Bioequivalence Evaluation of Two Entecavir Tablet Formulations after Single Oral Administration in Healthy Male Volunteers
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ABSTRACT

Purpose: The aim of this study was to assess the bioequivalence of two oral formulations (test and reference) of 1 mg entecavir, genotypically resistant to potent antiviral activity against HBV DNA polymerase.

Methods: The bioavailability was evaluated by a two period crossover design with a 5-week washout period. A 30 mg healthy volunteer Male Volunteers Plasma samples, obtained over 72 h in each period, were analyzed by a validated liquid chromatographic-mass spectrometry method in a single chamber assay. The pharmacokinetic parameters were calculated by the non-compartmental analysis of plasma concentrations. Analysis of variance was carried out using log-transformed AUC0-72h and Cmax and 90% confidence intervals for AUC0-72h and Cmax were calculated.

Results: The geometric mean of AUC0-72h were 201607.72 vs. 232811.41 pg h/mL (test vs. reference), and the geometric means of Cmax were 9895.34 vs. 9346.25 pg/mL (test vs. reference). The geometric mean ratio of the test formulation to reference formulation for AUC0-72h and Cmax were 0.969 and 0.948, respectively, and the 90% CI for AUC0-72h and Cmax were 95.26% to 98.63% and 95.90% to 99.25%, respectively, satisfying the bioequivalence criteria of both the European Committee for Proprietary Medicinal Products and the US FDA and Drug Administration Guidelines.

Conclusions: These results indicate that the two formulations of 1 mg entecavir are bioequivalent in terms of maximum exposure and extent of drug absorption and, thus, may be prescribed interchangeably.

METHODS

1. Clinical Protocol
- Standard 2 × 3 crossover model in a randomized order
- Subjects: Healthy male volunteer patients with a clinical screening test
- Age: ranging from 21 to 53
- BMI: 22.4 to 26.5 (normal range: 18.5 to 25.0)
- Sample size: 40 (withdrawal: 1)
- Baseline: 1.2 mg/mL (test) vs. 1.1 mg/mL (reference)
- Sample loading: 0.5, 1.5, 2.5, 3.5, 4.5, 5.5, 6.5, 7.5, 8.5, 9.5, 10.5 (2 times)
- Detection: 0.5, 1.5, 2.5, 3.5, 4.5, 5.5, 6.5, 7.5, 8.5, 9.5, 10.5 (2 times)
- washout period: 5 weeks

2. Chromatographic Conditions
- HPLC: Shimadzu (Series 6000, Japan)
- Detector: 5000 (Model 347, USA)
- Column: C18 (5 μm, 4.6 mm × 250 mm)
- Mobile phase: 10% methanol:90% water (acidified with 10 µL/L H3PO4, adjusted to pH 3.5 with ammonia solution)
- Flow rate: 1.0 mL/min
- UV detection: 254 nm

RESULTS

1. Chromatograms

2. Calibration Curve

3. Extraction of Entecavir from Plasma

4. Pharmacokinetic Analysis

5. Statistical Analysis of Data

6. Pharmacokinetic Parameters

7. Statistical Results of Bioequivalence Evaluation between Two Entecavir 1 mg Tablets

8. Precision and Accuracy

9. Mean Plasma Concentration-Time Profile

CONCLUSION

These results indicate that the two formulations of entecavir tablets are bioequivalent in terms of maximum exposure and extent of drug absorption and, thus, may be prescribed interchangeably.