1 14 December 2017
2 EMA/CHMP/800789/2017
3 Committee for Medicinal Products for Human Use (CHMP)

4 Ledipasvir/sofosbuvir film-coated tablet 90 mg/400 mg 5 product-specific bioequivalence guidance

6 Draft

Draft Agreed by Pharmacokinetics Working Party (PKWP)	November 2017
Adopted by CHMP for release for consultation	14 December 2017
Start of public consultation	31 January 2018
End of consultation (deadline for comments)	30 April 2018

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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, ledipasvir/sofosbuvir***

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Ledipasvir/sofosbuvir film-coated tablet 90 mg/400 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:** ledipasvir 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: ledipasvir 90 mg and sofosbuvir 400 mg **Background:** 90 mg/ 400 mg is the only available combination strength

	Number of studies: one single dose study
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h} and C_{max} for ledipasvir and AUC_{0-t} and C_{max} for sofosbovir.
	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).