1 1 April 2016
2 EMA/CHMP/154772/2016
3 Committee for Medicinal Products for Human Use (CHMP)

4 Everolimus tablets 0.25, 0.5, 0.75 and 1mg; 2.5, 5 and 5 10mg, dispersible tablets 0.1 and 0.25mg; 2, 3 and 5mg 6 product-specific bioequivalence guidance*

7 Draft

Agreed by Pharmacokinetics Working Party	February 2016
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Comments should be provided using this template. The completed comments form should be sent to PKWPsecretariat@ema.europa.eu.

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Keywords	***Bioequivalence, generics, everolimus***

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

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

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:** everolimus is 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, fasted for the suspension of tablet, and fasted and fed for dispersible tablets. **Background:** Formulation dependent food effects have been detected with reference products. Differences have been also detected depending on the mode of administration, i.e. intact or suspended tablet. Accordingly, 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.
	Strength: 10mg for the tablets 5mg 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 (10mg intact tablet fasted and fed, and 10 mg suspended tablet fasted) Dispersible tablets: two single dose studies (5mg fasted and fed) **Background:** single dose fed and fasted with the highest strength for tablets and dispersible tablets due to specific formulation characteristics (formulation related solubility) and relevant food effect, also dependent on mode of administration.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☐ **plasma/serum** ☒ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72}, C_{max}
	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 (CVintra > 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.

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

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:** everolimus is 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:** Formulation dependent food effects have been detected with reference products. Accordingly, the reference product (tablets or dispersible tablets) should be consistently taken with or without food according to the SmPC.

	Strength: 1mg for the tablets 0.25mg for the dispersible tablets **Background:** Highest strength to be used for a drug with linear pharmacokinetics and low solubility
	Number of studies: Four single dose studies Tablets: two single dose studies (10mg tablet fasted and fed) Dispersible tablets: two single dose studies (5mg fasted and fed) **Background:** single dose fed and fasted with the highest strength for tablets and dispersible tablets due to specific formulation characteristics (formulation related solubility) and relevant food effect.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☐ **plasma/serum** ☒ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72}, C_{max}
	90% confidence interval: 90.00 – 111.11 % for AUC_{0-72} and 80.00– 125.00 % for C_{max} **Background:** Everolimus is 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 (CVintra > 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).