15 December 2016
EMA/CHMP/620299/2016
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on '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' (EMA/CHMP/151597/2015)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Novartis Pharma AG
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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Novartis welcomes the opportunity to comment on the Draft everolimus product-specific bioequivalence guidance.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 12-14 and 31-32	1	Comments: On page 1, line 12-14, of the draft guidance, it is indicated: "Section A of this guideline is applicable for oncologic indications, and section B for transplant indications.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." Novartis would like to highlight that the everolimus tablets and dispersible tablets registered for the oncologic-only indications (Afinitor and Votubia 2.5 mg, 5 mg, 10 mg tablets and 2 mg, 3 mg and 5 mg dispersible tablets) and the transplant-only indications (Certican 0.25, 0.5, 0.75 and 1mg tablets and 0.1 mg and 0.25 mg dispersible tablets) do not have the same quantitative composition. In an in vivo bioequivalence study from the innovator company, Afinitor tablets (1 x 5-mg) and Certican tablets (5 x 1-mg) were not bioequivalent. Therefore, for an application covering all indications, the requirements from both sections A and B would need to be fulfilled by conducting all the section A required studies and all the section B required studies while taking into account the respective confidence	Partly accepted. The comment is well taken, although, it is not fully clear what the meaning is of "…do not have the same quantitative composition." From a regulatory perspective, dose-proportionality of products is primarily asked from the generic applicant in case bioequivalence studies are waived for additional strengths, since the quantitative composition of the innovator product is usually not publicly available. However, considering the current recommendation, generic applicants are asked to perform adequate bioequivalence studies for the product series, as compared to the respective reference products related to each indication.

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		intervals. To avoid any confusion on this point, Novartis is proposing a clarification to the draft wordings as shown below. Alternatively the wording in line 12-14 could also be deleted from the guidance. Proposed change: Line 12-14: "*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 *both* section A *and section B* recommendations ~~but~~ taking into account section B ~~in terms of the~~ 90% confidence interval for *the* transplant indications." Line 31-32: "*** 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 section A (oncologic-only)*~~covered by the reference product~~."	
Page 3 Section A BE study design section	1	Comments: As explained in the background section *"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*	Not accepted. The current proposal is following a scientific advice on this issue recommending the fasted study for the suspended tablet as being sufficient, if bioequivalence has been demonstrated with the intact tablet in the fasted and fed state.

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		dispersible tablets) should be consistently taken with or without food according to the SmPC.". Novartis would suggest that the study investigating 10 mg suspended tablet is also performed in fed conditions. Proposed changes: "Fasted and fed for the intact tablet, fasted *and fed* for the suspension of tablet, and fasted and fed for dispersible tablets. […] **Number of studies***:** Five single dose studies Tablets: three single dose studies (10mg intact tablet fasted and fed, and 10 mg suspended tablet fasted *and fed*)"	
Page 6 Section B BE study design section "Number of studies"	1	Comments: Please refer to the first comment above. The everolimus tablets and dispersible tablets registered for the oncologic-only indications (Afinitor and Votubia 2.5 mg, 5 mg, 10 mg tablets and 2 mg, 3 mg and 5 mg dispersible tablets) and the transplant-only indications (Certican 0.25, 0.5, 0.75 and 1 mg tablets and 0.1 mg and 0.25 mg dispersible tablets) do not have the same quantitative composition. In an in vivo bioequivalence study from the innovator company, Afinitor tablets (1 x 5-mg) and Certican tablets (5 x 1-	Partly accepted. The comments are well taken. A mistake in section B regarding the highest strength has been corrected. However, bioanalytical methods are constantly evolving and AUC is not necessarily needed to cover 72 h or even more to be robust enough for bioequivalence purposes since elimination processes are not primarily formulation dependent for IR products. Hence, the following note is proposed in order to raise awareness for this issue: applicants may use single doses > 1 mg (e.g. 2 tablets) considering possible

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		mg) were not bioequivalent. Given the above information, the highest strengths of the formulations for the transplant indications (Certican) should be used in the BE studies listed in Section B (1 mg tablets and 0.25 mg dispersible tablets). The single-dose escalation study of Certican tablets in healthy subjects from the innovator company used doses of 0.5, 1, 2, and 4 mg. Everolimus was detectable postdose in blood at ≥72 hours only at 2 and 4 mg. In order to derive a robust AUC_{0-72h} for statistical testing, Novartis would recommend to consider a Certican dose of 3 mg (using 1 mg tablets and 0.25 mg dispersible tablets) for BE studies. Proposed changes: **"Number of studies:** Four single dose studies Tablets: two single dose studies (*3~~10~~mg dose of 1 mg* tablets *(3x 1-mg)* fasted and fed) Dispersible tablets: two single dose studies (*3~~5~~mg dose of 0.25 mg dispersible tablets (12 x 0.25-mg)* fasted and fed)"	bioanalytical limitations in order to achieve robust pharmacokinetic characteristics.
	2	1) If innovator is not claiming Transplant indication for 2.5mg/5mg/10mg strength, how generic can get approval for transplant indication even if BE meets NTI criteria? 2) In our opinion ***suspended***	1) In general, generic applicants are bound to SmPCs of the innovator. Hence, meeting tighter bioequivalence criteria as for NTIs would not justify any change regarding indications if not covered by the innovator SmPC. 2) The specific recommendation refers to study results

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		<u>tablets</u> bioequivalence study is not required, not being asked in EU earlier in any products. How we can comment to agency on same. 3) Dispersible tablets 0.1 and 0.25mg; 2, 3 and 5mg are for transplant indication and RLD for that is 5mg and CI needs to be 90-111. Hence for 10mg we don't need to meet NTI criteria but must for 5mg dispersible product as indication will be of transplant.	available at the agency and respective scientific advice outcome. It is related to specific drug substance characteristics known for everolimus rather than the type of formulation (suspension) as such. 3) The comment is well taken and corrections are made according to respective product strengths.