HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

# TRANSPARENCY COMMITTEE

## Opinion

## 19 February 2014

## ORPHACOL 50 mg, hard capsule

**B/30 (CIP 34009 416 886 0 7)**
**B/60 (CIP 34009 416 887 7 5)**

## ORPHACOL 250 mg, hard capsule

**B/30 (CIP: 34009 416 890 8 6)**

Applicant: CTRS

| | |
|---|---|
| INN | cholic acid |
| ATC Code (2012) | A05AA03 (Bile acid preparations) |
| Reason for the request | **Inclusion** |
| List concerned | **Hospital use** (French Public Health Code L.5123-2) |
| Indication concerned | **"Treatment of inborn errors in primary bile acid synthesis due to 3β-hydroxy-$\Delta^5$-$C_{27}$-steroid oxidoreductase deficiency or $\Delta^4$-3-oxosteroid-5β-reductase deficiency in infants, children and adolescents aged 1 month to 18 years and adults."** |

| | |
|---|---|
| **Actual Benefit** | **Substantial.** |
| **Improvement in Actual Benefit** | **The benefits of using cholic acid in the treatment of inborn errors in primary bile acid synthesis due to 3β-hydroxy-$\Delta^5$-$C_{27}$-steroid oxidoreductase deficiency or $\Delta^4$-3-oxosteroid-5β-reductase deficiency as soon as they are diagnosed have been established since 1993, when the first hospital preparation was made available in France by the AP-HP [Paris public hospital system], followed by temporary authorisations for use by a named patient [ATU nominative in French] since 2007. In particular, none of the 20 patients followed in France and treated with cholic acid since this date have needed a liver transplant, the only other treatment option. Treatment with cholic acid allows postponing liver transplantation and improving overall symptomatology, normalising lab work results and improving histological liver lesions, with good safety. Several women treated with cholic acid have carried pregnancies to term and given birth to healthy children.**<br>**There is an absence of a treatment alternative, other than resorting to liver transplant, for these inborn deficiencies with fatal outcome in the early years of life without treatment. The Transparency Committee considers that ORPHACOL proprietary medicinal products provide a major improvement in actual benefit (IAB I) in the therapeutic strategy.** |
| **Therapeutic use** | **There is an international consensus in the literature that cholic acid is the treatment of choice for 3β-HSD deficiency.**<br>**As for $\Delta^4$-3-oxoR deficiency, except for one patient, all the treatments reported in the literature using cholic acid were effective, alone or in combination.**<br>**In France, of the three patients treated for this deficiency, two are currently on ORPHACOL monotherapy.** |
| **Recommendation** | **-** |

# 01 ADMINISTRATIVE AND REGULATORY INFORMATION

| | |
|---|---|
| Marketing Authorisation (procedure) | Initial date (centralised procedure): 12 September 2013.<br>Marketing authorisation granted under exceptional circumstances.<br>(*In October 2009, initial application under exceptional circumstances based on the well-established medical use of the active ingredient - positive Opinion of the Committee for Medicinal Products for Human Use of the EMA 16 December 2010 - Notification of decision to refuse marketing authorisation on the grounds that the combination of two procedures is inconsistent with Community law - Decision overturned by the European Court of Justice 4 July 2013*) |
| Prescribing and dispensing conditions / special status | List I<br>Medicine for hospital prescription only.<br>Prescription by specialists in gastroenterology and hepatology only.<br>Medicine requiring special monitoring during treatment.<br>Orphan medicine (designation granted on 18 December 2002, confirmed on 12 January 2011).<br>Temporary authorisation for use by a named patient.<br>Retrocession. |

| | | |
|---|---|---|
| ATC Classification | 2012 | |
| | A | Alimentary tract and metabolism |
| | A05 | Bile and liver therapy |
| | A05A | Bile therapy |
| | A05AA | Bile acid preparations |
| | A05AA03 | Cholic acid |

# 02 BACKGROUND

The company is requesting the inclusion of ORPHACOL 50 mg and ORPHACOL 250 mg, hard capsule, whose active ingredient is cholic acid, on the list of proprietary medicinal products approved for hospital use.

In France, cholic acid has been available first in the form of a hospital preparation (1993) and then under a temporary authorisation for use by a named patient (since October 2007).

Cholic acid is quantitatively the most important of the primary bile acids, the essential constituents of bile.
ORPHACOL is the first medicine with a marketing authorisation for treatment of 3β-hydroxy-$\Delta^5$-$C_{27}$-steroid oxidoreductase or $\Delta^4$-3-oxosteroid-5β-reductase deficiencies.

# 03 THERAPEUTIC INDICATIONS

"Treatment of inborn errors in primary bile acid synthesis due to 3β-hydroxy-$\Delta^5$-$C_{27}$-steroid oxidoreductase deficiency or $\Delta^4$-3-oxosteroid-5β-reductase deficiency in infants, children and adolescents aged 1 month to 18 years and adults."

# 04 DOSAGE

"Treatment must be initiated and monitored by an experienced hepatologist or a paediatric 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. Patients should be monitored as follows: 3-monthly during the first year, 6-monthly during the subsequent three years and annually thereafter.

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-$\Delta^5$-$C_{27}$-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.

$\Delta^4$-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."

# 05 THERAPEUTIC NEED

Physiologically, cholic acid (main bile acid) represents 2/3 and chenodeoxycholic acid represents 1/3 of the primary bile acids. Bile acids are necessary for bile secretion by hepatocytes and are indispensable for the absorption of dietary fats and fat-soluble vitamins. These physiological organic components are confined almost exclusively to the enterohepatic circulation. Biosynthesis of these two primary bile acids, cholic acid and chenodeoxycholic acid, from cholesterol, involves at least 16 different enzymes, the majority of which are preferentially expressed in the liver. It is regulated by negative feedback control exerted by the end products and some of their metabolites. These metabolites, the secondary bile acids, are produced by the intestinal bacterial flora and include in particular deoxycholic acid, lithocholic acid, and ursodeoxycholic acid.

