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Everolimus tablets 0.25 mg, 0.5 mg, 0.75 mg and 1 mg; 2.5 mg, 5 mg and 10 mg, dispersible tablets 0.1 mg and 0.25 mg; 2 mg, 3 mg and 5 mg product-specific bioequivalence guidance

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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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Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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Everolimus tablets 0.25 mg, 0.5 mg, 0.75 mg and 1 mg; 2.5 mg, 5 mg and 10 mg, dispersible tablets 0.1 mg and 0.25 mg; 2 mg, 3 mg and 5 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)*

Section A of this guideline is applicable for oncologic indications, and section B for transplant indications. May an applicant want to apply for all indications, please follow section A recommendations but taking into account section B in terms of the 90% confidence interval for transplant indications.

Section A. Everolimus tablets 2.5 mg, 5 mg and 10 mg, dispersible tablets 2 mg, 3 mg and 5 mg product-specific bioequivalence guidance (oncologic-only indication)

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Everolimus is a low solubility compound with limited absorption**.**
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over or parallel**
	healthy volunteers
	☐ **fasting** ☐ **fed** ☒ **both** ☐ **either fasting or fed**

	Fasted and fed for the intact tablet, fasted for the suspension of tablet, and fasted and fed for dispersible tablets. **Background:** The reference product (tablets – either intact or as a suspension or dispersible tablets) should be consistently taken with or without food according to the SmPC. Since the specific formulation (e.g. particle size and excipients) is known to be critical to the performance of the formulation in fed conditions, it cannot be assumed that the impact of food will be the same regardless of formulation. Differences have also been detected depending on the mode of administration, i.e. intact or suspended tablet.
	Strength: 10 mg for the tablets. 5 mg for the dispersible tablets. **Background:** Highest strength to be used for a drug with linear pharmacokinetics and low solubility.
	Number of studies*:** Five single dose studies. Tablets: Three single dose studies (10 mg intact tablet fasted and fed, and 10 mg suspended tablet fasted). Dispersible tablets: Two single dose studies (5 mg fasted and fed).
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☐ **plasma/serum** ☒ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72} and C_{max}
	90% confidence interval: 80.00–125.00 %

Section B. Everolimus tablets 0.25 mg, 0.5 mg, 0.75 mg and 1 mg, dispersible tablets 0.1 mg and 0.25 mg product-specific bioequivalence guidance (transplant-only indication)

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** everolimus may be considered a low solubility compound with limited absorption.
BE Study design *in case a BCS biowaiver is not feasible*	**single dose** **cross-over or parallel**
	healthy volunteers
	☐ **fasting** ☐ **fed** ☒ **both** ☐ **either fasting or fed** Fasted and fed for the intact tablet and fasted and fed for dispersible tablets. **Background:** The reference product (tablets or dispersible tablets) should be consistently taken with or without food according to the SmPC. Since the specific formulation (e.g. particle size and excipients) is known to be critical to the performance of the formulation in fed conditions, 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.
	Strength: 1 mg for the tablets 0.25 mg for the dispersible tablets. **Background:** highest strength to be used for a drug with linear pharmacokinetics and low solubility. Higher doses (i.e. multiple 1 mg and/or multiple 0.25 mg doses) could be used if considered necessary.
	Number of studies: four single dose studies. Tablets: Two single dose studies (1 mg tablet fasted and fed).

	Dispersible tablets: Two single dose studies (0.25 mg fasted and fed).
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☐ **plasma/serum** ☒ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment*	**Main pharmacokinetic variables:** AUC_{0-72h}, and C_{max}
	90% confidence interval: 90.00-111.11 % for AUC_{0-72} and 80.00-125.00 % for C_{max} **Background:** Everolimus is considered a narrow therapeutic index drug in the transplant setting.

* 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).

*** This is the minimum number of studies to be conducted provided that the applicant is aiming to apply for all the formulations in all the indications covered by the reference product.