ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Orphacol 50 mg hard capsules
Orphacol 250 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Orphacol 50 mg capsules
Each hard capsule contains 50 mg of cholic acid.

Orphacol 250 mg capsules
Each hard capsule contains 250 mg of cholic acid.

Excipient(s) with known effect: Lactose monohydrate (145.79 mg per capsule of 50 mg and 66.98 mg per capsule of 250 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Orphacol 50 mg capsules
Oblong, opaque, blue and white capsule.

Orphacol 250 mg capsules
Oblong, opaque, green and white capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Orphacol 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.

4.2 Posology and method of administration

Treatment must be initiated and monitored by an experienced gastroenterologist/hepatologist or a paediatric gastroenterologist/hepatologist in the case of paediatric patients.

In case of persistent lack of therapeutic response to cholic acid monotherapy, other treatment options should be considered (see section 4.4). Patients should be monitored as follows: 3-monthly during the first year, 6-monthly during the subsequent three years and annually thereafter (see below).

Posology

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

3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency

The daily dose 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.

Δ^4-3-Oxosteroid-5β-reductase deficiency

The daily dose 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.

During the initiation of 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 suitable analytical techniques. 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.

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 Orphacol. The dose should be adjusted accordingly, as described above.

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.

After the initiation period, serum and/or urine bile acids (using suitable analytical techniques) 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 (see section 4.6).

Special populations

Elderly population (≥65 years old)

There is no experience in elderly patients. The dose of cholic acid should be adjusted individually.

Renal impairment

No data are available for patients with renal impairment. The dose of cholic acid should be adjusted individually.

Hepatic impairment
Limited data are available for patients with minor to severe hepatic impairment related to 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency or Δ^4-3-Oxosteroid-5β-reductase deficiency. Patients are expected to present with some degree of hepatic impairment at diagnosis, which improves under cholic acid therapy. The dose of cholic acid should be adjusted individually.

No experience exists in patients with hepatic impairment from causes other than 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency or Δ^4-3-Oxosteroid-5β-reductase deficiency and no dose recommendation can be given. Patients with hepatic impairment should be monitored closely (see section 4.4).

Familial hypertriglyceridemia
Patients with newly diagnosed or a family history of familial hypertriglyceridemia are expected to poorly absorb cholic acid in the intestine. The cholic acid dose for patients with familial hypertriglyceridemia will have to be established and adjusted as described, but an elevated dose, notably higher than the 500 mg daily limit for adult patients, may be required and safe.

Paediatric population
Cholic acid therapy has been used for infants from one month of age, and for children and adolescents. The dose recommendations reflect the use in this population. The daily dose in infants from 1 month to 2 years of age, children and adolescents ranges from 5 to 15 mg/kg and must be adjusted individually for each patient.

Method of administration
Orphacol capsules must be taken with food at approximately the same time each day, in the morning and/or evening. Administration with food may increase cholic acid bioavailability and improve tolerability. Regular and fixed times of administration support the patient's or caregiver's compliance. Capsules must be swallowed whole with water, without chewing.
For infants and children who cannot swallow capsules, the capsules may be opened and the content added to infant formula or juice. For additional information, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant use of phenobarbital and primidone with cholic acid (see section 4.5).

4.4 Special warnings and precautions for use

Cases of severe hepatotoxicity, including cases with fatal outcome, have been reported, with the use of cholic acid. Treatment with cholic acid in patients with pre-existing hepatic impairment should be given under close monitoring and, for all patients, 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 severe hepatic failure.

Familial hypertriglyceridemia

Patients with newly diagnosed or a family history of familial hypertriglyceridaemia may have poor absorption of cholic acid from the intestine. The dose of cholic acid in such patients should be established and adjusted as described, but an elevated dose, notably higher than the 500 mg daily limit for adult patients, may be required.

Excipients
Orphacol capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Phenobarbital and primidone, which is partially metabolized in phenobarbital, antagonise the effect of cholic acid. Use of phenobarbital or primidone in patients with 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency or Δ^4-3-Oxosteroid-5β-reductase deficiency treated with cholic acid is contraindicated (see section 4.3). Alternative treatments should be used.

Ciclosporin alters the pharmacokinetics of cholic acid by inhibition of the hepatic uptake and hepatobiliary secretion of bile acids, as well as its pharmacodynamics by inhibition of cholesterol 7α-hydroxylase. Co-administration should be avoided. If administration of ciclosporin is considered necessary, serum and urine bile acid levels should be closely monitored and the cholic acid dose adjusted accordingly.

