26 July 2018
EMA/CHMP/395071/2018
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Cholic acid capsules 50 mg and 250 mg product-specific bioequivalence guidance' (EMA/CHMP/800759/2017)

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

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

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	It is important to realise for the evaluation of cholic acid as a pharmacological agent that its pharmacokinetic characteristics, including its metabolism, are fundamentally different from that of a conventional synthetic small molecule pharmaceutical in that once administered, any exogenously administered cholic acid will behave like an endogenous molecule in all respects. Apart with isotope labelling, there will be no possibility to distinguish between endogenous cholic acid and exogenous cholic acid. In addition, cholic acid undergoing enterohepatic recirculation, and negative feedback, when administering exogenous cholic acid to healthy volunteers, the natural endogenous pool of cholic acid in those volunteers would decrease, making impossible to obtain any reliable results.	It is acknowledged that cholic acid PK characteristics are different from small molecules as it behaves like an endogenous molecule in all aspects. The role of enterohepatic re-circulation is also recognised. However, it is possible to measure cholic acid in plasma. In addition, baseline subtraction is recommended to account for the variability in the endogenous pool of cholic acid. Therefore, no change in the draft guidance is recommended.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 17 Bioequivalence study design	1	Comment: Distinction of exogenously applied cholic acid from endogenous cholic acid is only possible by isotope labelling; such labelling techniques are well-established. However, they are of limited utility in determining the bioavailability of a solid oral formulation such as Orphacol, as within in the formulation, the labelled compound may behave differently from the unlabelled compound, e.g. due to a different particle size. Indeed, significant differences in apparent kinetic parameters (pool size, fractional turnover rate) have been observed and are documented in the literature.	This is agreed, the use of labelled compound is not recommended.
Line 17 Healthy volunteers	1	Comment: Healthy volunteers are expected to show pharmacokinetic and pharmacodynamic responses to cholic acid that are fundamentally different from that of patients, as patients synthesise no or very little endogenous primary bile acids, including cholic acid. Also, classical single-dose studies in patients are not possible as patients need to remain on ongoing treatment to avoid liver damage.	Cholic acid is expected to behave exactly like an endogenous compound in both healthy and patient populations. Therefore, adult healthy volunteers are appropriate for assessing bioequivalence.
Line 17 Plasma/Serum	1	Comment: As a bile acid, cholic acid is subject to highly efficient first-pass hepatic extraction and enterohepatic	It is agreed that invasive techniques are not required as it is possible to measure cholic acid in plasma. As for patient data, cholic acid is expected to behave exactly like an endogenous

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		recirculation. An accurate determination of the absorption kinetics would thus require blood sampling from the portal vein, which is only ethically possible in the context of a surgical intervention. Sampling of peripheral plasma is a suitable method only for relative bioavailability and bioequivalence studies of bile acids with a low endogenous concentration, but not cholic acid. A secondary measure is enrichment of the applied bile acid in the duodenal bile, which requires duodenal intubation or the less invasive, but also less reliable, use of the Enterotest® string sampling method. Therefore, a pharmacokinetic study in adult healthy volunteers would in principle be possible but would either be highly invasive for this kind of study, or be fraught with substantial imprecision of the data. For the determination of patient data, it needs to be taken into account that the patient population includes a large number of infants, children and adolescents. From an ethical point of view, the combined use of isotope labelling, blood sampling and/or bile sampling (possibly through duodenal intubation) in these paediatric populations is hardly acceptable. On the other hand, extrapolation of adult patient data to children is problematic due to the ongoing hepatic maturation during infancy and childhood.	compound in both healthy and patient populations. Therefore, adult healthy volunteers are appropriate for assessing bioequivalence.

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Line 17 Cross-over	1	Comment: As cholic acid is an endogenous molecule, distinction between two different cholic acid medicinal products would be impossible to see, excepted with isotope labelling.	It is agreed that distinction between exogenous and endogenous cholic acid is not possible. However, baseline subtraction is recommended to account for the variability in the endogenous pool of cholic acid.
Line 17 Single-dose	1	Comment: The bile acid pool is largely confined within the enterohepatic circulation and there is poor systemic distribution, resulting in low total serum bile acid concentrations of about 1-12 µmol/L. The total bile acid concentration in human peripheral serum fluctuates in relation to meal intake between 2-5 µM during night-time (fasting) lows to 10-16 µM during daytime highs. In the hepatic venous portal plasma (i.e. within the enterohepatic circulation), fasting cholic acid concentration averaged 6.13 ± 2.57 µmol/L while maximum postprandial concentrations averaged 18.42 ± 4.17 µmol/L. Cholic acid is present in serum and plasma of normal humans, including children and pregnant females, in a range between 0.05-6.7 µmol/L. Values for normal children are broadly in the same range as for healthy adults. As noted by above, serum bile acid concentrations vary considerably over the day and in relation to meal intake, so this broad normal range may be expected. It is likely to assume, although it has not been formally shown, that cholic acid serum levels fluctuate in line with the levels of	This is disagreed. Single dose study design is possible because it avoids the feedback mechanisms (feedback mechanisms will need time to build up) which could enhance intra- and inter-subject variability. Additionally, baseline subtraction is recommended to account for the variability in the endogenous pool of cholic acid.

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		total bile acids. Therefore, due to intra- and inter-subject variability, a single-dose study would not give reliable results.	