EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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

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
End of consultation (deadline for comments)	31 March 2017

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

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:** The combination includes compounds with high and low solubility.
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:** it is the only available combination strength.

	Number of studies: one single dose study
Analyte	☒ **parent** ☒ **metabolite** ☐ **both** **Background:** 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 Disoproxil**.** 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).