1 24 September 2015
2 EMA/CHMP/PKWP/151748/2015
3 Committee for Medicinal Products for Human Use (CHMP)

4 Entecavir film-coated tablets 0.5 and 1 mg, oral solution 5 0.05mg/ml product-specific bioequivalence guidance

6 Draft

Draft Agreed by Pharmacokinetics Working Party	April 2015
Adoption by CHMP for release for consultation	24 September 2015
Start of public consultation	1 October 2015
End of consultation (deadline for comments)	1 January 2016

7
8

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

9

Keywords	***Bioequivalence, generics, entecavir***

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Entecavir film-coated tablets 0.5 and 1 mg, oral solution 0.05mg/ml 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:** The available data on solubility and absorption does not allow the BCS classification of entecavir. A BCS biowaiver could be applicable if the applicant generates data according to the BCS criteria to support its classification as BCS class I or III.
BE 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: 1mg **Background:** Highest strength to be used for a drug with linear pharmacokinetics. It may also be possible

	to use the lower strength 0.5 mg if solubility is shown to be high since pharmacokinetics is linear.
	Number of studies: Tablets: one single dose study. Oral solution: studies may be waived if the amount of maltitol used is very similar to the reference product.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h}, Cmax
	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 (CVintra > 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).