15 December 2016
EMA/CHMP/805860/2016
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Fingolimod capsules 0.5 mg product-specific bioequivalence guidance' (EMA/CHMP/154812/2016)

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

Stakeholder no.	Name of organisation or individual
1	Novartis Europharm Ltd.

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	As mentioned in the Gilenya SmPC, initiation of Gilenya treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays, including the occurrence of isolated reports of transient, spontaneously resolving complete AV block. Consequently, the SmPC recommends "first-dose monitoring" of heart rate and blood pressure in all multiple sclerosis patients when initiating treatment and when treatment has been interrupted for specified periods of time. Against this background, it would also be appropriate to perform first-dose monitoring in BE studies. For a crossover study design, the period between single doses may be several weeks to allow drug to washout between doses. Therefore, first-dose monitoring is relevant for both the first and second dose in a two-way crossover study. Proposed change: In an appropriate section, e.g. "Other critical design aspects" in the "Requirements for Bioequivalence Demonstration", include the following text in line with the SmPC of Gilenya: "*All subjects should have an ECG and blood pressure measurement performed prior to and 6 hours after the fingolimod dose. All subjects should be monitored for a period of 6 hours for signs and symptoms of bradycardia with hourly heart rate and blood pressure measurement. Continuous (real time) ECG monitoring during this 6 hour period is recommended.*"	It is agreed that first administration of Fingolimod to patients or healthy volunteers should be made under strict cardio-vascular safety monitoring as stated in the SmPC of Gilenya. However, this is not within the scope of the investigation of product-specific bioequivalence, which focuses only on PK considerations. Conclusively, even if the concern on healthy volunteers is relevant and has to be handled by the investigator, this will not be inserted in the present bioequivalence guidance.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 15, "Requirements for Bioequivalence Demonstration" table, BE study design		Comment: Fingolimod itself is pharmacologically inactive; whereas, the metabolite fingolimod-phosphate exerts the pharmacological effect. Given the importance of fingolimod-phosphate for efficacy, it would be of interest to provide pharmacokinetic parameters for this metabolite as supportive information. Proposed change: In the "Requirements for Bioequivalence Demonstration" table recommend to measure the metabolite fingolimod-phosphate in blood and to provide both individual C_{max} and AUC_{0-72} values along with the test/reference geometric mean ratios as supportive information.	Considering that: i. Demonstration of bioequivalence for the parent drug instead of the metabolite (even active) is always preferable in the context of bioequivalence evaluation (please refer to the current guidance on BE), ii. Blood concentrations versus time profile could be accurately established for Fingolimod, Evaluation of pharmacokinetics and statistics for the metabolite fingolimod-phosphate is not considered useful and would lead to undesirable multiple comparisons.
Line 15, "Requirements for Bioequivalence Demonstration" table, BE study design		The Gilenya SmPC mentions that food does not alter Cmax or AUC of fingolimod, but that the Cmax of fingolimod-phosphate was increased and AUC was unchanged. Consequently, the posology section states "Gilenya can be taken with or without food." Given that the innovator formulation had a food effect (albeit not clinically relevant) and that patients may take fingolimod differently from day to day (with meals or apart from meals), it is important to assess whether a generic formulation delivers fingolimod consistently	Additional demonstration of BE under fed conditions is not deemed to be necessary presently, because food intake does not lead to a significant change of the extent and/or the rate of fingolimod absorption and there is no evidence that food effect is formulation dependent. In order to claim that a bioequivalence study in fed state is necessary in addition to the bioequivalence study in fasted state, it would be necessary to demonstrate that different formulations of fingolimod have shown a different food effect."

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		under both conditions. Proposed change: recommend BE studies conducted under fed and fasting conditions.	