19 September 2019
EMA/CHMP/401588/2019
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Ezetimibe tablet 10 mg product-specific bioequivalence guidance' (EMA/CHMP/802491/2018)

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

Stakeholder no.	Name of organisation or individual
1	STADA Arzneimittel AG
2	SciencePharma Poland

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

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Table "Analyte"	1	Comment: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, section 4.1.5 provides only two different scenarios regarding the choice of analyte. The clearly preferred option is to analyse the parent drug ("*In principle, evaluation of bioequivalence should be based upon measured concentrations of the parent compound. The reason for this is that Cmax of a parent compound is usually more sensitive to detect differences between formulations in absorption rate than Cmax of a metabolite.*"). This is even applicable to inactive prodrugs for which the parent drug should be analysed unless the plasma profile cannot be reliably characterized due to short half-life and/or too low plasma concentrations. The second option (which is acceptable only in exceptional cases as per guideline) is to analyze the metabolite ("*The use of a metabolite as a surrogate for an active parent compound is not encouraged….* "). Therefore, according to the guideline, bioequivalence should be shown either for the parent drug (only) or for the metabolite (only). The currently proposed change of the Ezetimibe guidance is therefore not in line with the current guideline as here the bioequivalence assessment should be made on the	Not accepted. The guideline is correctly cited in that it states 'in principle' the parent compound should be measured and 'usually' C_{max} of the metabolite is less sensitive to detect possible formulation differences. However, ezetimibe displays the exceptional scenario that Cmax of the metabolite is obviously more sensitive for bioequivalence purposes in contrast to the parent maximum which occurs hours later and predominantly reflects enterohepatic circulation. C_{max} of total ezetimibe (unconjugated + conjugated ezetimibe) mainly reflects the metabolite, and is a better measurement to compare biopharmaceutic product performance than parent compound. In addition, the glucuronide is as active as the parent drug, with 16-fold greater peak exposure (C_{max}) than that of the parent drug and 10-fold higher AUC. In conclusion, the PSBGL does not contradict the current guideline which cannot address all possible scenarios. Instead the terms like 'in principle' and 'usual' are employed in order to leave room for scientific justification in specific cases.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		basis of the sum of parent and metabolite. It is correct that Ezetimibe undergoes extensive entero-hepatic recycling and it is acknowledged that this pharmacokinetic characteristic raises the question how the biopharmaceutical drug product performance can be evaluated in the best way. However, it is not obvious why the proposed change, i.e. determining bioequivalence based on the sum of parent and metabolite should resolve this issue significantly better than the applicable guideline stipulation which is to measure the parent drug only. Therefore, the proposed deviation from the applicable guideline does not appear to be justified. <u>Proposed change (if any):</u> Only analysis of the parent drug should be required	
Bioequivalence Assessment	1	Bioequivalence assessment should be made only based on the parent drug (reasoning see above).	Not accepted. See explanation above
Table, "BCS Classification**"	2	Comment: There seems to be an explanation missing to the text marked with "**". It is suggested to add the explanation or to correct the text in the table, as it is misleading. Proposed change (if any): -	Accepted.
Table,	2	Comment:	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
"Bioequivalence assessment", "Main pharmacokinetic variable"		In the guidance, AUC_{0-72h} and C_{max} are indicated as the main PK variables to assess the bioequivalence of ezetimibe. We would like to note that the main site of ezetimibe action is the intestine, where it inhibits the absorption of cholesterol. Moreover, the PK of ezetimibe indicates that it undergoes extensive first-pass metabolism in the liver and is submitted to enterohepatic circulation, which results in multiple peaks of high blood concentration. Having in mind the site and mechanism of action of the active substance, as well as its PK characteristics, in our opinion the C_{max} parameter is not really indicative of the bioequivalence. It is suggested that only the AUC_{0-72h} should be put in the guidance as the main variable, as this parameter is of most relevance from the point of view of ezetimibe activity. Proposed change (if any): Main pharmacokinetic variables: AUC_{0-72h}, ~~C_{max}~~	It is agreed that C_{max} of the parent (after approximately 4 h post-dose) cannot be considered a sensitive measure to detect formulation related differences between products if they are there, although conceptually 'clinical relevance' of specific pharmacokinetic characteristics is generally not considered as being most important for bioequivalence decision making. However, C_{max} of the glucuronide has been found sensitive for that purpose. See also response above.