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Committee for Medicinal Products for Human Use (CHMP)

Metformin immediate-release film-coated tablets 500, 850 and 1000 mg and 1000 mg/5ml oral solution product-specific bioequivalence guidance

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* This revision addresses textual amendments in accordance with the ICH M13A guideline and adds the requirements for oral solution.

Keywords	***Bioequivalence, generics, metformin***

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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:** Metformin hydrochloride is considered a high solubility compound with limited absorption.
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** The SmPC recommends intake in fed state to minimise the risk of gastrointestinal irritations. A fed study is, therefore, acceptable. However, a fasted study is also acceptable.
	Strength: For tablets: 1000 mg. For oral solution: 1000 mg/5ml used at 1000 mg dose (corresponding to the highest tablet strength). **Background:** Highest strength to be used for a drug with linear pharmacokinetics.

	According to the SmPC of the reference product, "*metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear*". However, according to publicly available data the non-linearity of metformin pharmacokinetics in the dose range is not large enough and pharmacokinetics can, therefore be regarded as linear.
	Number of studies: Tablets: One single dose study. Solution: One single dose study. A study with the oral solution may be waived if all excipients are qualitatively the same and quantitatively similar as in the reference 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 seem 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).