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Committee for Medicinal Products for Human Use (CHMP)

Deferasirox, dispersible tablets (125 mg, 250 mg and 500 mg), film-coated tablets (90 mg, 180 mg, and 360 mg), and granules (90 mg, 180 mg and 360 mg) product-specific bioequivalence guidance

Draft Agreed by Pharmacokinetics Working Party (PKWP)	19 November 2020
Adopted by CHMP for release for consultation	10 December 2020
Start of public consultation	18 December 2020
End of consultation (deadline for comments)	31 March 2021
Agreed by Pharmacokinetics Working Party	
Adopted by CHMP	
Date for coming into effect	

Comments should be provided using this template. The completed comments form should be sent to PKWPsecretariat@ema.europa.eu.

Keywords	***Bioequivalence, generics, deferasirox***

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Disclaimer:

This guidance should not be understood as being legally enforceable and is without prejudice to the need to ensure that the data submitted in support of a marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.

Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** deferasirox is considered a low solubility compound.
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	Film-coated tablets and granules: ☐ **fasting** ☐ **fed** ☒ **both** ☐ **either fasting or fed** Deferasirox film-coated tablets and granules can be taken with or without food according to the SmPC. Since the specific formulation (excipients) is known to be critical to the performance in fed conditions both fasted and fed state comparisons of test to reference formulations are required.

	Low fat, light meal study conditions (approximately 250 to 300 kcal, meal fat content <10% of calories) according to the SmPC of the originator product. A waiver for this fed study may be applicable if excipients that might affect bioavailability are qualitatively the same and quantitatively similar between test and reference product. Dispersible tablets: ☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed** Deferasirox dispersible tablets should be taken without food according to the SmPC, therefore, one study under fasting conditions is sufficient.
	Strength: dispersible tablets: 500mg, film-coated tablets and granules: 360 mg **Background:** highest strength to be used for a drug with linear pharmacokinetics and low solubility.
	Film-coated tablets and granules **Number of studies: 2** **Background:** two single dose studies (fasted and fed) **Dispersible tablets** **Number of studies: 1** **Background:** one single dose study (fasted)
	Other design aspects:
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**

Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t} and C_{max}
	90% confidence interval: 80.00 – 125.00%

* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to recommend at this stage the use of a replicate design to demonstrate high intra-subject variability and widen the acceptance range of C_{max}. If high intra-individual variability (CV_{intra} > 30%) is expected, the applicants might follow respective guideline recommendations.

** This tentative BCS classification of the drug substance serves to define whether *in vivo* studies seems to be mandatory (BCS class II and IV) or, on the contrary (BCS Class I and III), the Applicant may choose between two options: *in vivo* approach or *in vitro* approach based on a BCS biowaiver. In this latter case, the BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility experiments, literature, etc.). However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being BCS class I or III (e.g. *in vitro* dissolution being less than 85% within 15 min (BCS class III) or 30 min (BCS class I) either for test or reference, or unacceptable differences in the excipient composition).