ORPHACOL aims to alleviate deficient synthesis of cholic acid related to two enzymes: deficiency in 3β-hydroxy-$\Delta^5$-$C_{27}$-steroid oxidoreductase (3β-HSD) or $\Delta^4$-3-oxo-steroid-5β-reductase (Δ4-3-oxoR).

This deficient synthesis leads to the production and accumulation of abnormal, highly hepatotoxic metabolites from bile acids that cause serious cholestasis and then progressive irreversible liver failure which is almost always fatal in the absence of treatment. The disease usually manifests in the first years, or even months (for $\Delta^4$-3-oxoR deficiency), of life.

These extremely rare disorders are hereditary recessive autosomal diseases strongly linked to consanguinity. 3β-hydroxy-C27-steroid dehydrogenase/isomerase and Δ4-3-oxosteroid-5β-reductase deficiencies are linked to mutations in the HSD3B7 gene (chromosome 16) and the AKR1D1 gene (SRD5B1) (chromosome 7), respectively.

In the majority of cases, the clinical presentation appears in the first months of life. However, diagnostic confirmation may be late due to erroneous diagnosis; non-expert clinicians may be confused by atypical symptoms.
The clinical expression of these two deficiencies is linked, on the one hand, to liver disease as such and, on the other hand, to the consequences of abnormal bile composition that has an impact on the absorption of dietary fats and fat-soluble vitamins.

The classic presentation is a child with signs of cholestasis with jaundice, hepatomegaly, elevated transaminases and hyperbilirubinaemia, contrasting with an absence of pruritus, normal serum activity of gamma-GT, and a normal or low serum concentration of bile acids.
Depending on the time between the first symptoms and the confirmation of the diagnosis, children may have signs of rickets (vitamin D malabsorption), coagulation disorders (vitamin K malabsorption), and hepatocellular insufficiency.
Steatorrhoea is 5-6 times higher than normal. Absence of deep tendon reflexes, secondary to malabsorption of vitamin E, is common.

Urinalysis by mass spectrometry coupled with chromatography (FAB-MS or GC-MS) shows elevated urine excretion of bile acids consistent with cholestasis, but qualitatively an absence of primary bile acids and the presence of abnormal bile acid metabolites in the urine (and possibly in the blood). The diagnosis is definitively confirmed by gene sequencing.

In the absence of appropriate therapeutic management, the outcome is almost always fatal with progressive and irreversible liver failure.

Previously, only palliative treatments to correct metabolic disturbances associated with these diseases (in particular, deficiencies in fat-soluble vitamins, A, D and K, which are essential for normal growth) or the use of very rare bile acids were available in the therapeutic arsenal. The only alternative that could avoid a fatal outcome for these two diseases was liver transplantation, with all its limitations, especially in the first months of life.

Providing exogenous cholic acid at physiological doses (≤ 500 mg/day for adults) allows:
- Re-establishment of the bile acid-dependent component of bile flow, restoring the secretion of bile and biliary elimination of toxic metabolites.
- Inhibition of the production of hepatotoxic and cholestasic primary bile acid precursors by negative feedback control of cholesterol 7-alpha-hydroxylase, the key enzyme in the bile acid synthesis chain.
- Improvement in the child's growth by correcting intestinal malabsorption of fats and fat-soluble vitamins.

Treatment with cholic acid, if started sufficiently early, leads to progressive improvement in clinical presentation with return to a normal life.

# 06 CLINICALLY RELEVANT COMPARATORS

## 06.1 Medicinal products

✓ **Based on chenodeoxycholic acid or ursodeoxycholic acid**

For information purposes, proprietary medicinal products based on other bile acids, chenodeoxycholic acid (the second primary bile acid) or ursodeoxycholic acid (secondary bile acid), have been used off-label:

| NAME (INN) *Company* | Same TC* Yes / No | Indication | Date of opinion | AB | Reimbursement Yes/No |
|---|---|---|---|---|---|
| CHENODEX 250 mg, tablet<br><br>(chenodeoxycholic acid)<br><br>*Sale discontinued since 1999* | Yes | Cholesterol gallstones | - | - | Cancellation 17/01/2005 |
| URSOLVAN, hard capsules<br><br>(ursodeoxycholic acid)<br><br>Sanofi-Aventis France | Yes | Cholesterol gallstones: Cholelithiasis with few or no symptoms, radiolucent, with a diameter less than 15 mm, in a functional gallbladder (evidenced by oral cholecystography), in patients with a major contraindication to surgery.<br>Chronic cholestatic liver disease:<br>In particular, primary biliary cirrhosis, sclerosing cholangitis, cystic fibrosis liver disease. | 20 March 2013 | The actual benefit of URSOLVAN remains substantial in symptomatic and uncomplicated gallstones, with a diameter less than 15 mm, in a functional gallbladder (evidenced by oral cholecystography), in patients with a major contraindication to surgery.<br><br>The actual benefit of URSOLVAN remains substantial in chronic intrahepatic cholestasis. | Soc. Sec. (65%)<br>For hospital use |

*therapeutic category

Two proprietary medicinal products based on these same other bile acids are currently available with temporary authorisation for use by a named patient status:

- XENBILOX 250 mg (chenodeoxycholic acid), capsule,
- URSOFALK 50 mg/ml (ursodeoxycholic acid) oral suspension.

In principle, treatment combining cholic acid and chenodeoxycholic acid could prove more effective than monotherapy with cholic acid, since it would reproduce the endogenous composition of primary bile acids. However, the administration of chenodeoxycholic acid in these two deficiencies is contraindicated for several reasons:
- The secondary metabolite of chenodeoxycholic acid is lithocholic acid, which is known for its high hepatotoxicity at high doses[1]; chenodeoxycholic acid is formally contraindicated in liver damage or failure (see CHENODEX SPC).
- Chenodeoxycholic acid may cause diarrhoea, even at therapeutic doses, and especially above therapeutic doses.[2][3]

[1] Kakis G, Yousef IM. Pathogenesis of lithocholate- and taurolithocholate-induced intrahepatic cholestasis in rats. Gastroenterology, 1978. 75(4): 595-607.

For some patients with a deficit in $\Delta^4$-3-oxosteroid-5β-reductase, the combination of cholic acid with a low dose of ursodeoxycholic acid (4 mg/kg) may sometimes be necessary[4,5,6,7,8,9].

