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

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| Draft agreed by Pharmacokinetics Working Party (PKWP) | October 2013 |
| Adoption by CHMP for release for consultation | 24 October 2013 |
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| End of consultation (deadline for comments) | 15 February 2014 |
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*This guideline was previously published as part of a “compilation of individual product-specific guidance on demonstration of bioequivalence Rev.3 EMA/CHMP/736403/2014”


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



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

# Sirolimus coated tablets 0.5, 1 and 2 mg, oral solution 1 mg/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)

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| **BCS Classification** | **BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two**<br>**Background:** sirolimus may be considered a low solubility compound. |
| **Bioequivalence study design**<br>*in case a BCS biowaiver is not feasible or applied* | **single dose**<br>**cross-over** |
| | **healthy volunteers** |
| | ☐ **fasting** ☐ **fed** ☒ **both** ☐ **either fasting or fed**<br>Both fasting and fed are necessary due to specific formulation characteristics. A high-fat meal is recommended. |

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| | **Strength:** Tablets: 2 mg and 0.5 mg<br>Oral solution: 1 mg/ml<br>**Background:**<br>Tablets: highest strength to be used for a drug with linear pharmacokinetics and low solubility. For tablets dose proportionality has been demonstrated between 2 mg and 5 mg doses. 0.5 mg tablets are not strictly bioequivalent with the higher strengths in terms of Cmax.<br>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:** four studies: single dose fasting and fed at 2 mg and single dose fasting and fed at 0.5 mg |
| **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 $AUC_{0-t}$<br>**Background:** sirolimus is a narrow therapeutic index drug. |