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Effect of Concomitant Medications Affecting Gastric pH and Motility on Posaconazole Tablet Pharmacokinetics

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ABSTRACT

Background: Pharmacokinetic (PK) interactions that result in altered exposure of posaconazole (POS) should be taken into account when POS is coadministered with other medications that affect gastric pH or motility. The objective of this study was to characterize the PK interactions of a single 400-mg dose of POS tablets when coadministered with concomitant medications (antacid, ranitidine, esomeprazole, or metoclopramide) in healthy adults in the fasting state. This study evaluated the effect of concomitant medications altering gastric pH (antacid, ranitidine, and esomeprazole) and gastric motility (metoclopramide) on the PK of POS tablets using a 5-way crossover design in 20 healthy volunteers. In each treatment period, a single 400-mg dose of POS tablets was administered in the fasting state (approximately 10 hours after an overnight fast), with the first dose of POS tablets administered at 00:00 hours. Plasma samples were assayed for POS using validated liquid chromatography with tandem mass spectrometric detection. Posaconazole tablet pharmacokinetics were similar when the drug was administered alone or with medications altering gastric pH (antacid, ranitidine, and esomeprazole) or gastric motility (metoclopramide).

OBJECTIVES

• To evaluate the effect of concomitant medications altering gastric pH (antacid, ranitidine, and esomeprazole) and gastric motility (metoclopramide) on the pharmacokinetics (PK) of POS tablets.
• To evaluate the safety and tolerability of POS tablets with drugs affecting gastric pH or gastric motility.

METHODS

This was a prospective, open-label, 5-way crossover study in healthy volunteers. Concomitant medications altering gastric pH or gastric motility were administered 2 hours before and 8 hours after POS tablet administration. The PK of a single 400-mg dose of POS tablets is similar when the drug is administered alone or with medications altering gastric pH (antacid, ranitidine, and esomeprazole) or gastric motility (metoclopramide).

RESULTS: The PK of a single 400-mg dose of POS tablets is similar when the drug is administered alone or with medications altering gastric pH (antacid, ranitidine, and esomeprazole) or gastric motility (metoclopramide).

Safety: All AEs were mild to moderate in severity. Overall, 19/21 (90%) subjects reported at least 1 treatment-emergent AE (TEAE). The most common treatment-emergent AEs were related to food intake (100% of the subjects). The most frequent TEAEs were abdominal pain (90%), nausea (43%), constipation (29%), diarrhea (23%), flatulence (14%), and vomiting (14%). The occurrence of TEAEs was consistent with the overall safety profile observed in previous studies and studies of POS tablets. The incidence of TEAEs was not increased with the administration of POS tablets in the presence of concomitant medications.

REFERENCES


Figure 1. Study design.
Figure 2. Plasma concentration vs time profile after a single 400 mg oral dose of POS tablet alone.
Figure 3. Effect of concomitant medications on the area under the curve (AUC) and maximum observed concentration (Cmax) after a single 400 mg oral dose of POS tablet alone or in combination with concomitant medications altering gastric pH (antacid, ranitidine, and esomeprazole) or gastric motility (metoclopramide).
Figure 4. Effect of concomitant medications on the area under the curve (AUC) and maximum observed concentration (Cmax) after a single 400 mg oral dose of POS tablet alone or in combination with concomitant medications altering gastric pH (antacid, ranitidine, and esomeprazole) or gastric motility (metoclopramide).
Figure 5. Individual ratios, geometric mean ratio (POS tablet + medication/POS tablet) and 90% CI of AUC0–last and Cmax after a single 400 mg oral dose of POS tablet alone or in combination with concomitant medications altering gastric pH (antacid, ranitidine, and esomeprazole) or gastric motility (metoclopramide).
Figure 6. Individual ratios, geometric mean ratio (POS tablet + medication/POS tablet) and 90% CI of AUC0–last and Cmax after a single 400 mg oral dose of POS tablet alone or in combination with concomitant medications altering gastric pH (antacid, ranitidine, and esomeprazole) or gastric motility (metoclopramide).