▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions to the Netherlands Pharmacovigilance Centre Lareb. You can use the report form available on internet (www.lareb.nl).

Educational materials for physicians

This material describes the recommendations about the important risks of cholic acid, especially prescription of a supratherapeutic dose and gallstones.

The materials have been reviewed and approved by the Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen, CGB).

Cholic acid is indicated 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 in infants, children and adolescents aged 1 month to 18 years and adults.

Summary

This material describes the recommendations about the risks of cholic acid, especially prescription of a supratherapeutic dose and gallstones.

Prescription of a supratherapeutic dose is considered an important identified risk. Clinical features of cholic acid overdose include pruritus, diarrhoea, and elevation of serum gamma-glutamyl transferase and alanine aminotransferase activities and of total serum bile acid concentration. They usually resolve after reduction of the therapeutic dose. **Frequent monitoring of liver parameters, serum and/or urine bile acid levels is expected to be sufficient in order to prevent the clinical presentation associated with this risk.**

Gallstones are considered an important potential risk associated with the cholic acid treatment. Regular monitoring should be part of the follow-up of the patients. **Any occurrence of gallstones should be reported as an adverse reaction** to national competent authority or to Theravia.

Dose considerations to avoid supratherapeutic dose

Prescription of a supratherapeutic dose is considered an important identified risk based on reported cases of cholic acid use in supratherapeutic doses in clinical practice [1-3]. It has been consistently observed that for effective therapy, younger and lighter patients need higher doses per kilogram body weight than older/heavier patients. This may be linked to allometric differences, differences hepatic maturation and/or activation of alternative synthetic pathways for primary bile acids during growth and maturation of the paediatric patients with 3β-hydroxy-Δ5-C27-steroid oxidoreductase (3β-HSD) deficiency or Δ4 3 oxosteroid-5β-reductase (Δ4-3-oxoR) deficiency. As a hypothetic mechanism for the observed effect, due to variable growth and maturation speeds in a child, the effective dose may temporarily drop faster than downward dosage adjustments are made by the treating physician. Clinical features of cholic acid overdose include pruritus, diarrhoea, and elevation

of serum gamma-glutamyl transferase and alanine aminotransferase activities and of total serum bile acid concentration [3]. Clinical signs and abnormal laboratory parameters resolve after reduction of the therapeutic dose [3]. Upon correction of dosage, no long-term sequalae is expected. **Frequent monitoring of liver parameters, serum and/or urine bile acid levels is expected to be sufficient in order to prevent the clinical presentation associated with this risk.**

Treatment must be initiated and monitored by an experienced gastroenterologist/hepatologist or a paediatric gastroenterologist/hepatologist in the case of paediatric patients. Patients should be monitored as follows: 3-monthly during the first year, 6-monthly during the subsequent three years and annually thereafter to avoid administration of a supratherapeutic dose.

The dose must be adjusted for each patient in a specialised unit according to blood and/or urine chromatographic bile acid profiles.

The daily dose to treat 3β-hydroxy-Δ^5-C_{27}-steroid oxidoreductase and Δ^4-3-oxosteroid-5β-reductase deficiencies ranges from 5 to 15 mg/kg in infants, children, adolescents and adults. In all age groups, the minimum dose is 50 mg and the dose is adjusted in 50 mg steps. In adults, the daily dose should not exceed 500 mg.

The daily dose may be divided if it consists of more than one capsule in order to mimic the continuous production of cholic acid in the body and to reduce the number of capsules that need to be taken per administration.

The Table 1 provides an indication on the estimated number of cholic acid capsules to be administered daily for infants and young children based on their weight and the necessary dose in mg/kg.

Table 1. Estimated daily number of cholic acid capsules based on the weight and dosage in mg/kg

