1 December 2025
EMA/151700/2025 Rev. 1*
Committee for Medicinal Products for Human Use (CHMP)

Sirolimus coated tablets 0.5, 1 and 2 mg, oral solution 1 mg/ml product-specific bioequivalence guidance

Draft agreed by Pharmacokinetics Working Party (PKWP)	October 2013
Adoption by CHMP for release for consultation	24 October 2013
Start of public consultation	15 November 2013
End of consultation (deadline for comments)	15 February 2014
Agreed by Pharmacokinetics Working Party (PKWP)	29 April 2015
Adoption by CHMP	21 May 2015
Date of coming into effect	1 December 2015
Draft revision agreed by Methodology Working Party (MWP)	29 April 2025
Adoption by CHMP	12 May 2015
Start of public consultation	10 July 2025
End of consultation (deadline for comments)	31 October 2025
Adopted by CHMP	1 December 2025
Date of coming into effect	1 June 2026

*This revision addresses the requirements for a fasting study only and not both a fasting and fed study for the oral solution in accordance with the ICH M13A guideline.

Keywords	***Bioequivalence, generics, sirolimus***

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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)

<table>
<tr><td>BCS Classification</td><td>BCS Class: ☐ I ☐ III ☒ Neither of the two
Background: Sirolimus may be considered a low solubility compound.</td></tr>
<tr><td rowspan="3">Bioequivalence study design
in case a BCS biowaiver is not feasible or applied</td><td>single dose
cross-over</td></tr>
<tr><td>healthy volunteers</td></tr>
<tr><td>☒ fasting ☐ fed ☒ both ☐ either fasting or fed
Tablets: Sirolimus tablets are considered a “high risk product”. Since the specific formulation (e.g. manufacture, excipients) of the tablets 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.</td></tr>
</table>

	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. Oral solution: A fasting study is sufficient.
	Strength: Tablets: 2 mg and 0.5 mg Oral solution: 1 mg/ml used at 2 mg dose (corresponding to highest tablet strength) **Background:** Tablets: highest strength to be used for a drug with linear pharmacokinetics. The 0.5 mg tablets are not strictly bioequivalent with the higher strengths in terms of C_{max}. Oral solution: a bioequivalence study for the solution will be necessary unless the composition is qualitatively the same and quantitatively similar to the originator. If there is a quantitative difference in solubility enhancers, a bioequivalence study will be necessary if the differences cannot be justified by other data.
	Number of studies **For tablets:** Four studies: single dose fasting and fed at 2 mg and single dose fasting and fed at 0.5 mg. The fed study for the 0.5 mg strength can be waived if the 0.5 mg and 2 mg tablets are dose-proportional. **For oral solution:** One single dose fasting study.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☐ **plasma/serum** ☒ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**

Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t} and C_{max}
	90% confidence interval: 80.00 – 125.00% for C_{max} and 90.00 - 111.11% for AUC_{0-t} **Background:** sirolimus is a narrow therapeutic index drug.