15 December 2016
EMA/CHMP/693923/2016
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on Pazopanib film-coated tablet 200 mg and 400 mg product-specific bioequivalence guidance (EMA/CHMP/154805/2016)

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

Stakeholder no.	Name of organisation or individual
1	Pharma Desk Solutions Private Limited
2	Novartis Pharma AG

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	We would like to bring to your notice, one of our observed concerns with respect to difference of opinion between "USFDA" and "EMA" related to Product Specific Bioequivalence Recommendations on 'Pazopanib". "USFDA" has released the "OGD" on Pazopanib, dated: Sep 2012, asking the pharmaceutical companies to conduct "Steady State Study" in Advanced Renal Cell Carcinoma Patients (with a dose of 4 X 200 mg) whereas "EMA" asking to conduct single dose bioequivalence studies using strengths 200 mg & 400 mg on healthy subjects. While reviewing the literature over the public domain pertaining to pazopanib, the safety studies on healthy subjects (dose administered 100 mg) reveal that rise in liver enzymes by three fold increase from the base line level have been led to termination of the study. Even increase in systolic blood pressure was observed. Hence, keeping in view of safety profile of the drug, we are in the opinion of conducting the study in Advanced Renal Cell Carcinoma Patients instead of on healthy subjects. Enclosure: OGD of Pazopanib by USFDA.	Not accepted. There is not considered to be any safety issue in relation to conducting bioequivalence studies with pazopanib in healthy subjects, when the product will be administered as a single dose.
2	Novartis welcomes the opportunity to comment on the Draft Votrient product-specific bioequivalence guidance. The changes proposed by Novartis to the EMA text are as follow:	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	The proposed additional text is in red The proposed deleted text is in ~~red strikethrough~~	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
BCS Classification**	2	Comments: In the Background section Novartis proposes to add the approved treatment dose. (The proposed additional text is in red and the proposed deleted text is in ~~red strikethrough~~) Proposed change: Pazopanib is a BCS class II compound. Pazopanib is slightly soluble in 0.1 M HCl (0.65 mg/mL) and practically insoluble in pH 7.0 and pH 11.0. Pazopanib may be considered a low solubility compound with a solubility-limited absorption. The approved dose is 800mg.	Not accepted. Detailed information on solubility are not intended to be included in this section. It is considered sufficient to include information that a BCS-biowaiver is not possible.
Page 2 BE study design section	2	Comments: Novartis would like to suggest also a parallel design in addition to the cross-over design already proposed by EMA. The reason is that cross over design requires adequate washout period to ensure lack of carry-over from the first dose. This may not be practical for drugs with long pharmacokinetic half-lives. The geometric mean of pazopanib half-life ranged from 18.1 to 52.3 hours. The mean t1/2 for pazopanib is 30.9 hours so adequate washout between doses may be long (more than 1 week) and therefore, a parallel design may be	A cross-over design is preferable when feasible. A washout period of a few weeks is not considered too long for a bioequivalence study with a cross-over design. A parallel design increases the variability and requires more subjects to be included in the study and moreover comparability of the treatment groups.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		justified. (The proposed additional text is in red and the proposed deleted text is in ~~red strikethrough~~) Proposed changes: **single dose or parallel** **cross-over**	
Page 2 BE study design section	2	Comments: Novartis would like to point out that available tablet strengths for Votrient are 200 and 400 mg tablets, the approved dose is 800 mg. Given the solubility-limited absorption of pazopanib and the non-linear bioavailability at higher doses as indicated by 40% higher bioavailability for 400 mg compared to 800 mg, therefore, demonstration of bioequivalence should consider the highest & the lowest doses. Therefore, Novartis would like to recommend two studies to demonstrate bioequivalence: one study at 800 mg (approved dose) and another at the lowest available dose of 200 mg. The two studies may be either randomized, single dose/parallel studies or randomised, two-period, two-sequence single dose cross-over studies. Novartis' recommendation is also supported by the EMA guidance on investigation of BE section 4.1.6. (The proposed additional text is in red and the proposed deleted text is in ~~red strikethrough~~)	Not accepted. The highest strength (not the highest clinical dose) is recommended to be used in a bioequivalence study where the purpose is to compare a test and reference formulation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed changes: **Strength:** 200 and 400 mg **Background:** Less than dose proportional increase in PK exposure due to ~~limited~~ solubility-limited absorption **Number of studies:** two randomized single dose/parallel studies or two randomised, two-period, two-sequence single dose cross-over studies **Background:** One study for ~~each of the strengths~~ the approved dose of 800mg and one with the lowest dose strength of 200mg.	