	CA dosage in mg/kg										
Weight (kg)	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
3	0	0	0	0	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg
4	0	0	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg
5	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	2 x 50mg
6	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg
7	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg
8	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg
9	1 x 50mg	1 x 50mg	1 x 50mg	1 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	3 x 50mg	3 x 50mg
10	1 x 50mg	1 x 50mg	1 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	3 x 50mg	3 x 50mg	3 x 50mg
11	1 x 50mg	1 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	3 x 50mg	3 x 50mg	3 x 50mg	3 x 50mg
12	1 x 50mg	1 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	3 x 50mg	3 x 50mg	3 x 50mg	3 x 50mg	4 x 50mg
13	1 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	3 x 50mg	3 x 50mg	3 x 50mg	3 x 50mg	4 x 50mg	4 x 50mg
14	1 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	3 x 50mg	3 x 50mg	3 x 50mg	3 x 50mg	4 x 50mg	4 x 50mg	4 x 50mg
15	2 x 50mg	2 x 50mg	2 x 50mg	2 x 50mg	3 x 50mg	3 x 50mg	3 x 50mg	4 x 50mg	4 x 50mg	4 x 50mg	1 x 250mg
16	2 x 50mg	2 x 50mg	2 x 50mg	3 x 50mg	3 x 50mg	3 x 50mg	4 x 50mg	4 x 50mg	4 x 50mg	4 x 50mg	1 x 250mg
17	2 x 50mg	2 x 50mg	2 x 50mg	3 x 50mg	3 x 50mg	3 x 50mg	4 x 50mg	4 x 50mg	4 x 50mg	1 x 250mg	1 x 250mg
18	2 x 50mg	2 x 50mg	3 x 50mg	3 x 50mg	3 x 50mg	4 x 50mg	4 x 50mg	4 x 50mg	1 x 250mg	1 x 250mg	1 x 250mg
19	2 x 50mg	2 x 50mg	3 x 50mg	3 x 50mg	3 x 50mg	4 x 50mg	4 x 50mg	1 x 250mg	1 x 250mg	1 x 250mg	1 x 50 mg + 1 x 250mg
20	2 x 50mg	2 x 50mg	3 x 50mg	3 x 50mg	4 x 50 mg	4 x 50 mg	4 x 50 mg	1 x 250mg	1 x 250mg	1 x 50 mg + 1 x 250mg	1 x 50 mg + 1 x 250mg

During the initiation of cholic acid therapy and dose adjustment, serum and/or urine bile acid levels should be monitored intensively (at least every three months during the first year of treatment, every six months during the second year) using gas chromatography-mass spectrometry (GC-MS) or equivalent technology coupled to mass spectrometry. Patients that have previously been treated with other bile acids or other cholic acid preparations should be closely monitored in the same manner during the initiation of treatment with cholic acid. Please refer to the list of qualified laboratories in the document below. You may also contact Theravia directly if you need assistance with bile acid analysis.

The concentrations of the abnormal bile acid metabolites synthesised in 3β-hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency (3β, 7α-dihydroxy- and 3β, 7α, 12α-trihydroxy-5-cholenoic acids) or in Δ^4-3-oxosteroid-5β-reductase deficiency (3-oxo-7α-hydroxy- and 3-oxo-7α, 12α-dihydroxy-4-cholenoic acids) should be determined. At each investigation, the need for dose adjustment should be considered. The lowest dose of cholic acid that effectively reduces the bile acid metabolites to as close to zero as possible should be chosen.

Liver parameters should also be monitored, preferentially more frequently than serum and/or urine bile acid levels. Concurrent elevation of serum gamma glutamyltransferase (GGT), alanine aminotransferase (ALT) and/or serum bile acids above normal levels may indicate overdose. Transient elevations of transaminases at the initiation of cholic acid treatment have been observed and do not indicate the need for a dose reduction if GGT is not elevated and if serum bile acid levels are falling or in the normal range. Particular attention must be paid to the observation that infants need higher cholic acid doses on a per kilogram basis than adolescents and adults to achieve metabolic control. Maintaining the initial per kilogram dosage may hence lead to overdose; the lowest effective dose should be actively titrated.

After the initiation period, serum and/or urine bile acids (using mass spectrometry technology) and liver parameters should be determined annually, at a minimum, and the dose adjusted accordingly. Additional or more frequent investigations should be undertaken to monitor therapy during periods of fast growth, concomitant disease and pregnancy.

Treatment with cholic acid should be stopped if abnormal hepatocellular function, as measured by prothrombin time, does not improve within 3 months of the initiation of cholic acid treatment. A concomitant decrease of urine total bile acids should be observed. Treatment should be stopped earlier if there are clear indicators of terminal hepatic disease.

In case of persistent lack of therapeutic response to cholic acid monotherapy, other treatment option should be considered.