- ✓ **Based on cholic acid**

In France, cholic acid was made available in 1993 in the form of a hospital preparation developed by the AP-HP Etablissement Pharmaceutique [Pharmaceutical Institution]. After several years of internal development at the AP-HP, the AP-HP Etablissement Pharmaceutique obtained orphan status for cholic acid in 2002. A partnership agreement was signed in 2007 between the AP-HP and CTRS. In 2007, CTRS registered cholic acid under the name ORPHACOL and temporary authorisations for use (replacing hospital preparations) were granted in France. The proprietary medicinal product was then registered on the European level.

A proprietary medicinal product based on cholic acid, CHOLBAM 50 mg and 250 mg, hard capsules, is available under a temporary authorisation for use by a cohort [ATU de cohorte in French] granted by the ANSM [French National Medicines and Health Products Safety Agency] on 19 July 2013, amended in November 2013 and then in January 2014.[10] This proprietary medicinal product obtained a positive opinion from the CHMP [Committee for Medicinal Product for Human Use] in January 2014[11] (which revised a CHMP opinion of November 2013) in an indication which is now different from that for ORPHACOL, namely the treatment of congenital abnormalities in primary bile acid synthesis due to a deficiency in the following enzymes:

- sterol 27-hydroxylase (manifested by cerebrotendinous xanthomatosis, CTX),
- 2-(or α-) methylacyl-CoA racemase (AMACR),
- cholesterol 7 α-hydroxylase (CYP7A1),

in infants from age one month, children, adolescents up to age 18 and adults for continuous lifetime treatment.

[2] Setchell KDR et al. Oral bile acid therapy in the treatment of inborn errors in bile acid synthesis associated with liver disease, in Bile acids as therapeutic agents. From basic science to clinical practice, G. Paumgartner, A. Stiehl, and W. Gerok. Editors. 1991, KIuwer Academic: Boston. 367-373.

[3] Sigma-tau Arzneimittel GmbH, Chenofalk (Chenodeoxycholic Acid 250 mg) - Summary of Product Characteristics, 2008: Germany.

[4] Gonzales E et al. Oral cholic acid for hereditary defects of primary bile acid synthesis: a safe and effective long-term therapy. Gastroenterology 2009; 137: 1310-1320.

[5] Setchell KD et al. Identification of a new inborn error in bile acid synthesis: mutation of the oxysterol 7alpha-hydroxylase gene causes severe neonatal liver disease. J Clin Invest, 1998. 102(9): p. 1690-703.

[6] Daugherty CC et al. Resolution of liver biopsy alterations in three siblings with bile acid treatment of an inborn error of bile acid metabolism (delta 4 3 oxosteroid 5 beta-reductase deficiency). Hepatology 1993; 18: 1096-101.

[7] Balistreri WF. Fetal and neonatal bile acid synthesis and metabolism--clinical implications. J Inherit Metab Dis 1991; 14: 459-77.

[8] Balistreri W.F. Inborn errors of bile acid biosynthesis: Clinical and therapeutic aspects. In Bile Acids in Gastroenterology: Basic and Clinical Advances, A.F. Hofmann, G. Paumgartner, and A. Stiehl, Editors. 1995, Kluwer Academic Publishers: London. 333-353.

[9] Balistreri WF. Inborn errors of bile acid biosynthesis and transport. Novel forms of metabolic liver disease. Gastroenterol Clin North Am 1999; 28: 145-72, vii.

[10] ANSM. Protocole d'utilisation thérapeutique et de recueil d'informations CHOLBAM 50 mg et 250 mg, gélules (Acide Cholique). February 2014 – Version 3

[11] EMA. Committee for Medicinal Products for Human Use (CHMP). Summary of opinion (initial authorisation). Cholic acid FGK - cholic acid. EMA/CHMP/30450/2014. 23 January 2014.

## 06.2 Other health technologies

The alternative is liver transplant surgery, which has not been performed since cholic acid became available, initially in the form of hospital preparations (1993) and then under a temporary authorisation for use by a named patient (2007).

In publications identified by the company, the follow-up of four cases of liver transplant is discussed:

- Two in subjects with 3β-HSD deficiency. One who had to have a liver transplant due to late diagnosis and therefore a very impaired general condition; for the second case, there is no follow-up information available[12].
- Two in subjects with $\Delta^4$-3-oxoR deficiencies. One transplanted patient, a Sri-Lankan treated in the United Kingdom, died post transplant at age 19 weeks;[13] for the second, a Taiwanese subject, there is no information available.[14]

### ◗ Conclusion

**There is no clinically relevant comparator with a valid Marketing Authorisation.**

# 07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

- Marketing Authorisation:

Procedure underway in Switzerland (filed fourth quarter 2013)

- Reimbursement:

| Country | REIMBURSEMENT | |
|---|---|---|
| | YES/NO<br>If not, why not | Population(s)<br>That of the Marketing Authorisation or restricted |
| Switzerland | YES | Indications: the same; Disability Insurance compassionate programme. |

Foreign applications for reimbursement (Italy, United Kingdom, etc.) will be filed soon.

[12] Cheng JB. et al. Molecular genetics of 3beta-hydroxy-Delta5-C27-steroid oxidoreductase deficiency in 16 patients with loss of bile acid synthesis and liver disease. J Clin Endocrinol Metab 2003; 88: 1833-41.
[13] Lemonde HA et al. Mutations in SRD5B1 (AKR1D1), the gene encoding delta (4) 3 oxosteroid 5beta-reductase, in hepatitis and liver failure in infancy. Gut 2003; 52: 1494-9.
[14] Ueki I et al. SRD5B1 gene analysis needed for the accurate diagnosis of primary 3-oxo-Delta-steroid 5beta-reductase deficiency. J Gastroenterol Hepatol 2009 24: 776-85

# 08 ANALYSIS OF AVAILABLE DATA

The data provided by the company in support of its application are:
- data from a cohort of 15 patients followed by the Paediatric Hepatology Department of the Bicêtre University Hospital Centre (AP-HP) from 1993 to 2007.[4,15] These patients were treated as part of a Hospital Clinical Research Programme and then under temporary authorisations for named patient use starting in 2007.
- data from the database (Orphabase) created by CTRS from information submitted by clinicians and pertaining to 20 patients followed in France (presented in section 08.3 Usage/prescription data).
- literature data.

