Assessment of In Vivo Bioperformance of Enalapril Maleate in Co-Renitec Tablets Manufactured at Two Facilities via Deconvolution Analysis and PBBM

Abstract

Co-Renitec is a fixed-dose combination of enalapril maleate and hydrochlorothiazide. To support a sourcing change from Merck manufacturing site A to site B, dissolution profiles were generated on batches of product from both sites. Dissolution comparison of 20 mg/12.5 mg tablets manufactured at these 2 sites was performed using USP2 apparatus at 50 rpm in 900 mL water. A slower dissolution of the formulations from site B was observed for enalapril maleate, resulting in F2 failure in 3 versus 3 batches comparison between the formulations of these 2 sites.

To explore the clinical relevance of this observation, the absorption of enalapril was characterized based on data from a definite bioavailability study, using both Physiologically Based Biopharmaceutics Modeling (PBBM) and a "rate of absorption" analysis. Physiologically-based absorption models of enalapril were established in GastroPlus using available clinical data. This deconvolution approach analyzing the rate of dissolution and absorption were explored, which required fewer model assumptions than PBBM.

Based on the M&S results from both PBBM and deconvolution analysis, any minor dissolution differences at earlier timepoints (~15 min) are not considered of physiological relevance. Since the dissolution data from both manufacturing sites are complete within 30 min, a clinical bioequivalence study is not deemed necessary.

BACKGROUND

- Enalapril maleate physicochemical properties
  - ClouEP: 2.45 (Englund et al., 2010)
  - pKa: 3.0 and 5.4 (IKA package)
- pH-solubility profile: >25 mL/dose at physiologic pH
- Dose: 5 mg, 10 mg, 20 mg, and 40 mg
- Oral absorption of the drug: 59%–73% according to Vasotec NDA package, with an average of 64% from 5–40 mg oral doses
- Based on the estimation of fraction absorbed, enalapril maleate can be classified as a BCS II compound – Human Jejunum Permeability: 1.57 × 10⁻⁶ cm/s (Lennernas et al., 2007)

PROBLEM STATEMENT AND OPTIONS

- Co-Renitec (VASODRITEC) is a fixed-dose combination of enalapril maleate and hydrochlorothiazide
- As part of the overall manufacturing strategy, Merck had proposed to switch the manufacturing of Co-Renitec formulations from site A to site B to supply the market of geographic location of site A
- Dissolution comparison of 20 mg/12.5 mg tablets manufactured at these 2 commercial sites was performed (USP2, 50 rpm, 900 mL water)
- Slow down of dissolution of the formulations from site B was observed for enalapril maleate, resulting in failure of F2 in comparison of 3 versus 3 batches
- HVC was not established previously

Options to support filing of this manufacturing site change:
- Run a clinical bioequivalence study
- Generate a bioimpair impact report that the differences in the dosage profiles are not expected to impact bioavailability including a M&S analysis in the report

PBMM RESULTS

- Calculated pharmacokinetics parameters (left) and simulated PK profiles (right) of enalapril after 5 mg, 10 mg, 20 mg, and 40 mg oral dosage of enalapril maleate via PBBM
- Based on the PBMM results, comparable exposure (less than 5% difference in exposure) is expected for batches from both sites at 5 mg ~ 40 mg doses
- However, a couple of key assumptions have to be taken to establish the current model, which could potentially impact the argument with agency using PBMM approach:
  - There is no means to validate the predictions of the model (ie, an external validation that would be required for an IVIVC for a slow batch as these data do not exist)
  - In order to fit the available clinical oral PK data, the models explored in the report had to assume a different combination of regional absorption scenarios with low permeability values in ileum with no means to verify or defend the regional absorption model
- "Fewer" assumptions are better for regulatory argument – which leads to Option 2

CONCLUSIONS

- To explore the clinical relevance of dissolution slow-down for formulation from manufacturing site A to site B, the absorption of enalapril was characterized based on data from a definite bioavailability study, using both PBMM and deconvolution based analysis assuming 1:1 translation of in vitro to in vivo dissolution
- The PK data from enalapril (MK-421) for individual subjects after 5 mg dose of enalapril maleate or 5 mg, 10 mg, 20 mg, and 40 mg oral doses of enalapril maleate tablets were obtained and calculated from the absolute bioavailability study. A first-order 2-compartment PK model was used to describe the PK profiles following IV administration of 5 mg dose of enalapril maleate tablets
- From that the unit impulse response (UIR) functions were calculated for all subjects. Macro PK constants (a, b, c, d) were calculated and PK profiles of enalapril (MK-421) for individual subjects after 5 mg dose of enalapril maleate were fitted
- Cumulative %fraction inputs of enalapril as a function of time were estimated using deconvolution for individual subjects. The average of %F2 and %F3 as a function of time were calculated from the data from individual subjects at different doses (5 mg, 10 mg, 20 mg, and 40 mg)
- All deconvolution were conducted in Phoenix WinNonlin v6.3

DECONVOLUTION ANALYSIS RESULTS

Calculated pharmacokinetics macro constant (UIR) of enalapril for individual subjects after 5 mg intravenous dose of enalapril maleate using a first-order 2-compartment PK model

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<th>Alpha (1/hr)</th>
<th>Alpha_CV%</th>
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</table>

Overlay of average deconvolution output (percent in vivo absorption versus time) at 5 mg, 10 mg, 20 mg, and 40 mg oral doses with in vitro dissolution profiles of enalapril for site A and site B formulation batches

- For studied enalapril doses, the absorption followed typical first-order kinetics, and the calculated in vivo absorption reaches a plateau around 2–3 hours post dosing, which is in line with the BCS III classification of the compound based on 60%–70% fraction absorbed
- The timeframe of absorption is much longer than the observed dissolution time in simple aqueous media where complete dissolution is achieved within 30 min for all batches tested
- Therefore any differences in dissolution within that timeframe between different batches are not expected to have an impact on pharmacokinetics

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