



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

26 July 2018  
EMA/CHMP/800789/2017  
Committee for Medicinal Products for Human Use (CHMP)

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

<b>Draft Agreed by Pharmacokinetics Working Party (PKWP)</b>	November 2017
<b>Adopted by CHMP for release for consultation</b>	14 December 2017
<b>Start of public consultation</b>	31 January 2018
<b>End of consultation (deadline for comments)</b>	30 April 2018
<b>Agreed by PKWP</b>	June 2018
<b>Adopted by CHMP</b>	26 July 2018
<b>Date of coming into effect</b>	1 February 2019

<b>Keywords</b>	<i>Bioequivalence, generics, ledipasvir, sofosbuvir</i>
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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)\*

<p><b>BCS Classification**</b></p>	<p><b>BCS Class:</b> <input type="checkbox"/> I    <input type="checkbox"/> III    <input checked="" type="checkbox"/> <b>Neither of the two</b></p> <p><b>Background:</b> ledipasvir is considered a low solubility compound.</p>
<p><b>Bioequivalence study design</b></p> <p><i>in case a BCS biowaiver is not feasible or applied</i></p>	<p><b>single dose</b></p> <p><b>cross-over</b></p> <hr/> <p><b>healthy volunteers</b></p> <hr/> <p><input checked="" type="checkbox"/> <b>fasting</b>    <input type="checkbox"/> <b>fed</b>    <input type="checkbox"/> <b>both</b>    <input type="checkbox"/> <b>either fasting or fed</b></p> <hr/> <p><b>Strength:</b> ledipasvir 90 mg and sofosbuvir 400 mg</p> <p><b>Background:</b> 90 mg/ 400 mg is the only available combination strength.</p>

	<b>Number of studies:</b> one single dose study.
<b>Analyte</b>	<input checked="" type="checkbox"/> <b>parent</b> <input type="checkbox"/> <b>metabolite</b> <input type="checkbox"/> <b>both</b>
	<input checked="" type="checkbox"/> <b>plasma/serum</b> <input type="checkbox"/> <b>blood</b> <input type="checkbox"/> <b>urine</b>
	<b>Enantioselective analytical method:</b> <input type="checkbox"/> <b>yes</b> <input checked="" type="checkbox"/> <b>no</b>
<b>Bioequivalence assessment</b>	<b>Main pharmacokinetic variables:</b> AUC <sub>0-72h</sub> and C <sub>max</sub> for ledipasvir and AUC <sub>0-t</sub> and C <sub>max</sub> for sofosbuvir.
	<b>90% confidence interval:</b> 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<sub>max</sub>. If high intra-individual variability (CV<sub>intra</sub> > 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).