Bile acid sequestrants (cholestyramine, colestipol, colesevelam) and certain antacids (e.g. aluminium hydroxide) bind bile acids and lead to their elimination. Administration of these medicinal products is expected to reduce the effect of cholic acid. The dose of bile acid sequestrants or antacids must be separated from the dose of cholic acid by an interval of 5 hours, regardless of which medicinal product is administered first.

Ursodeoxycholic acid competitively inhibits absorption of other bile acids, including cholic acid, and replaces them in the enterohepatic pool, reducing the effectiveness of negative feedback inhibition on bile acid synthesis provided by oral cholic acid. For patients who are prescribed a combination of ursodeoxycholic acid and cholic acid in single doses, the administration of both medicinal products should be separated: one product should be given in the morning and the other product should be given in the evening, regardless of which medicinal product is given first. For those patients, who are prescribed a combination of ursodeoxycholic acid and cholic acid, in divided doses of cholic acid and/or ursodeoxycholic acid over the day, the administration of these medicinal products should be separated by several hours.

The effect of food on the bioavailability of cholic acid has not been studied. There is a theoretical possibility that administration with food may increase cholic acid bioavailability and improve tolerability.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
There is no need for contraceptive measures in women of childbearing potential treated with cholic acid or their partners. Women of childbearing potential should conduct a pregnancy test as soon as a pregnancy is suspected.

Pregnancy
There is a limited amount of data (less than 20 pregnancy outcomes) from the use of cholic acid in pregnant women. The exposed pregnancies showed no adverse reactions to cholic acid and resulted in

normal, healthy children. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

It is extremely important that pregnant women continue their therapy during pregnancy. As a precautionary measure, pregnant women and their unborn children should be closely monitored.

Breastfeeding
Cholic acid and its metabolites are excreted in human milk, but at therapeutic doses of Orphacol, no effects on the breastfed newborns/infants are anticipated. Orphacol can be used during breast-feeding.

Fertility
No data on the effects of cholic acid on fertility are available. At therapeutic doses, no effect on fertility is anticipated.

4.7 Effects on ability to drive and use machines

Cholic acid has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Due to the rarity of the diseases, the information about the most serious and/or most frequently occurring adverse reactions is limited. Diarrhoea, increased transaminases and pruritus have been associated with overdosage and disappeared after dose reduction. Development of gallstones associated with long-term treatment have been reported in very limited number of patients.

Tabulated list of adverse reactions
The following table lists adverse reactions reported in the literature under treatment with cholic acid. The frequency of these reactions is not known (cannot be estimated from the available data).

MedDRA System Organ Class	**Adverse reaction**
Gastrointestinal disorders	Diarrhoea
Hepatobiliary disorders	Transaminases increased Gallstones
Skin and subcutaneous tissue disorders	Pruritus

Description of selected adverse reactions
The development of pruritus and/or diarrhoea has been observed during treatment with Orphacol. These reactions abated after dose reduction and are suggestive of overdose. Patients presenting with pruritus and/or persistent diarrhoea should be investigated for a potential overdose by a serum and/or urine bile acid assay (see section 4.9).

Gallstones have been reported after long-term therapy.

Paediatric population
The presented safety information is derived principally from paediatric patients. The available literature is not sufficient to detect a difference in the safety of cholic acid within paediatric age groups or between paediatric patients and adults.

Other special populations
Please refer to section 4.2 for use of Orphacol in special populations.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Episodes of symptomatic overdose have been reported, including accidental overdose. Clinical features were limited to pruritus and diarrhoea. Laboratory tests showed elevation of serum gamma glutamyltransferase (GGT) transaminases and serum bile acid concentrations. Reduction of the dose led to resolution of the clinical signs and correction of abnormal laboratory parameters.

In the case of an accidental overdose, treatment should be continued at the recommended dose after normalisation of clinical signs and/or biological abnormalities.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bile and liver therapy, bile acid and derivatives, ATC code: A05AA03

Cholic acid is the predominant primary bile acid in man. In patients with inborn deficiency of 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase and Δ^4-3-Oxosteroid-5β-reductase, the biosynthesis of primary bile acids is reduced or absent. Both inborn diseases are extremely rare, with a prevalence in Europe of about 3 to 5 patients with 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency per 10 million inhabitants, and an estimated ten-fold lower prevalence for Δ^4-3-Oxosteroid-5β-reductase deficiency. In the absence of treatment, unphysiologic cholestatic and hepatotoxic bile acid metabolites are predominant in the liver, serum and urine. The rational basis for treatment consists of restoration of the bile acid-dependent component of bile flow enabling restoration of biliary secretion and biliary elimination of toxic metabolites; inhibition of the production of the toxic bile acid metabolites by negative feedback on cholesterol 7α-hydroxylase, which is the rate-limiting enzyme in bile acid synthesis; and improvement of the patient's nutritional status by correcting intestinal malabsorption of fats and fat-soluble vitamins.

