31 May 2018
EMA/CHMP/258276/2017
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Dabigatran etexilate, hard capsules, 75 mg, 110 mg and 150 mg product-specific bioequivalence guidance' (EMA/CHMP/805498/2016)

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

Stakeholder no.	Name of organisation or individual
1	Boehringer Ingelheim

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Boehringer Ingelheim (BI) welcomes the opportunity to comment on the Draft product-specific bioequivalence guidance for dabigatran etexilate, hard capsules, 75 mg, 110 mg and 150 mg. Based on Boehringer Ingelheim´s experience testing alternative formulations of dabigatran etexilate as pro-drug during drug development of PRADAXA® (originator brand of dabigatran etexilate), BI suggests the requirement to conduct an additional BE study under conditions of elevated gastric pH, i.e. with concomitant use of a proton pump inhibitor (PPI) such as pantoprazole. This study should be conducted besides the regular BE study under fasting conditions to ensure bioequivalence of any generic formulation of dabigatran etexilate with PRADAXA® for the following reason: The bioavailability of dabigatran etexilate is sensitive to variable acidity in the GI tract. In case dabigatran etexilate is not provided in an appropriate formulation less sensitive to changes in gastric pH conditions, the bioavailability may be considerably reduced at conditions of elevated gastric pH. The marketed formulation of dabigatran etexilate (PRADAXA®) was developed to address elevations in gastric pH which are frequent in the target population. Accordingly, when PRADAXA® was co administered with pantoprazole, an only modest decrease in the dabigatran area under the plasma concentration time curve of approximately 30 % was observed. In the pivotal clinical trials for PRADAXA®, pantoprazole and other proton pump inhibitors (PPI) were co administered with PRADAXA® and concomitant PPI treatment did not appear to impact	

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	PK or the benefit risk ratio of PRADAXA® (see also SmPC for PRADAXA® hard capsules, section 4.5). A proposed generic version of PRADAXA® that does not adequately replicate the PRADAXA® formulation and release profile may appear bioequivalent under low gastric pH conditions usually seen in healthy volunteer bioequivalence studies, but may in fact not be bioequivalent under higher gastric pH conditions. Therefore, bioavailability of the new formulation and the reference PRADAXA® should be compared in a bioequivalence study at elevated gastric pH after pre-treatment with a proton pump inhibitor.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Table, right column, fourth line from the top (Bioequivalence study design)		The following text/requirement should be added, as explained above in the **General Comments** *An additional BE study under conditions of elevated gastric pH, i.e. after multiple day pre-treatment with a proton pump inhibitor (PPI) such as pantoprazole, should be conducted in addition to the regular BE study under fasting conditions*.	Accepted.
Table, right column, sixth line from the top (Analyte)		The following background information is stated in the current version of the Guideline: **"Background:** Dabigatran etexilate is a prodrug. After oral administration, it is rapidly and completely converted to dabigatran, which is the active form in plasma" Comment: Dabigatran etexilate is converted to dabigatran only after absorption, but not directly after oral administration. This should be more precisely expressed by an adapted wording as follows: **"Background:** Dabigatran etexilate is a prodrug. After oral administration and absorption, it is rapidly and completely converted to dabigatran, which is the active form in plasma"	Accepted.