Pharmacokinetics of Rolapitant in Subjects with Mild or Moderate Hepatic Impairment

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Purpose

Rolapitant is a selective and long acting neurokinin (NK) 1 receptor antagonist for the treatment of chemotherapy-induced nausea and vomiting (CINV). Hepatic excretion is the major elimination route of rolapitant in humans. The objective of this study was to evaluate pharmacokinetics and safety of rolapitant in subjects with mild and moderate hepatic impairment.

Methods

A single dose of 180 mg rolapitant was administered orally to subjects with mild (Group 1, n=6) or moderate (Group 2, n=6) hepatic impairment. Matching healthy subjects were dosed as a control group (Group 3, n=8). Plasma samples were collected up to approximately 504 hours. The pharmacokinetics of rolapitant and its active metabolite SCH 720881 were compared between subjects with hepatic impairment and healthy controls.

Results

Following administration of 180 mg rolapitant, the plasma concentration-time profile of rolapitant in all three groups was characterized by a rapid absorption phase with median time to reach maximum concentration ($t_{\text{max}}$) ranging from 3.00 to 3.96 hours post dose. The geometric mean ratios (GMR) of Group 1 (Mild) and 2 (Moderate) compared to Group 3 (Normal) for observed maximum plasma concentration ($C_{\text{max}}$) of rolapitant were 92.3% (90% confidence interval or CI: 68.2-125%) and 75.0% (90% CI: 55.4-102%), respectively. For the area under the plasma concentration-time curve from time zero to 120 hours ($\text{AUC}_{0-120}$) of rolapitant, the ratios were 92.3% (Mild, 90% CI: 73.2-116%) and 81.1% (Moderate, 90% CI: 64.4-102%) of the healthy control group, respectively. For the area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration ($\text{AUC}_{0-t}$) of rolapitant, the ratios were 95.9% (Mild, 90% CI: 74.9-123%) and 100% (Moderate, 90% CI: 78.3-128%), respectively. Similar findings were observed for SCH720881 in subjects with mild and moderate hepatic impairment. There were no clinically significant findings in clinical laboratory tests, vital signs, electrocardiograms, or physical examinations in all three groups.

Conclusion

Subjects with mild hepatic impairment had comparable PK profiles and exposure for both rolapitant and metabolite SCH 720881 to normal subjects. Mean exposure to both rolapitant and metabolite SCH 720881 slightly decreased in subjects with moderate hepatic impairment compared to normal subjects. The decrease of exposure is not considered clinically relevant and dose adjustment for patients with mild to moderate hepatic impairment is not required.