No controlled study can be envisaged for ethical reasons since the disease preferentially involves newborns and the disease is life-threatening for untreated patients.

## 08.1 Efficacy

### 8.1.1 Data from the French cohort

The French cohort includes 15 patients followed by the Paediatric Hepatology Department of Bicêtre UHC. The analysis relates to the 1993 to 2007 period.
Information concerning the period preceding the formal diagnosis and initiation of cholic acid (CA) was collected retrospectively. The diagnosis was suspected due to the existence of cholestasis with normal (or subnormal) γGT without pruritus, combined with lowered or normal serum bile acids. The diagnosis was confirmed with FAB or GC-MS (gas chromatography) of urine bile acids after ruling out other causes of cholestasis. Molecular confirmation was sought by analysis of the patient gene coding either for 3β-hydroxy-Δ5-C27-steroid oxidoreductase or $\Delta^4$-3-oxosteroid-5β-reductase.

**Endpoints**

**- Clinical evaluation** routinely including weight, height, intestinal transit, existence of pruritus, checking for hepatomegaly, splenomegaly, jaundice and deep tendon reflexes, performed before treatment and then every 3 months the first year, every 6 months up to the fifth year and then every year. For evaluation of overall survival, recourse to liver transplant was considered treatment failure.

**- Laboratory evaluation** of liver function: blood measured at the same frequency: AST, ALT, γGT, ALP, total and conjugated bilirubin, total bile acid, prothrombin time and factor V. A complete blood count, blood electrolytes, cholesterol, triglycerides and α-fetoprotein completed this assessment.
GC-MS was used to evaluate serum bile acids every year.
GC-MS was used to evaluate urine bile acids at the end of 3 months of treatment and then every 6 months in the next year and every year thereafter.

**- Abdominal ultrasound** was performed every year.

**- Histological evaluation** by biopsy was performed before the start of cholic acid treatment and at the end of 5 years of treatment. All biopsies conducted on patients were reread and re-analysed according to a standardised collection form by the same anatomical pathologist; the fibrosis stage and activity grade was evaluated on the METAVIR scale.[16]

[15] Gonzales E. Déficits héréditaires de synthèse des acides biliaires primaires : effets à long terme d'un traitement par l'acide cholique. MD thesis. Pierre and Marie Curie University Publicly defended 30 November 2006. No. 2006PA06S029.
[16] METAVIR Cooperative Study Group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. Hepatology 1994; 20: 15-20.

**Results**
A total of 13 patients had a 3β-HSD deficiency and 2 patients had a $\Delta^4$-3-oxoR deficiency (see Table 1).

The first symptoms generally appeared in the first months of life, between 0.1 and 0.9 years, a little later for four patients.
Once the diagnosis was established, the children were treated by cholic acid. Before the formal diagnosis, the patients were treated by ursodeoxycholic acid (UDCA) in order to prevent any primary bile acid overdose if one of these deficiencies was not confirmed. Moreover, some patients were not treated by the Bicêtre team until later and were treated by ursodeoxycholic acid, the only bile acid preparation then available.

**Table 1: Summary of the treatments administered for the 15 patients of the French cohort**

| Summary of treatments | | | | | | |
|---|---|---|---|---|---|---|
| | Age of the first symptoms | Age at diagnosis | Age UDCA | Age CA + UDCA | Age CA | Duration CA |
| **Patients with a 3β-hydroxy-$\Delta^5$-$C_{27}$-steroid oxidoreductase deficiency** | | | | | | |
| A | 0.3 | 3.4 | 0.3 | 3.9 | 4.4 | 20.0 |
| B | 0.1 | 3.6 | 3.6 | 4.3 | 4.9 | 20.0 |
| C | 3.9 | 7.8 | 4.2 | 7.8 | 8.3 | 20.0 |
| D1 | 0.5 | 3.1 | 3 | 4.3 | 4.8 | 20.0 |
| D2 | 0.4 | 0.4 | 0.5 | - | 0.55 | 10.6 |
| E1 | 0.9 | 4.8 | 3.8 | 5.3 | 5.8 | 20.0 |
| E2 | 0.75 | 13 | 10.3 | 13.1 | 13.6 | 20.0 |
| F | 1.75 | 2.1 | 2.2 | - | 2.3 | 17.4 |
| G1 | 2 | 2.1 | 2.2 | - | 2.3 | 17.4 |
| G2 | 2.4 | 11.5 | 11.6 | - | 11.7 | 17.4 |
| H | 0.2 | 0.2 | 0.2 | 0.3 | 1.3 | 16.3 |
| I1 | 0.5 | 5 | 4.8 | - | 5.2 | 12.0 |
| I2 | 0.1 | 0.1 | - | - | 0.2 | 11.3 |
| **Patients with a $\Delta^4$-3-oxosteroid-5β-reductase deficiency** | | | | | | |
| J1 | 0.1 | 0.4 | 0.4 | 0.8 | 1.9 | 16.0 |
| J2 | 0.1 | 0.4 | 0.4 | 0.8 | 1.9 | 16.0 |

*The following are specified by year: the age of the first symptoms suggesting the disease, the age of the patient at the time of diagnosis, the age of UDCA treatment initiation, the age CA was added, the age UDCA was discontinued and replaced with CA alone and the total duration of cholic acid treatment.*

The shortest duration of cholic acid treatment is 10.6 years, the longest is more than 20 years.

- ✓ **Initial characteristics of 13 patients with a 3β-HSD deficiency**

These 13 children come from 9 families. Parental consanguinity was known for four families. Among these four families, three had already lost a child due to a chronic progressive liver disorder.

The patients were still alive after a median treatment duration of 17.35 years with a documented return to normal quality of life. No patient underwent a liver transplant.

**Clinical data**
The mean weight was -0.39 SD, six patients had a weight less than or equal to -1 SD. The mean height was -0.38 SD, six patients had a height less than or equal to -1 SD.

