1 April 2015
EMA/CHMP/116907/2014
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Draft posaconazole product-specific bioequivalence guidance' (CHMP/PKWP/EMA/423719/2013)

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

Stakeholder no.	Name of organisation or individual
1	Merck Sharp & Dohme (MSD)
2	Zentiva, k.s., Czech Republic (Jiri Hofmann)

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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Line 15, BE study design	1	**Comment:** The BE study design in the draft guidance lists the "fed" condition as requirement for BE demonstration. We propose that the requirement is adapted to "both". There is need for fed and fasted BE studies on the grounds that in practice patients will take the currently approved oral suspension formulation with a variety of foods of different calorific / fat content and hence, by requiring both, fed and fasted BE studies, the entire spectrum of "take with food" as specified in the current label is covered. **Proposed change (if any):** - Change the checked box from "fed" to "both". - Keep the comment on "fed". - Add the comment on "fasting": *Fasting as defined in the Guideline on the investigation of Bioequivalence (section 4.1.4).*	As the requirement is to take this product with food, according to the current guidelines only a fed study is required. However the PKWP acknowledges the innovator's point on the variety of foods, particularly as this drug is taken several times a day. In order to consider the need for studies in the fed and fasted state, the innovator will need to submit data demonstrating the differing effects of different types of food on differing immediate release formulations e.g. suspensions and tablets as justification.
Line 15, BE study design	1	**Comment:** We agree on having the possibility to perform a replicate cross-over design study based on intra-patient variability of posaconazole. However, while maintaining the replicate cross-over design study, we propose that the EU guidance is further aligned with the draft BE FDA guidance, in order to have consistent guidance globally. See link to FDA guidance and see the FDA draft text below.	As the requirement is to take this product with food, according to the current guidelines only a fed study is required. However the PKWP acknowledges the innovator's point on the variety of foods, particularly as this drug is taken several times a day. In order to consider the need for studies in the fed and fasted state, the innovator will need to submit data demonstrating the differing effects of different types of food on differing immediate release formulations e.g. suspensions and tablets as justification.

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		http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm089500.pdf 1. Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover *in-vivo* Strength: 40 mg/ml (dose 400 mg) Subjects: Normal healthy males and females, general population. Additional Comments: Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: Single-dose, two-treatment, two-period crossover *in-vivo* Strength: 40 mg/ml (dose 400 mg) Subjects: Normal healthy males and females, general population. Additional comments: Please see comment above. **Proposed change (if any):**	
Line(s) 15 to 16 (Table)	2	**Comment:** Intra-individual variability for the pharmacokinetic parameters of posaconazole appears to be larger than 30% (Noxafil, EMEA/H/C/000610, EPAR Scientific	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Discussion). Therefore, a replicate cross-over design study is suggested by the draft Product-Specific Bioequivalence Guidance. As per the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr), for studies in replicate design, the widening of CMAX acceptance criteria is acceptable provided that the wider acceptance interval is considered clinically irrelevant (with respect to safety and efficacy). This is the case of posaconazole since a correlation between the total medicinal product exposure (expressed as the area under the time-concentration profile; AUC) divided by the minimal inhibitory concentration (MIC) and clinical outcome was observed (SmPC Noxafil). Different dosing recommendations (e.g. refractory IFI: 4x200 mg or 2x400 mg) in relation to food intake support the fact that AUC not the CMAX is relevant for the therapy. Posaconazole does not change its safety profile even with highly different plasma concentrations. An increase in CMAX (26%) and AUC (29%) was observed in elderly subjects relative to younger subjects, however, the safety profile of posaconazole was similar for both groups (SmPC Noxafil). In addition, during clinical trials, patients who received posaconazole doses up to 1,600 mg/day experienced no different adverse reactions from those reported with patients at the lower doses (SmPC Noxafil). In conclusion, widened acceptance criteria for CMAX may be used for posaconazole.	

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		Proposed change: Table 'Requirements for bioequivalence demonstration (PKWP)': Section Bioequivalence assessment, 90% confidence interval should be modified to allow scaling for CMAX. Change wording to: 80.00 – 125.00 for AUC0-72h and widened acceptance criteria for CMAX (based on scaled-average-bioequivalence).	
Line 16	2	**Comment:** Intra-individual variability in the pharmacokinetic parameters of posaconazole appears to be larger than 30% (Noxafil, EMEA/H/C/000610, EPAR Scientific Discussion). **Proposed change**: Delete text: * As drug variability has not been reviewed, this guidance is not applicable to highly variables drugs.	Accepted.