1 December 2025
EMA/151702/2025 Rev. 1*
Committee for Medicinal Products for Human Use (CHMP)

Ledipasvir/sofosbuvir film-coated tablet 45 mg/200 mg and 90 mg/400 mg, coated granules 33.75mg/150mg and 45mg/200mg product-specific bioequivalence guidance

Draft Agreed by Pharmacokinetics Working Party (PKWP)	November 2017
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Date of coming into effect	1 June 2026

* This revision addresses the requirements for a fasted and fed study and not a fasted study only in accordance with the ICH M13A guideline, for the additional strength of 45 mg/200 mg and for the new coated granules with the strengths 33.75mg/150mg and 45mg/200mg.

Keywords	***Bioequivalence, generics, ledipasvir, sofosbuvir***

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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:** 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
	Film-coated tablets and coated granules: ☐ **fasting** ☐ **fed** ☒ **both** ☐ **either fasting or fed** **Background:** Ledipasvir/sofosbuvir is considered a "high risk product". Since the specific formulation (e.g. manufacture, excipients) of the tablets and granules is known to be critical to the performance of the formulation, it cannot be assumed that the impact of food will be the same regardless of formulation. Therefore, both fasted and fed state comparisons of test to reference formulations are required.

	A waiver for this fed study may be applicable if the products are manufactured using the same technology and if excipients that might affect bioavailability are qualitatively the same and quantitatively similar between test and reference product.
	Strength: Film-coated tablet: Ledipasvir 90 mg and sofosbuvir 400 mg, Coated granules: Ledipasvir 45mg and sofosbuvir 200mg **Background:** Highest strength to be used for drugs with linear pharmacokinetics.
	Number of studies: Film-coated tablets and coated granules: two single dose studies, one in the fasting state and one in the fed state.
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 sofosbuvir.
	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).