**Laboratory data**
Total bilirubin was elevated in nine patients with a mean of 68.5 µmol/l (6 – 254; normal < 17). Conjugated bilirubin averaged 47.3 µmol/l (2-214, normal <5). AST values were on average 183 IU/l (25-1469, normal <45). ALT averaged 173 IU/l (16-1412, normal < 40). ALP averaged 455 [IU/l] (111-1165, normal < 320). GGT averaged 25.6 IU/l (normal < 30). A single patient had

liver function tests within normal limits, while two patients had minimal abnormalities in liver tests. Five patients had coagulation disorders, with a PR < 70%.
Steatorrhoea evaluated in 8 of 13 patients was abnormally elevated in 7 of them and normal in one. The mean value was 10.4 g/24 h (0.34-28; normal < 2.5 g/24 h).
In 10 patients tested for vitamin A or E deficiency, two had a vitamin A deficiency and eight had a vitamin E deficiency.
Total serum bile acid assay was normal or low in the nine patients for whom this assay was performed.

**Radiological data**
Liver ultrasound was normal in five patients. Hepatomegaly was present in eight patients, associated with splenomegaly in four patients. Nine patients had jaundice. One patient had radiological signs of rickets. Kidney ultrasound showed renal cysts in five patients.

**Histological data**
One patient had subnormal hepatic histology, two other patients had giant cell cholestatic hepatitis and 10 other patients had chronic active cholestatic liver disease.
Among the 12 pathological hepatic histologies, 12 patients had portal bridging fibrosis, severe in 10 of them, including one at the cirrhosis stage. Lobular fibrosis was also clear in these 12 patients. Liver disease was active histologically in 11 of these patients.
Hepatocyte cholestasis was seen in seven patients; there was indirect evidence of cholestasis in the other six (duct dilatation, pseudo-acinar formation, biliary metaplasia). No patient presented ductal proliferation suggesting obstructive cholestasis.

**Dosages**
Cholic acid was administered:
- either at the dose of 15 mg/kg/day combined with ursodeoxycholic acid (UDCA) for several months for the first six patients treated.
- or at a dose comprised between 5 and 15 mg/kg/day in combination for a short, even very short, period with UDCA or directly in monotherapy for the seven other patients.

At the start of treatment, the dose administered was progressively increased according to the clinical response as well as the urine concentration of atypical metabolites. It had to be reduced in a few patients due to signs of overdose (serum GGT and ALT elevation, pruritus, diarrhoea, elevated total serum bile acids).

- ✓ **Characteristics of patients with a 3β-HSD deficiency after 5 years of treatment by cholic acid**

Only the data from 12 patients could be completely analysed at the end of a mean treatment duration of 5.2 years (4.3-7.3).

**Clinical results**
The median age was 10 years (4.6-18.4). The mean weight was +1.1 SD and the mean height was +0.88 SD. A single patient had a smaller weight and/or height with negative SDs. In the 12 patients, 3 still had no deep tendon reflexes.

**Laboratory results**
Ten patients had normal hepatic biology. For two other patients, the only abnormality observed was an increase in total bilirubin, respectively to 37 and 25 µmol/l.
Mean serum bilirubin was 10.3 µmol/l (4-37). Transaminases and GGT were normal in all the patients. The mean PR was 87% (70-100).
Steatorrhoea evaluated in 7 of the 12 patients was normal (2.1 g/24 h on average (1.8 - 3.2)), except in one patient at 3.2 g/24 h. Vitamin E was 11.5 µmol/l on average (7.2-21.7), abnormal in five patients (too high, certainly due to supplementation). Total serum bile acid assay in all the patients was normal, below 5 µmol/l.

**Biochemical results**
The analysis of urine bile acids by GC-MS showed a reduction in the amount of total bile acids to 0.49 µmol/mmol of creatinine on average. On GC-MS analysis, total serum bile acids were normal (<5 µmol/l), essentially composed of deoxycholic acid and cholic acid.
Urine GC-MS examination showed a clear reduction in 3-oxo-$\Delta^4$ metabolite production.

**Radiological results**
The liver ultrasound performed in all the patients remained abnormal in two patients (isolated splenomegaly on ultrasound for one and isolated vesicular lithiasis for the other). No patient had hepatomegaly visible with ultrasound. Renal ultrasound was normal in all patients; in particular, the renal microcysts had completely regressed with treatment of 2 to 4 years in five patients. A pathophysiological role for the abnormal metabolites produced specifically in the case of 3β-HSD deficiency is suspected in the genesis of these cysts. Note that no impact on renal function was observed.

**Histological results**
The histological results show an improvement in all patients. While they presented cholestasis and, in 10 of them, very severe portal fibrosis before treatment initiation, the histological data recorded after a mean follow-up of 6.2 years of treatment (5.1-11.5 years) are improved very significantly.

- ✓ **Patients with a Δ4-3-oxosteroid-5β-reductase deficiency**

Two children, homozygous twins, with this deficiency are part of the Bicêtre UHC cohort. Their follow-up is 5 years. Treatment with bile acid was initiated from 4 weeks after birth.

**Dosage**
For the two patients with a $\Delta^4$-3-oxoR deficiency, cholic acid was administered:
- at the dose of 10 mg/kg/day in combination with UDCA the first year and then UDCA was discontinued for one of the patients and continued for the other.
- in monotherapy, the cholic acid dose was on average 12.9 mg/kg (2.3 18.9 mg/kg) at the start of treatment and then 5.5 mg/kg (2.5 9.8 mg/kg) as a result of the patient's development in age and weight.
The mean dosage of cholic acid was 5.3 mg/kg/day (4.8-5.7 mg/kg/day), mean total quantity per day: 225 mg).

The results on all the endpoint criteria, whether in terms of overall survival or clinical, biological or histological criteria, are positive. These two patients are still alive after more than 15 years of treatment, including 13 years with a normal quality of life, without having had a liver transplant. All other criteria show clear improvement.

