10 June 2025
EMA/CHMP/472383/2020 Rev. 1*
Committee for Medicinal Products for Human Use (CHMP)

Deferasirox film-coated tablets 90 mg, 180 mg and 360mg, 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	17 December 2020
End of consultation (deadline for comments)	31 March 2021
Agreed by Pharmacokinetics Working Party	22 April 2021
Adopted by CHMP	20 May 2021
Date for coming into effect	1 January 2022
Draft revision agreed by Methodology Working Party (MWP)	29 April 2025
Adopted by CHMP	10 June 2025
Date of coming into effect	1 January 2026

* This revision addresses textual changes in accordance with the ICH M13A guideline

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 (MWP)*

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
	☐ **fasting** ☐ **fed** ☒ **both** ☐ **either fasting or fed** **Background:** Deferasirox is considered a "high-risk product". Since the specific formulation (excipients) of the tablet is known to be critical to the performance of the formulation in fed conditions, it cannot be assumed that the impact of food will be the same regardless of formulation. Therefore, both fasted and fed state comparisons of test to reference formulations are required.

	A waiver for this fed study may be applicable if it can be shown that the products are manufactured using the same technology and if excipients that might affect bioavailability are qualitatively the same and quantitatively similar between test and reference product.
	Strength: Film-coated tablets and granules: 360 mg **Background:** Highest strength to be used for a drug with linear pharmacokinetics.
	Number of studies: Two single dose studies for film-coated tablets, two single dose studies for granules.
	Other design aspects: 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.
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).