Educational material

Important safety information concerning Orphacol® (cholic acid)

▼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.

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.

This material for hepatologists aims to:

- Provide correct diagnosis and therapeutic managements of these two deficiencies;
- Inform on expected and potential risks associated with the treatment, especially prescription of a supratherapeutic dose and gallstones.

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1. What are 3β-hydroxy-Δ5-C27-steroid oxidoreductase deficiency and Δ4-3-oxosteroid-5β-reductase deficiency?

Two main types of primary bile acid synthesis defects have been identified including 3β-hydroxy-Δ^5-C_{27}-steroid oxidoreductase [3β-HSD] (microsomal enzyme) deficiency and Δ^4-3-oxosteroid-5β-reductase [Δ^4-3-oxoR] (cytosolic enzyme) deficiency. These two enzymes are involved early in the bile acid synthetic pathway and the consequences of abnormalities in these enzymes are absence of primary bile acid synthesis and accumulation of abnormal bile acid metabolites that are cholestatic and toxic for the liver. This results in cholestasis followed by irreversible progressive liver failure in the absence of treatment.

If you are interested to participate into this database or would like to get more information, please contact Theravia. We are collecting treatment information in a central database called Orphabase. You are invited to participate to this collaborative effort by entering treatment data of patients with 3β-hydroxy-Δ^5-C_{27}-steroid dehydrogenase/isomerase or Δ^4-3-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. Moreover, any suspected adverse reactions should be reported to Theravia or the national competent authorities (see safety information in section 5 and the list of contacts in section 6).

2. How are 3β-hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency and Δ^4-3-oxosteroid-5β-reductase deficiency diagnosed?

The following signs are suggestive of the diagnosis of 3β-HSD or Δ^4-3-oxoR deficiency:

- Cholestasis and/or hepatocellular insufficiency during the first months of life or in childhood,
- And/or malabsorption syndrome (steatorrhoea, clinical signs associated with fat-soluble vitamin deficiencies),
- And/or cirrhosis or hepatomegaly.

With unexplained elevation of serum transaminases and conjugated bilirubin in combination with:

- An absence of pruritus.
- Normal serum gamma-glutamyl transferase (GGT) activity,
- Normal or very low total serum bile acids.

Hepatic histological signs include:

- Canalicular cholestasis, without bile duct proliferation and sometimes with signs of giant-cell hepatitis.
- Portal and lobular fibrosis with features of septal fibrosis or cirrhosis depending on the stage.

Confirmation of diagnosis

Initial confirmation of the diagnosis is based on urinary and serum bile acid analysis by gas chromatography linked to mass spectrometry (GC-MS) and/or electrospray ionization tandem spectrometry (ESI-MS/MS)(4) or equivalent technology coupled to mass spectrometry. This analysis demonstrates a typical profile for each deficiency, confirming the specific diagnosis. Analysis of the *HSD3B7* or *AKR1D1 (SRD5B1)* genes also enables a subsequent confirmation of the diagnosis.

Please refer to the list of qualified laboratories who perform the required analyses in section 6.

You may also contact Theravia directly if you need assistance with bile acid analysis.

A diagnostic Flow Chart is shown on the latest page of this educational material (page 11) .

3. Dose considerations to avoid supratherapeutic dose.

Treatment with Orphacol® must be initiated and monitored by an experienced hepatologist or a paediatric 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 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.

The following table gives indication on the estimated number of capsules to be administered for infants and young children.

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

Monitoring of patients

During the initiation of Orphacol® 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. Please refer to the list of qualified laboratories in section 6. 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 Orphacol® that effectively reduces the bile acid metabolites to as close to zero as possible should be chosen**.

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 Orphacol® should be stopped if in case of abnormal hepatocellular function, as measured by prothrombin time, does not improve within 3 months of the initiation of Orphacol® 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 Orphacol® monotherapy, another treatment option should be considered.

4. How is Orphacol® administered?

Orphacol® capsules must be taken with food at approximately the same time each day, in the morning and/or evening. 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 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.

5. What are expected and potential risks associated with the treatment?
What are signs of overdosage?
What should be done if gallstones are found?

Overdose

Episodes of **symptomatic overdose** have been reported, including accidental overdose. Clinical features were limited to **pruritus and diarrhea**. In laboratory investigations, **serum transaminase and bile acid levels were increased**. Reduction of the dose led to resolution of the clinical signs and correction of abnormal laboratory parameters.

Undesirable effects

- **Gallstones** have been reported after long-term therapy. **Any occurrence of gallstones should be reported as an adverse reaction** to national competent authority or to Theravia (see the list of contacts in section 6).

- The **development of pruritus and/or diarrhoea as well as increased serum transaminase and bile acid levels** 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.

Please refer to the Summary of Product Characteristics for a full list of undesirable effects potentially associated with Orphacol treatment (available here).

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. Please report any suspected adverse reactions via HPRA Pharmacovigilance (Website: www.hpra.ie).

Further contact details for reporting of suspected adverse events in Ireland can be found on page 9.

Interaction with other medicinal products

- Phenobarbital and primidone (which is partially metabolized in phenobarbital) antagonises the effect of cholic acid. Concomitant use is contraindicated.
- Ciclosporin alters the pharmacokinetics of cholic acid. Concomitant use should be avoided; if this is impossible, serum and urine bile acid levels should be closely monitored and the cholic acid dose adjusted accordingly.
- Bile acid sequestrants and certain antacids (containing e.g. aluminium hydroxide): Administration of these medicinal products is expected to reduce the effect of cholic acid if administered at the same time. Administration should be separated by at least 5 hours.
- Ursodeoxycholic acid inhibits the absorption of cholic acid and replaces it in the enterohepatic circulation, reducing the effectiveness of negative feedback inhibition on bile acids synthesis provided by oral CA. Administration with cholic acid must be avoided and administration should be separated by several hours.

Contraindications

- Hypersensitivity to cholic acid or to any of the excipients (lactose monohydrate, colloidal anhydrous silica, magnesium stearate, gelatin, titanium dioxide (E171), carmine blue (E132) or, for 250 mg capsules only, yellow iron oxide (E172)).
- Concomitant use of phenobarbital and primidone with cholic acid.

Precautions

No experience exists in patients with 3β-HSD deficiency or Δ^4-3-oxoR deficiency and hepatic impairment from additional causes. In such circumstances, no dose recommendation can be given. Patients with hepatic impairment should be monitored closely.

Cases of severe hepatotoxicity, including cases with fatal outcome, have been reported in the literature, 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.

6. Contacts

Details of the national competent authorities to communicate adverse reactions

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

Analytical Laboratories

PARIS
Laboratoire de Biologie
c/o Chef du Service de biologie/Head of the laboratory
Groupe hospitalier Paris Saint-Joseph
185, rue Raymond Losserand
75014 Paris
FRANCE
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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.

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7. Bibliography

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Diagnostic flowchart