### 8.1.2 Data from the literature

- One publication presents a summary of the response to cholic acid treatment in a group of 25 patients.[17] During diagnosis, the patients had various degrees of hyperbilirubinaemia, elevated transaminases and, on clinical examination, hepatosplenomegaly. The authors report the large number of patients with malabsorption of fat-soluble vitamins.

Some of these patients were treated with chenodeoxycholic acid (the only bile acid available at the time and used to dissolve gallstones). However, the appearance of diarrhoea in very young children as well as increased serum transaminases in some patients, led the authors to replace it with cholic acid.

The combination of ursodeoxycholic acid with cholic acid was also prescribed, on the assumption that the choleretic properties of ursodeoxycholic acid could offer an additional advantage by stimulating bile flow. However, it was observed that the reduction in abnormal metabolite production was insufficient when cholic acid was administered in combination with ursodeoxycholic acid. The limited efficacy of this combination could be explained by a competitive inhibition of intestinal absorption of cholic acid by ursodeoxycholic acid.

Reduction in the urine content of atypical metabolites is observed very quickly and transaminases become normal in the first months of treatment.
The authors conclude that treatment with cholic acid avoids liver transplant by re-establishing the regulation of bile acid synthesis. No adverse event was observed when cholic acid was used.

- A retrospective study conducted in the largest British referral centre for paediatric hepatology is the third largest cohort.[18] From a database pertaining to 1625 children, 18 cases of deficiencies were identified, 12 of which were boys (between 8 weeks and 11 years old). Two cases were excluded from analysis for lack of follow-up. Consanguinity was identified in six families.

Of the 16 cases retained, two children who were siblings were asymptomatic at diagnosis and had no apparent clinical signs of liver disease. In another set of siblings, two of the three children had a particularly severe clinical presentation of the disease but, in the absence of treatment, these children did not live to age 5.

The mean age of the 14 children (10 boys/4 girls), during the first consultation, was 8 weeks (from 2 to 36).
The clinical presentation was dominated by neonatal cholestasis, onset of rickets, steatorrhoea and often underdevelopment. Ten of these children had a vitamin D deficiency, as well as vitamin E (n=8) and vitamin A (n=6) deficiencies. Hepatic histology showed significant changes (giant cell hepatitis, canalicular cholestasis, portal fibrosis, etc.).

Five of these children were treated by a combination of cholic acid and chenodeoxycholic acid (7 mg/kg/day each), seven by chenodeoxycholic acid alone (7-18 mg/kg/day). The last child included, with severe symptoms, was treated by cholic acid alone (4 mg/kg/day, then 8 mg/kg/day at 1 month); chenodeoxycholic acid was ruled out due to its toxicity in the presence of severe hepatic dysfunction. Three children died before any treatment due to particularly severe liver failure.

After a mean follow-up of 3.5 years (between 1 and 17 years) 12 of the 13 children treated had no clinical signs or problems absorbing fat soluble vitamins and returned to normal growth. The last patient was lost to follow-up.

[17] Setchell KDR, Defects in bile acid synthesis - specific and treatable causes of metabolic liver disease, in Bile Acid Biology and Its Therapeutic Implications: Proceedings of the Falk Symposium 141 (XVIII International Bile Acid Meeting) Held in Stockholm, Sweden, June 18-19 2004, G. Paumgartner, et al., Editors. 2004, Springer. 3-16.
[18] Subramaniam P. et al. Variable clinical spectrum of the most common inborn error of bile acid metabolism--3beta-hydroxy-Delta 5-C27-steroid dehydrogenase deficiency. J Pediatr Gastroenterol Nutr 2010; 50: 61-6.

The authors conclude that early diagnosis is necessary in the presence of persistent neonatal cholestatic jaundice to identify a possible 3β-HSD deficiency.

- The company also presented data from two publications relating to one case study[19,20] and two publications[6,13] relating to three case studies. Since these are case studies, they are not discussed in this document.

## 08.2 Safety Adverse effects

### 8.2.1 Data from the French cohort

✓ **Patients with a 3β-HSD deficiency**

The mean dosage of cholic acid was 6.3 mg/kg/day (3-9 mg/kg/day, mean total quantity per day: 323 mg). The maximum dosage was 500 mg/day.
For four patients, signs of cholic acid overdose, documented by a total serum bile acid assay that was above normal (>50 µmol/l versus a normal value of <15 µmol/l), were observed.
Two episodes of symptomatic overdose occurred in one patient, of accidental origin (56 mg/kg in one dose or nearly 10 times the daily dose). Toxicity is clinically manifested by pruritus and diarrhoea and biologically manifested by an increase in GGT and transaminases. All these manifestations regressed in a few days after CA was discontinued, and then the CA could be reintroduced without incident.
Gallstones were reported in one patient.

In more than 180 cumulative patient-years of treatment at the time of analysis, no serious adverse event was reported.
Between 1993 and 2007, four pregnancies in two patients treated with cholic acid progressed satisfactorily with the birth of four healthy children.

### 8.2.2 SPC data

According to the SPC, the frequency of adverse effects is undetermined (cannot be estimated from the available data). The adverse effects appearing in the SPC are: diarrhoea, increased transaminases, gallstones and pruritus. Furthermore, the SPC states that the development of pruritus and/or diarrhoea was observed during ORPHACOL treatment. These reactions were attenuated after dose reduction and suggest an overdose. Gallstones were reported after long-term treatment.

### 8.2.3 Data from other sources

The analysis conducted on the data from patients followed in France (20 patients under a temporary authorisation for use) provides a follow-up of more than 280 treatment-years with ORPHACOL.

With dosages generally comprised between 5 and 20 mg/kg/day, no serious adverse event has been reported.

The side effects reported are mainly rare cases of pruritus or diarrhoea. These effects were likely linked to an overdose and resolved with a reduction of the dosage.

[19] Witzleben CL, Piccoli DA, Setchell K. A new category of causes of intrahepatic cholestasis. Pediatric Pathology. 1992; 12: 269-74.
[20] Kobayashi M, et al. 3beta-hydroxy-delta5-C27-steroid dehydrogenase/isomerase deficiency in a 23-year-old woman. Pediatr Int. 2000; 42(6): 685-8.

