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Therapeutic equivalence of two esomeprazole delayed release powder for oral suspension formulations

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Background: Esomeprazole is a proton pump inhibitor (PPI) that suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cells (final step in acid production). This effect is dose-related up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion. Esomeprazole is a weak base that is acid labile and is rapidly degraded in the acidic environment of the stomach. This has led to development of enteric coated formulations of esomeprazole, to protect the active ingredient from degradation by gastric acid, though this also delays absorption. The oral suspension offers an alternative for patients (e.g., elderly people and children) who require PPI therapy for acidity-related conditions but who have difficulty in swallowing tablets or capsules. Thus, a generic powder formulation for delayed release oral suspension of esomeprazole was developed by Ranbaxy Laboratories Limited, India for special population. For registration of the product for marketing, it is mandatory to assess the pharmacokinetics and bioavailability of the generic formulation in comparison with reference formulation (NEXIUM® for delayed-release oral suspension).

Objective: To determine and compare the rate and extent of absorption of esomeprazole between the test formulation, Esomeprazole magnesium for delayed release oral suspension (containing esomeprazole 40 mg) of Ranbaxy Laboratories Limited, India and the reference formulation, NEXIUM® 40 mg (esomeprazole magnesium) for delayed-release oral suspension (containing esomeprazole 40 mg) of AstraZeneca, LP USA in healthy, adult, human male subjects under fasting condition.

Methods: The study was conducted as open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover, bioequivalence study with eighteen (18) male subjects of Asian origin, in the age range of 18-45 years.

The following procedure was followed to ensure administration of complete dose to each subject and to reduce the variability in administration of suspension: The contents (powder for oral suspension of test or reference formulations) were emptied into 15 mL of water and stirred, and left for 5 minutes to thicken. It was stirred and provided to subjects for drinking within 30 minutes. The dosing cup was then rinsed with about 10 mL of water at least twice and subjects were asked to swallow the rinse. The subjects were then asked to rinse their mouth with about 40 mL of water. Remaining drinking water from 240 mL was administered. The dosing was performed under supervision of trained study personnel.

The two treatments were separated by a washout period of 07 days.

Blood samples were collected pre-dose and up to 18 hours post dose in each period for determination of plasma esomeprazole concentrations and calculation of the pharmacokinetic parameters. ANOVA was performed on the log (natural)-transformed pharmacokinetic parameters. A 90% confidence interval for the ratios of the test and reference product averages (least square means) were calculated for esomeprazole to establish bioequivalence.

Results: The results of statistical analysis showed that 90% confidence intervals for esomeprazole were within bioequivalence acceptance criteria of 80 to 125%. The 90% confidence intervals obtained for esomeprazole for $C_{max,}$ AU_{C0-t} and AU_{C0-t} were 102.58% (90.97% – 115.67%), 96.86% (87.20% – 107.60%) and 96.88% (87.29% – 107.54%), respectively. The two treatments were well tolerated by the study subjects.

Conclusion: Based on these results, esomeprazole magnesium for delayed release oral suspension (containing esomeprazole 40 mg) of Ranbaxy Laboratories Limited, India is concluded to be bioequivalent to NEXIUM® 40 mg (esomeprazole magnesium) for delayed-release oral suspension (containing esomeprazole 40 mg) of AstraZeneca LP are bioequivalent in healthy, adult, male, human subjects under fasting condition.