PART VI: Summary of the risk management plan

Summary of risk management plan for Orphacol (cholic acid)

This is a summary of the risk management plan (RMP) for Orphacol. The RMP details important risks of Orphacol, how these risks can be minimised, and how more information will be obtained about Orphacol's risks and uncertainties (missing information).

Orphacol's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Orphacol should be used.

This summary of the RMP for Orphacol should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Orphacol's RMP.

I. The medicine and what it is used for

Orphacol is authorised for the treatment of inborn errors in primary bile acid synthesis due to 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency or Δ^4-3-Oxosteroid-5β-reductase deficiency (see SmPC for the full indication). It contains cholic acid as the active substance and it is given orally.

Further information about the evaluation of Orphacol's benefits can be found in Orphacol's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Orphacol, together with measures to minimise such risks and the proposed studies for learning more about Orphacol's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Orphacol, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Orphacol is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Orphacol are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Orphacol. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Prescription of a supratherapeutic dose
Important potential risks	Gallstones Carcinogenicity
Missing information	Long-term data in large patient population Medication error in infants and children

II.B Summary of important risks

Identified risk: Prescription of a supratherapeutic dose	
Evidence for linking the risk to the medicine	This identified risk is based on reported cases of cholic acid use in supratherapeutic doses in clinical practice [1-3].
Risk factors and risk groups	Besides the lower weight paediatric patients, there are currently no other established risk factors or risk groups
Risk minimisation measures	<u>Routine risk minimisation measures</u> SmPC sections 4.2 PL section 3 Monitoring of liver parameters, serum and/or urine bile acid levels in SmPC section 4.2 Restricted medical prescription <u>Additional risk minimisation measures</u> Educational material through Orphacol Educational Web Site
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Orphacol Patient Surveillance Database See section II.C of this summary for an overview of the post-authorisation development plan.

Potential risk: Gallstones	
Evidence for linking the risk to the medicine	This potential risk is based on non-clinical data and reported cases of gallstone development associated with cholic acid use in clinical practice [3-7].
Risk factors and risk groups	There are no currently established risk factors and risk groups, although patients with 3β-HSD deficiency have higher prevalence of gallstones which may be related

Potential risk: Gallstones	
	to the disease, e.g. through lack of bile flux, super-saturation of bile, or a lithogenic effect of the abnormal 3β,7α-dihydroxy- and 3β,7α,12α-trihydroxy-5-cholenoic acids.
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.8 PL section 4 Additional risk minimisation measures Educational material through Orphacol Educational Web Site
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Orphacol Patient Surveillance Database See section II.C of this summary for an overview of the post-authorisation development plan.

Potential risk: Carcinogenicity	
Evidence for linking the risk to the medicine	This potential risk is based on the short- or medium-term non-clinical carcinogenicity studies available in the literature. In animal studies, bile acids such as cholic acid have shown to increase the risk of certain cancers. In humans, a high concentration of intestinal bile acid correlates with an increased risk for colon cancer. However, a causal link has not been confirmed.
Risk factors and risk groups	Not yet established.
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Orphacol Patient Surveillance Database See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term data in large patient population	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 5.1
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Orphacol Patient Surveillance Database See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Medication error in infants and children	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.2, 6.6 Additional risk minimisation measures Explore the development of formulation appropriate for use in infants and children.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Orphacol Patient Surveillance Database

Purpose of the study:

Orphacol Patient Surveillance Database has been developed by the MAH to monitor the safety and efficacy in patients treated with Orphacol.

The main objective of the database is to increase the amount of available data on the treatment of inborn errors in primary bile acid synthesis due to 3β-HSD and Δ4-3-oxoR deficiency with Orphacol in infants, children, adolescents and adults, and especially of data on efficacy and safety of treatment with cholic acid.

This database serves as a tool for all healthcare professionals treating patients with Orphacol to record and access clinical information regarding patients, including demographic and familial data, diagnostic information, data on treatment and adverse events/reactions. Such data are in principle available from the regular (at least annual) clinical and laboratory investigations in patients, and the database will serve to capture this information. These data will be used to further increase the available safety and efficacy information and refine the therapeutic recommendations as required.

In addition, through the publication of educational material, which is available on the same website that serves as portal to the patients' database, it is planned that the patient database will provide information on:

- The actual level of risk of gallstones
- The effectiveness of the proposed Summary of Product Characteristics (SmPC) intended to minimise or eliminate the risk of prescription of a supratherapeutic dose.

All educational material on website is prepared in accordance with the approved product information, national competent authority requirements, and monitored by MAH's Scientific Service. Approved educational material is available in a PDF format for the countries where they are approved by local authorities.

List of addressed safety concerns:

Prescription of a supratherapeutic dose

Gallstones

Carcinogenicity

Long-term data in large patient population

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Orphacol.

Reference list

1. Jacquemin E, Gerhardt MF, et al. Long-term effects of bile acid therapy in children with defects of primary bile acid synthesis: 3 beta-hydroxy-C27-steroid-dehydrogenase/isomerase and delta-4-3-oxosteroid 5 beta-reductase deficiencies. G. P. van Berge Henegouwen DK, U. Leuschner, G. Paumgartner and A. Stiehl., Dordrecht, Boston, London, Kluwer Academic Publishers; 2000. 278-82.

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4. Tepperman J, Caldwell FT, Tepperman HM. Induction of gallstones in mice by feeding a cholesterol-cholic acid containing diet. The American Journal of Physiology 1964; 206:628-34.

5. Besancon F, Marche C, Parrot J. [Experimental lithiasis due to excess cholic acid in mice]. Biologie et Gastro-enterologie. 1970; 2:147-60.

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