.99 (3.09, 5.08)</td>
<td>1.0 (0.99, 1.01)</td>
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<tr>
<td>CL/F</td>
<td>14.85 (12.26, 18.08)</td>
<td>14.96 (12.37, 18.59)</td>
<td>1.0 (0.99, 1.01)</td>
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<tr>
<td>CLr/F</td>
<td>5.34 (3.23)</td>
<td>5.45 (3.26)</td>
<td>1.0 (0.99, 1.01)</td>
<td></td>
</tr>
</tbody>
</table>

- Doravirine is metabolized primarily via CYP2C19, with subsequent sulfation; other metabolic pathways include CYP1A2.
- Doravirine does not appear to be an inducer or inhibitor of CYP enzymes.
- Co-administration of doravirine with PPIs is unlikely to interact with cation-containing antacids or acid-reducing agents due to its pharmacological activity.
- Co-administration of doravirine with pantoprazole is unlikely to interact with cation-containing antacids or acid-reducing agents due to its pharmacological activity.

DISCUSSION

- Co-administration of doravirine with an antacid suspension did not have a clinically meaningful effect on doravirine PK (Table 2, Figures 2 and 3).
- Co-administration of doravirine with pantoprazole did not have a clinically meaningful effect on doravirine PK (Table 3, Figures 4 and 5).

CONCLUSIONS

- Co-administration of a single dose of aluminum/magnesium-containing antacid or multiple doses of the PPI pantoprazole did not have a clinically meaningful effect on doravirine PK.
- Doravirine 100 mg was generally well tolerated alone and when co-administered with an antacid or pantoprazole in healthy male and female subjects.

Acknowledgments

The authors thank Dr. Rao Rao, PhD, of Pharma Medica Research Inc., for contributions to the study. Detailed acquisition and analysis of data were performed by the authors. Study materials and data analysis were provided by employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. This assistance was provided by Erin Bekes, PhD, of Complete Medical Communications, Hackensack, NJ, USA. This assistance was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

Disclosures

Funding for this research was provided by Merck & Co., Inc., Kenilworth, NJ USA.

References