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Committee for Medicinal Products for Human Use (CHMP)

Emtricitabine/rilpivirine/tenofovir disoproxil film-coated tablets 200 mg/25 mg/245 mg product-specific bioequivalence guidance

Draft agreed by Pharmacokinetics Working Party	October 2016
Adopted by CHMP for release for consultation	15 December 2016
Start of public consultation	22 December 2016
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Agreed by Pharmacokinetics Working Party	April 2017
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Keywords	***Bioequivalence, generics, emtricitabine / rilpivirine / tenofovir disoproxil***

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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:** Emtricitabine may be considered a high solubility compound. Rilpivirine may be considered a low solubility compound. Tenofovir disoproxil may be considered a high 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: 200 mg/25 mg/245 mg for emtricitabine/rilpivirine/tenofovir disoproxil. **Background:** 200 mg/25 mg/245 mg is the only available combination strength.
	Number of studies: one single dose study
Analyte	☒ **parent** ☒ **metabolite** ☐ **both** For emtricitabine and rilpivirine the parent, for tenofovir disoproxil the metabolite (as tenofovir).
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t} and C_{max} for emtricitabine and tenofovir**.** AUC_{0-72} and C_{max} for rilpivirine.
	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).