Gallstones

Gallstones are considered an important potential risk associated with the cholic acid treatment, and is based on non-clinical data and reported cases of gallstones development associated with cholic acid use in clinical practice [3-6, 8]. Cholic acid in combination with a high-cholesterol diet has been shown to induce gallstone formation in rodents [4-6]. Additionally, the production of unphysiological bile acids and its intermediaries due to the defect in cholic acid synthesis could also play a role in lithogenesis. This assumption is supported with the data showing that patients with 3β-HSD deficiency may present with gallstones at diagnosis of cholic acid deficiency[3]. The untreated patients with 3β-

HSD deficiency or Δ^4-3-oxoR deficiency have severe cholestasis and bile stasis is a known risk factor for the development of gallstones [7]. In addition, a reduction in primary bile acids (as present in untreated patients) favours cholesterol super-saturation and gallstone nucleation. Therefore, untreated patients are inherently at risk for the development of gallstones.

Gallstones have been reported after long-term therapy. Therefore, regular monitoring of the patients is recommended. **Any occurrence of gallstones should be reported as an adverse reaction** to national competent authority or to Theravia.

Importance of registering your patients in the Orphabase (Orphacol patient surveillance database)

As part of the Marketing Authorisation, Theravia has the obligation to monitor the safety and efficacy of Orphacol®(cholic acid) patients treated for the two approved indications via a Post Authorisation Safety Study (PASS). For this purpose, a database called Orphabase has been created, in which we are collecting data which allow to monitor the follow-up of the treated patients and to gather additional safety and efficacy information on the product. Information collected via Orphabase forms the basis of the annual reassessments by authorities to evaluate the benefit/risk profile of Orphacol (cholic acid). Orphabase allows the treating physicians to collect and assess his/her patients data in a structured manner. Also, the educational materials are kept updated and easily accessible for registered physicians. The annual report can bring additional scientific knowledge on the total cohort of Orphabase patients affected by those extremely rare disorders.

Theravia is encouraging you to participate to this collaborative effort by entering treatment data of patients with 3β-hydroxy-Δ5-C27-steroid dehydrogenase/isomerase or Δ4-3-oxosteroid-5β-reductase deficiency in your care into this database. You would then be able to access and use the data that you enter at any time. If you are interested in participating in this database or would like to get more information, please contact Theravia at question@theravia.com or you can make also a request to have access to this database via the website: www.databaseorphacol.com.

Analytical Laboratories

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c/o Chef du Service de biologie / Head of the laboratory
Groupe hospitalier Paris Saint-Joseph
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NB: this list will be continuously updated as Theravia identifies more analytical laboratories in Europe with the required capacity and expertise.

Contacts

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Additional materials can be obtained via Theravia, which can be reached via the below phone or email.

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 question@theravia.com

Additional information about *cholzuur* (cholic acid) is available in the Summary of Product Characteristics (SmPC) and patient information leaflet on www.geneesmiddeleninformatiebank.nl.

References:

1. Jacquemin E, Gerhardt MF, al. e. 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., editor. Dordrecht, Boston, London,: Kluwer Academic Publishers; 2000. 278-82 p.

2. Potin S, Desroches MC, Casaurang M, Jacquemin E, Vincent I, Furlan V, et al. Evaluation du traitement des déficits de synthèse des acides biliaires primaires par l'acide cholique et/ou l'acide ursodésoxycholique dans le cadre d'un essai clinique en pédiatrie. Journal de Pharmacie Clinique. 2001;20:193-6.

3. Gonzales E, Gerhardt MF, Fabre M, Setchell KD, Davit-Spraul A, Vincent I, et al. Oral cholic acid for hereditary defects of primary bile acid synthesis: a safe and effective long-term therapy. Gastroenterology. 2009;137(4):1310-20.e1-3.

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.

6. Wang DQ, Lammert F, Cohen DE, Paigen B, Carey MC. Cholic acid aids absorption, biliary secretion, and phase transitions of cholesterol in murine cholelithogenesis. The American journal of physiology. 1999;276(3):G751-60.

7. Thomas LA. Chapter 8 The Role of Bile Acids in Cholesterol-Rich Gallstone Formation. Bile Acids: Toxicology and Bioactivity: The Royal Society of Chemistry. 2008. p. 141-58.

8. Acalovschi M. Cholesterol gallstones: from epidemiology to prevention. Postgraduate medical journal. 2001;77(906):221-9.