Clinical experience has been reported in the literature from small cohorts of patients and single case reports; absolute patient numbers are small due to the rarity of the conditions. This rarity also made the conduct of controlled clinical studies impossible. Overall, cholic acid treatment results for about 60 patients with 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency are reported in the literature. Detailed long-term data on treatment with cholic acid monotherapy are available for 14 patients observed for up to 12.9 years. Cholic acid treatment results for seven patients with Δ^4-3-Oxosteroid-5β-reductase deficiency for up to 14 years are reported in the literature. Detailed medium- to long-term data are available for 5 of these patients, of whom 1 has been treated with cholic acid monotherapy. Oral cholic acid therapy has been shown to: postpone or obviate the need for liver transplantation; restore normal laboratory parameters; improve histological lesions of the liver, and significantly improve all of the patient's symptoms. Mass spectrometry analysis of urine during cholic acid therapy shows the presence of cholic acid and a marked reduction, or even complete elimination of the toxic bile acid metabolites. This reflects restoration of an effective feedback control of bile acid synthesis and a metabolic equilibrium. In addition, blood cholic acid concentration was normal and fat-soluble vitamins were restored to their normal range.

Paediatric population
The clinical experience reported in the literature is from a patient population with inborn deficiency of 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase or Δ^4-3-Oxosteroid-5β-reductase that includes principally infants from the age of one month, children and adolescents. However, absolute numbers of cases are small.

This medicinal product has been authorised under "Exceptional Circumstances".
This means that due to the rarity of the disease and for ethical reasons it has not been possible to obtain complete information on this medicinal product.
The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Cholic acid, a primary bile acid, is partially absorbed in the ileum. The remaining part is transformed by reduction of the 7α-hydroxy group to deoxycholic acid (3α, 12α-dihydroxy) by intestinal bacteria. Deoxycholic acid is a secondary bile acid. More than 90% of the primary and secondary bile acids are reabsorbed in the ileum by a specific active transporter and are recycled to the liver by the portal vein; the remainder is excreted in the faeces. A small fraction of bile acids is excreted in urine.

No pharmacokinetic study data for Orphacol are available.

5.3 Preclinical safety data

The available non-clinical data in the literature reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. The studies have however not been conducted to the same level of detail as for a pharmaceutical agent, as cholic acid is a physiological substance in animals and humans.

The intravenous LD_{50} of cholic acid in mice is 350 mg/kg body weight. Parenteral administration may cause haemolysis and cardiac arrest. Administered orally, bile acids and salts generally have only a minor toxic potential. The oral LD_{50} in mice is 1520 mg/kg. In repeated-dose studies, frequently reported effects of cholic acid have included decreased body weight, diarrhoea and liver damage with elevated transaminases. Increased liver weight and gallstones have been reported in repeated dose studies in which cholic acid was co-administered with cholesterol.

Cholic acid showed non-significant mutagenic activity in a battery of genotoxicity tests performed *in vitro*. Animal studies showed that cholic acid did not induce any teratogenic effect or foetal toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Lactose monohydrate,
Colloidal anhydrous silica,
Magnesium stearate.

Capsule shell Orphacol 50 mg capsule:

Gelatin (bovine origin),
Titanium dioxide (E171),
Carmine blue (E132).

Capsule shell Orphacol 250 mg capsule:
Gelatin (bovine origin),
Titanium dioxide (E171),
Carmine blue (E132),
Yellow Iron Oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

PVC/PVDC-aluminium blister of 10 capsules.
Pack sizes: 30, 60, 120.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Use in the paediatric population
See also section 4.2. For infants and children who cannot swallow capsules, the capsules may be opened and the content added to infant formula or infant-adapted apple/orange or apple/apricot juice. Other food such as fruit compote or yoghurt may be suitable for administration, but no data on the compatibility or palatability are available.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

THERAVIA
16 Rue Montrosier
92200 Neuilly-sur-Seine
France

8. MARKETING AUTHORISATION NUMBER(S)

Orphacol 50 mg capsule:

EU/1/13/870/001
EU/1/13/870/002
EU/1/13/870/003

Orphacol 250 mg capsule:
EU/1/13/870/004
EU/1/13/870/005
EU/1/13/870/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 September 2013
Date of latest renewal: 24 April 2019

10. DATE OF REVISION OF THE TEXT

07/10/2024

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu