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 the national reporting system listed in Appendix V.

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.

<u>Paediatric population</u>
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 30°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

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS OR RESTRICTIONS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATIONS TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

THERAVIA
16 Rue Montrosier
92200 Neuilly-sur-Seine
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH, in agreement with the competent authorities in the Member States, shall implement, prior to the launch, an educational programme for physicians aiming to provide educational material on correct diagnosis and therapeutic managements of 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 and to inform on expected and potential risks associated with the treatment.

The physician educational programme should contain the following key elements:

- Prescription of a supratherapeutic dose (MedDRA term: drug toxicity)

- Risk of gallstones

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due Date
theravia S.A. commits to monitor the safety and efficacy in patients treated with Orphacol from a patient surveillance database for which the protocol has been endorsed by the CHMP and is documented in the Orphacol RMP. The objectives of this surveillance programme is to monitor accumulating data on efficacy and safety in 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 with Orphacol in infants, children, adolescents and adults. Reports on recruitment progress of the patient surveillance database will be analysed and reported to the CHMP at the time of PSURs (for safety) and of the Annual Re-assessments (for efficacy and safety). Progress and results from the database will form the basis of the annual reassessments of the benefit/risk profile of Orphacol.	- PSUR - Annual Re-assessment

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Orphacol 50 mg hard capsules
Orphacol 250 mg hard capsules
Cholic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 50 mg cholic acid.
Each hard capsule contains 250 mg cholic acid.

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules
60 hard capsules
120 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not chew.
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

THERAVIA
16 Rue Montrosier
92200 Neuilly-sur-Seine
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/870/001 [30 hard capsules]
EU/1/13/870/002 [60 hard capsules]
EU/1/13/870/003 [120 hard capsules]
EU/1/13/870/004 [30 hard capsules]
EU/1/13/870/005 [60 hard capsules]
EU/1/13/870/006 [120 hard capsules]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Orphacol 50 mg capsules
Orphacol 250 mg capsules
Cholic acid

2. NAME OF THE MARKETING AUTHORISATION HOLDER

THERAVIA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Orphacol 50 mg hard capsules
Orphacol 250 mg hard capsules
Cholic acid

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Orphacol is and what it is used for

Orphacol contains cholic acid, a bile acid which is normally produced by the liver. Certain medical conditions are caused by defects in bile acid production and Orphacol is used to treat infants from one month to 2 years of age, children, adolescents and adults with these medical conditions. The cholic acid contained in Orphacol replaces the bile acids that are missing due to the defect in bile acid production.

2. What you need to know before you take Orphacol

Do not take Orphacol
- if you are allergic to cholic acid or any of the other ingredients of this medicine (listed in section 6).
- if you are taking phenobarbital or primidone, a medicine to treat epilepsy.

Warnings and precautions
During your treatment, your doctor will carry out various blood and urine tests at different time to see how your body is handling this medicine and to help work out the dose that you need. More frequent tests will be needed if you are growing fast, if you are ill (if you have e.g. liver problems), or if you are pregnant.

Other medicines and Orphacol
Tell your doctor or pharmacist if you are taking, have recently taken any or might take other medicines.

Some medicines used to lower cholesterol levels, so-called bile acid sequestrants (cholestyramine, colestipol, colesevelam), and medicines to treat heartburn that contain aluminium may lessen the effect of

Orphacol. If you take these medicines, take Orphacol at least 5 hours before or at least 5 hours after taking these other medicines.
Ciclosporin (a medicine used to suppress the immune system) may also change the effect of Orphacol. Please tell your doctor if you are taking ciclosporin.

Ursodeoxycholic acid may lessen the effect Orphacol if both medicines are taken at the same time. If you are prescribed ursodeoxycholic acid along with Orphacol in single doses, take one product in the morning and the other product in the evening. If you are prescribed divided doses of ursodeoxycholic acid and/or Orphacol, as these products should be administered separately by several hours, please ask for the advice of your doctor or pharmacist about proper sequence of administration.

Pregnancy and breast-feeding
Please consult your doctor if you plan to become pregnant. Take a pregnancy test as soon as you suspect you may be pregnant. It is very important to continue taking Orphacol during pregnancy.

If you become pregnant during treatment with Orphacol, your doctor will decide which treatment and dose is best in your situation. As a precaution, you and your unborn child should be closely monitored during pregnancy.

Orphacol can be used during breast-feeding. Tell your doctor if you plan to breast-feed or are breast-feeding before you take Orphacol.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Orphacol is not expected to have an effect on the ability to drive and use machines.

Orphacol contains lactose
Orphacol contains a certain sugar (lactose monohydrate). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Orphacol.

3. How to take Orphacol

Always take Orphacol exactly as your doctor has told you. Check with your doctor if you are not sure.

The usual starting dose is 5 to 15 mg per kilogram body weight every day in infants, children, adolescents and adults.

Before treatment your doctor will make an assessment from your laboratory tests to determine the correct dose for you. The dose will then be further adjusted by your doctor depending on your body's response.

Orphacol capsules are taken by mouth with a meal at approximately the same time each day, in the morning and/or evening. Taking Orphacol at regular times with a meal will help you remember to take this medicine, and may help your body to better take it up. Capsules must be swallowed whole with water. Do not chew.

If your doctor has prescribed a dose which requires you to take more than one capsule per day, you and your doctor can decide how this will be taken during the day. You may for example take one capsule in the morning and one in the evening. This way, you will have to take fewer capsules at once. However, this might not be possible if you have been prescribed at the same time another medicine containing ursodeoxycholic acid. In this case, you should seek advice from your doctor or pharmacist about proper sequence of administration of ursodeoxycholic acid and Orphacol over the day, as these products should be administered separately by several hours (see section 2).

Use in children
For babies and children who cannot swallow capsules, the capsule can be opened and its contents added to baby formula or apple/orange or apple/apricot juice adapted for small children.

If you take more Orphacol than you should
If you have taken more Orphacol than you should, contact your doctor as soon as possible. He will assess your laboratory test results and advise you when you should resume your treatment with your normal dose.

If you forget to take Orphacol
Take your next dose when you would normally take it. Do not take a double dose to make up for a forgotten dose.

If you stop taking Orphacol
There is a risk of permanently damaging your liver if you stop taking Orphacol. You should never stop taking Orphacol unless your doctor advises you to do so.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Several patients have experienced itching and/or diarrhoea, however, it is not known how likely this is to occur (frequency cannot be estimated from the available data). If itching and/or diarrhoea last for more than three days, tell your doctor.

For several patients an increase of liver enzymes (serum transaminases) have been reported during the treatment with Orphacol (frequency cannot be estimated from the available data). Your doctor will decide what to do if this happens to you.

Gallstones have been reported after long-term therapy with Orphacol.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Orphacol

Keep out of the reach and sight of children.

Do not use Orphacol after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Store below 30°C.

Medicines should not be disposed of via wasterwater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Orphacol contains

- The active substance is cholic acid.
  Orphacol 50 mg: Each hard capsule contains 50 mg of cholic acid.
  Orphacol 250 mg: Each hard capsule contains 250 mg of cholic acid.
- The other ingredients are:
  Content of capsules: Lactose monohydrate (see section 2 under 'Orphacol contains lactose' for more information), colloidal anhydrous silica, magnesium stearate
  Capsule shell:
  Orphacol 50 mg: gelatin, titanium dioxide (E171), carmine blue (E132);
  Orphacol 250 mg: gelatin, titanium dioxide (E171), carmine blue (E132), yellow iron oxide (E172).

What Orphacol looks like and contents of the pack

Orphacol is available as hard capsules (capsules) of oblong shape. Capsules of 50 mg cholic acid are blue and white and capsules of 250 mg cholic acid are green and white. They are contained in blisters of 10 capsules each.
Pack sizes are available in 30, 60 and 120 capsules.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
THERAVIA
16 Rue Montrosier
92200 Neuilly-sur-Seine
France

Manufacturer
THERAVIA
16 Rue Montrosier
92200 Neuilly-sur-Seine
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
THERAVIA
Tél/Tel: +32 (0)2 40 11 442
question@theravia.com

Lietuva
Immedica Pharma AB
Tel/Puh: +46 (0)8 533 39 500
info@immedica.com

България
THERAVIA
Тел.: +33 (0)1 72 69 01 86
question@theravia.com

Luxembourg/Luxemburg
THERAVIA
Tél/Tel: +352 278 62 329
question@theravia.com

Česká republika
THERAVIA
Tel.: +33 (0)1 72 69 01 86
question@theravia.com

Danmark
Immedica Pharma AB
Tlf: +46 (0)8 533 39 500
info@immedica.com

Deutschland
THERAVIA
Tel: +49 (0)3022153008
question@theravia.com

Eesti
Immedica Pharma AB
Tel/Puh: +46 (0)8 533 39 500
info@immedica.com

Ελλάδα
THERAVIA
Τηλ: +33 (0)1 72 69 01 86
question@theravia.com

España
THERAVIA
Tel: + (34) 914 146 613
question@theravia.com

France
THERAVIA
Tél: +33 (0)1 72 69 01 86
question@theravia.com

Hrvatska
Medis Adria d.o.o.
Tel: +385 (1) 230 3446
info@medisadria.hr

Ireland
THERAVIA
Tel: +353 (0)1 695 00 63
question@theravia.com

Ísland
Immedica Pharma AB
Sími: + 46 (0)8 533 39 500
info@immedica.com

Magyarország
Medis Hungary Kft
Tel: +36 (2) 380 1028
info@medis.hu

Malta
THERAVIA
Tel: +356 2776 1358
question@theravia.com

Nederland
THERAVIA
Tel: +31 (0)2 070 38 155
question@theravia.com

Norge
Immedica Pharma AB
Tel/Puh: +46 (0)8 533 39 500
info@immedica.com

Österreich
THERAVIA
Tel: +43 (0) 800 909 699
question@theravia.com

Polska
THERAVIA
Tel.: +33 (0)1 72 69 01 86
question@theravia.com

Portugal
THERAVIA
Tel: +33 (0)1 72 69 01 86
question@theravia.com

România
THERAVIA
Tel: +33 (0)1 72 69 01 86
question@theravia.com

Slovenija
Medis d.o.o.
Tel: +386 (1) 589 6900
info@medis.si

Slovenská republika
THERAVIA
Tel: +33 (0)1 72 69 01 86
question@theravia.com

Italia
THERAVIA
Tel: +39 (0)800 959 161
question@theravia.com

Κύπρος
THERAVIA
Τηλ: +33 (0)1 72 69 01 86
question@theravia.com

Latvija
Immedica Pharma AB
Tel: +46 (0)8 533 39 500
info@immedica.com

Suomi/Finland
Immedica Pharma AB
Tel/Puh: +46 (0)8 533 39 500
info@immedica.com

Sverige
Immedica Pharma AB
Tel: +46 (0)8 533 39 500
info@immedica.com

United Kingdom (Northern Ireland)
THERAVIA
Tel: +44 (0)3 301 002 375
question@theravia.com

This leaflet was last revised in

This medicine has been authorised under "Exceptional Circumstances".
This means that because of the rarity of this disease and for ethical reasons it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on the medicine every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/. There are also links to other websites about rare diseases and treatments.