### 8.2.4 Risk Management Plan

CTRS, in agreement with the competent authorities of the Member States, has set up, in advance of launching, a programme to train physicians in the diagnosis and treatment of these two rare disorders, as well as the monitoring thereof.

This monitoring notably pertains to
- the legitimacy of the diagnosis,
- the therapeutic management of the treatment,
- the expected or potential risks related to the treatment and reporting thereof,
- the risks related to prescribing a supratherapeutic dose (MedDRA term: drug toxicity),
- the risk of gallstones.

The development of gallstones is considered a potential risk that will be monitored as part of the risk management plan.

As part of the RMP, the company is committed to developing a liquid form, more suited to young patients.

## 08.3 Usage/prescription data

Since 16 October 2007, the date of the first temporary authorisation for use, CTRS has received 20 requests for temporary authorisations for use by a named patient from the paediatric departments of four UHCs (Bicêtre, Beaujon, Aix en Provence and Marseilles) and three requests for patients not residing in France (two Italian patients that are siblings and one Portuguese patient).

These 20 patients include 15 patients of the Bicêtre UHC cohort presented in section 8.1.1.

As of December 2005, four new children, respectively aged 4 months, 4.5 years, 3.5 months and 15 years have been diagnosed with a 3β-HSD deficiency. These patients are all treated by cholic acid as monotherapy.

One of the two patients with a $\Delta^4$-3-oxoR deficiency initially on UDCA alone for 4 months has remained on the UDCA/CA combination for more than 16 years.
Currently, except for this last patient, all the patients under the temporary authorisation for use by a named patient are treated by cholic acid as a monotherapy. There is currently more than 20 years of experience with cholic acid treatment.
CTRS has set up a complete database (Orphabase) including the entire medical history of the patients since 1993 from diagnosis to the current day. This database, secured in compliance with the CNIL [Data Protection and Civil Rights Council] directives, is reserved for the use of clinicians treating these patients and will be used as part of the Risk Management Plan tied to the marketing authorisation. This database will be progressively expanded to all the clinicians of the Member States who see patients treated with ORPHACOL.

**Efficacy**

**All of the 20 patients treated and included in the Orphabase database are still alive after a median treatment time of 16.08 years.**

Clinically:
Cholic acid allows recovering normal height and weight development; this normalisation of growth is explained by correcting the intestinal malabsorption of fat-soluble vitamins, steatorrhoea and cholestasis, each individually responsible for a detrimental impact on weight and height development.

Hepatically:
- Jaundice regresses most often in a few weeks,

- Splenomegaly and hepatomegaly regress rapidly and resolve completely within a few years,
- Steatorrhoea returns to normal within a few weeks as well as the absorption of fat-soluble vitamins, reflecting the recovery of a pool of bile acids in the enterohepatic circulation. *(Since levels of fat-soluble vitamins A, D and E become normal in all patients, supplementation should be discontinued to avoid an overdose).*
- Liver function tests, bilirubin and transaminases most often return to normal within a few months in almost all the patients; however in a few cases, bilirubin fluctuates around the upper normal value, but without jaundice recurring. In both 3β-HSD and $\Delta^4$-3-oxoR deficiencies, on treatment, GC-MS shows a reduction of urine secretion of bile acids, reflecting the resolution of cholestasis with restoration of bile-acid dependent biliary secretion. In particular, it shows a substantial reduction in the amount of abnormal metabolites excreted in the urine relative to the reduction in their production obtained by feedback control of 7α-hydroxylase.
- The liver ultrasound returns to normal in the majority of patients.
- Problems with haemostasis regress in the majority of cases in a few months.

To date, no children treated have required liver transplant.

Pregnancies have been carried to term in three patients and led to the birth of seven healthy children. Monitoring by GC-MS throughout these pregnancies confirmed, in addition to treatment compliance, the maintenance of a good equilibrium of bile acid metabolism.

## 08.4 Summary & discussion

The available data on the use of cholic acid in the treatment of inborn errors in primary bile acid synthesis due to 3β-hydroxy-Δ5-C27-steroid oxidoreductase deficiency or $\Delta^4$-3-oxosteroid-5β-reductase deficiency in infants, children, adolescents and adults come from:
- a publication concerning a cohort of 15 patients followed by the Paediatric Hepatology Department of the Bicêtre University Hospital Centre (AP-HP) from 1993 to 2007[4,21].
- analysis of the database created by CTRS (Orphabase) from information sent by clinicians including 20 patients followed in France.
- data from the literature.

Regarding patients followed at Bicêtre UHC, a total of 13 patients had a 3β-HSD deficiency and two patients had a $\Delta^4$-3-oxoR deficiency.
The first symptoms generally appeared in the first months of life, between 0.1 and 0.9 years, a little later for four patients. Once the diagnosis was established, the children were treated by cholic acid. Before the formal diagnosis, the patients were treated by ursodeoxycholic acid (UDCA) in order to prevent any primary bile acid overdose if one of these deficiencies was not confirmed. Moreover, some patients were not treated by the Bicêtre team until later and were treated by ursodeoxycholic acid, the only bile acid preparation then available.
The mean dosage of cholic acid in patients with a 3β-HSD deficiency was 6.3 mg/kg/day (3-9 mg/kg/day, mean total quantity per day: 323 mg). The maximum dosage was 500 mg/day.

Analysis of data from this cohort and the Orphabase database shows progressive improvement in the clinical and biological parameters of patients treated with cholic acid, notably:
- recovery of normal height and weight development,
- regression of jaundice, splenomegaly and hepatomegaly,
- return to normal of steatorrhoea and absorption of fat-soluble vitamins,
- return to normal of liver function parameters,
- regression of haemostasis disorders.

[21] Gonzales E. Déficits héréditaires de synthèse des acides biliaires primaires : effets à long terme d'un traitement par l'acide cholique. MD thesis. Pierre and Marie Curie University. Publicly defended 30 November 2006. No. 2006PA06S029.

None of the patients followed required liver transplant.

