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Committee for Medicinal Products for Human Use (CHMP)

Dolutegravir film-coated tablets 10 mg, 25 mg and 50 mg product-specific bioequivalence guidance

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* This revision addresses the removal of the requirement for a study with the 10 mg strength and the addition of the requirements for the dispersible tablet formulation

Keywords	***Bioequivalence, generics, dolutegravir***

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Dolutegravir film-coated tablets 10 mg, 25 mg and 50 mg, dispersible tablets 5 mg, product-specific bioequivalence guidance

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:** Dolutegravir sodium 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**
	Strength: Film coated tablets 50 mg Dispersible tablet: 5 mg

	Background: Film-coated tablet: highest strength to be used for a drug with linear pharmacokinetics. Dispersible tablet: 5 mg is the only strength
	Number of studies: One single dose study for the film-coated tablet. One single dose study for the dispersible tablet. **Background:** Dispersible tablets are not interchangeable with the film-coated tablets and bioequivalence needs to be shown separately for each formulation. Other critical aspects: the dispersible tablet should be dispersed in line with the instructions in the SmPC.
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).