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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

Draft

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Adopted by CHMP for release for consultation	22 June 2017
Start of public consultation	28 July 2017
End of consultation (deadline for comments)	31 October 2017

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

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

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Dolutegravir film-coated tablets 10 mg, 25 mg and 50 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 (PKWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Dolutegravir 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: 10 mg and 50 mg **Background:** Highest strength (50 mg) to be used for a drug with linear pharmacokinetics and low

	solubility. The 25 mg strength can be waived from the study with the 50 mg tablet. An additional study is required with 10 mg, since bioequivalence has not been unequivocally shown for the reference product 1x50 mg tablet compared to 5x10 mg tablets. Therefore, the reference product SmPC states that the 50 mg once daily dose should not be given as five 10 mg tablets.
	Number of studies: Two single dose studies (10 mg and 50 mg strengths). **Background:** See above.
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).

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