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ASSESSMENT OF IN VIVO BIOPERFORMANCE FOR ENALAPRIL MALEATE (MK-0421) BETWEEN CO-RENITEC TABLETS MANUFACTURED AT TWO DIFFERENT SITES VIA DECONVOLUTION ANALYSIS AND PBAM MODELING

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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 20mg/12.5mg tablets manufactured at these two sites was performed using USP2 apparatus at 50 rpm in 900mL water. Differences of dissolution of the formulations from the two sites were observed for enalapril maleate, resulting in F2 values of 34, 32, 28, 36, 33, 29, 36, 34, 29 in 3 versus 3 batches comparison between the formulations of these two 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 absorption modeling (PBAM) and deconvolution based analysis. Physiologically-based absorption models of enalapril were established in GastroPlus using available clinical data. Based on the PBAM results, comparable exposure (less than 5% difference in exposure) is expected for batches from both sites at 5mg ~ 40mg doses. However, several assumptions have to be taken to establish the PBAM, e.g. the models had to assume a 1:1 translation of in vitro to in vivo dissolution with no available data to validate, and there is only one dissolution condition available (900 mL water). There is also no means to validate the predictions of the model (i.e. an external validation that would be required for an IVIVC) for a slow batch as these clinical data do not exist. In order to fit the available clinical oral PK data, the models had to assume a different combination of regional absorption scenarios, with no means to justify or verify the regional absorption model.

Therefore, a deconvolution approach analyzing the rate of dissolution and absorption were explored, which required fewer model assumptions. In deconvolution analysis, the absorption of enalapril is relatively slow and occurs over 2-3 hours, 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. Any differences in dissolution within that timeframe between different batches are not expected to have an impact on pharmacokinetics.

Based the M&S results from both PBAM and deconvolution analysis, since the dissolution of batches from both manufacturing sites are complete within 30 min, any minor dissolution differences at earlier timepoints (e.g. 15 min) are not considered of physiological relevance. Therefore a clinical bioequivalence study is not deemed necessary.