EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg product-specific bioequivalence guidance

Draft agreed by Pharmacokinetics Working Party	April 2017
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End of consultation (deadline for comments)	31 October 2017
Agreed by Pharmacokinetics Working Party	April 2018
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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)*

Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**Single-dose fasting:** 240 mg strength in healthy subjects. **Single-dose fed:** 240 mg strength in healthy subjects. **Multiple dose:** N/A **Background:** Gastro-resistant multiple unit formulation. In case of single unit formulations and different strengths, single dose studies are needed for every strength (see section 6.2.2. of the guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1))
	Cross-over

	Other critical aspects: Standardized administration of aspirin administered 30 min prior to drug administrations could be considered to reduce flushing, which is the most frequent unfavourable AE in the fasting state**.**
Analyte	☐ **parent** ☒ **metabolite** ☐ **both** **Background:** Conclusions on bioequivalence should be based on levels of the main active metabolite monomethyl fumarate
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** **Single dose:** AUC_{0-t}, AUC_{inf}, C_{max} **Multiple dose:** N/A
	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} $C_{T,ss}$, and partial AUC. If high intra-individual variability (CVintra > 30%) is expected, the applicants might follow respective guideline recommendations.