13 December 2018
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Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Aliskiren film-coated tablet 150 mg and 300 mg product-specific bioequivalence guidance' (EMA/CHMP/291450/2018)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 19 / Table Bioequivalence study design	1	Comments: We consider the proposed single-dose, cross-over study in healthy volunteers as well as the choice of primary pharmacokinetic metrics, study strength, analyte and achiral analytical method adequate for demonstration of bioequivalence for aliskiren. However, we do not concur with the need to conduct studies both under fasting and fed conditions. In the below, we summarized our position. Meals with a high fat content reduce the Cmax and AUC of aliskiren by 85% and 70%, respectively. At steady state, meals with low fat content reduce the Cmax and AUC0-tau by 76% and 67%, respectively (SmPC of Rasilez, EMEA/H/C/000780). Despite the pronounced food effect on pharmacokinetics, in pivotal phase III clinical trials where aliskiren proved to be safe and efficacious, the dosing instructions in relation to food were non-specific and aliskiren could be taken without respect to fast/fed conditions (Rasilez, EMEA/H/C/000780, EPAR Scientific Discussion). In addition, the efficacy and safety of aliskiren has been shown similar in an 8-week randomized study in hypertension patients when aliskiren was taken either with a light meal or without meal (EudraCT number: 2011-005297-36; protocol number: CSPP100A2413). Based on results of this study, the posology in relation	Not accepted. It is noted that indeed the EMA Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), in those situations where SmPC allows the intake of reference medicinal product under fasting or fed conditions, the bioequivalence study should be conducted under fasting conditions as this represents the most sensitive condition to detect potential difference between formulations. However, in this specific case the SmPC specifies that the patient takes the preparation either always in the fasted or in the fed state and thus both fed and fasted studies are required. Indeed it is mandated that patients should establish a convenient daily schedule of medicinal product intake and maintain a steady temporal relationship with food intake. Thus both fed and fasted studies are warranted in this specific case.

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		to food intake for medicines containing aliskiren (aliskiren and alisikiren in combination with hydrochlorothiazide) has been extended in 2016 (variation application number WS/0849) to include the possibility to administer aliskiren without food. Patients should establish a routine pattern for taking aliskiren, either with or without a meal. As per EMA Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), in those situations where SmPC allows the intake of reference medicinal product under fasting or fed conditions, the bioequivalence study should be conducted under fasting conditions as this represents the most sensitive condition to detect potential difference between formulations. Notably, in a marketing authorization application for Rasilez HCT (EMEA/H/C/000964), bioequivalence studies under fasting conditions were conducted in order to bridge the clinical efficacy and safety data obtained with free combination drugs to the fixed combination. Based on CHMP conclusions, the results of bioequivalence studies under fasting conditions could be extrapolated to fed conditions (assessment report for Rasilez HCT, procedure No. EMEA/H/C/000964). In summary, aliskiren was efficacious in pivotal clinical trials without a fixed relation to meals. Moreover, efficacy and safety was shown similar when aliskiren was taken with or without meal in a separate study	

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		designed to evaluate the effect of light meal versus fasted condition. In the view of the above results and the fact that fed conditions are less sensitive to detect formulation difference, the bioequivalence study under fasting conditions is expected to adequately assess the formulation performance. This also corresponds to general recommendations of the EMA bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr) in case the reference product is administered under fasting or fed conditions. Finally, studies under fasted conditions were previously accepted by CHMP to obtain MA for new fixed dose combination containing aliskiren and hydrochlorothiazide. In conclusion, aliskiren bioequivalence study may be performed only under fasting conditions. Proposed change (if any): Table 'Requirements for bioequivalence demonstration (PKWP)': Section bioequivalence study design, in the recommendation regarding posology modify to: (1) ☒ fasting, ☐ fed, ☐either fasting or fed, and (2) delete the Background information. In the section Number of studies, modify to: one single dose study.	