For the two patients with a $\Delta^4$-3-oxoR deficiency, the mean dosage of cholic acid was 5.3 mg/kg/day (4.8-5.7 mg/kg/day, mean total quantity per day: 225 mg). The results on all the endpoints, whether overall survival or clinical, biological or histological criteria, are positive. These two patients are still alive after more than 15 years of treatment, including 13 years with a normal quality of life, without having had a liver transplant. All other criteria show clear improvement.

All of the 20 patients treated and included in the Orphabase are still alive after a median treatment time of 16.08 years.

Within the Bicêtre UHC cohort, four patients with a 3β-HSD deficiency showed signs of cholic acid overdose, documented by a total serum bile acid assay that was above normal (>50 µmol/l versus a normal value of <15 µmol/l).
Toxicity is clinically manifested by pruritus and diarrhoea and biologically manifested by an increase in GGT and transaminases. All these manifestations regressed in a few days after CA was discontinued, and the CA was subsequently reintroduced without incident.
Gallstones were reported in one patient.
Cortical and medullary renal microcysts were reported in 5 of 13 patients. These cysts regressed in all patients within 2 to 4 years.

The analysis of the data from patients followed in France (20 patients under a temporary authorisation for use) provides more than 280 treatment-years of experience with ORPHACOL. With doses generally comprised between 5 and 20 mg/kg/day, no serious adverse event has been reported. The side effects reported are mainly rare cases of pruritus or diarrhoea. These effects were likely linked to an overdose and resolved with a reduction of the dosage. Pregnancies have been carried to term in three patients and led to the birth of seven healthy children.

## 08.5 Planned studies

CTRS has committed to monitoring the safety and efficacy of the medicine in patients treated with ORPHACOL from the patient monitoring database (Orphabase), on the basis of a protocol documented in the RMP and approved by the CHMP.

Summary reports relating to patients enrolled in the database created by CTRS will be analysed and sent to the CHMP at the same time as the PSURs and the annual re-assessments of ORPHACOL's risk/benefit ratio.
This is not a post-authorisation safety study or a patient registry.

# 09 THERAPEUTIC USE

Two therapeutic strategies can be envisaged for treating 3β-HSD or $\Delta^4$-3-oxoR deficiencies: treatment with bile acids or liver transplant, a difficult procedure with major sequelae.

There are multiple objectives of cholic acid administration for treating these deficiencies:
- reducing the production of highly hepatotoxic and cholestatic atypical metabolites by re-establishing negative feedback control on the key enzyme for bile acid synthesis, cholesterol 7α-hydroxylase,
- normalising liver tissue,
- reconstituting a physiological pool of bile acids to ensure intestinal absorption of fats and fat-soluble vitamins,
- promoting bile acid-dependent bile secretion by re-establishing its normal constitution,
- improving the child's growth by correcting malabsorption of fats and fat-soluble vitamins,
- correcting rickets,
- avoiding recourse to liver transplant, or even patient death.

Cholic acid has been used for the treatment of 3β-HSD or $\Delta^4$-3-oxoR deficiencies for more than 20 years (since 1993, in the form of a hospital preparation and since 2007 under a temporary authorisation for use by a named patient).

There is an international consensus in the literature to confirm that cholic acid is the treatment of choice for 3β-HSD deficiency.

In $\Delta^4$-3-oxoR deficiency, except for one patient, for all the cases reported in the literature cholic acid was effective, alone or in combination. In France, in the three patients treated for this deficiency, two are currently on ORPHACOL monotherapy. For some patients, the combination of a low dose of ursodeoxycholic acid (4 mg/kg) may sometimes be necessary[4,6,7,22,23].

ORPHACOL, the first cholic acid based proprietary medicinal product administered in the form of oral capsules, is the gold standard treatment for 3β-HSD or Δ4-3-oxoR deficiencies. This is a lifelong treatment.

[22] Setchell KD et al. Identification of a new inborn error in bile acid synthesis: mutation of the oxysterol 7alpha-hydroxylase gene causes severe neonatal liver disease. J Clin Invest. 1998; 102(9): 1690-703.
[23] Balistreri WF. Inborn errors of bile acid biosynthesis Clinical and therapeutic aspects. In Bile Acids in Gastroenterology Basic and Clinical Advances, A.F Hofmann, G. Paumgartner, and A. Stiehl, Editors. 1995, Kluwer Academic Publishers: London. p. 333-353.

# 010 TRANSPARENCY COMMITTEE CONCLUSIONS

**In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:**

## 010.1 Actual benefit

◗ In the absence of treatment, 3β-HSD and $\Delta^4$-3-oxoR deficiencies are most often fatal in childhood.

◗ ORPHACOL, hard capsules, is a symptomatic therapy of inborn errors in primary bile acid synthesis due to 3β-HSD or $\Delta^4$-3-oxoR deficiencies.

◗ The efficacy/adverse effects ratio for ORPHACOL medicinal products is substantial.

◗ There is no pharmacological treatment alternative. The only alternative is surgical, with liver transplant.

◗ ORPHACOL, the first cholic acid based proprietary medicinal product administered in the oral capsule form, is the gold standard treatment for these deficiencies.

◗ Public health benefit:

Inborn errors in primary bile acid synthesis due to 3β-hydroxy-Δ5-C27-steroid oxidoreductase or $\Delta^4$-3-oxosteroid 5β reductase deficiencies are disorders that almost always have a fatal outcome in the absence of treatment. However, due to their rarity (fewer than 0.07 cases per 10,000 residents in the European Union), they constitute a low public health burden at best.
Improvement in the management of orphan diseases is part of the Plan National Maladies Rares [National Rare Diseases Plan] 2011-2014, and also the treatment of this disorder is a public health need.
In view of the available data (in particular data resulting from temporary authorisations for use), the expected impact of ORPHACOL on the morbidity and mortality of treated patients is substantial. Its expected impact on quality of life has not been documented by use of a validated instrument and cannot be quantified. Since this treatment can delay or avoid liver transplants, the only current alternative, ORPHACOL is expected to have an impact on healthcare organisation. However, in the absence of data, this impact cannot be quantified.
Since the data presented relate to very small numbers of subjects, the transposability of data to everyday practice cannot be guaranteed.
ORPHACOL therefore provides a partial response to an identified public health need.
Consequently, due, in particular, to the very small number of patients affected by the diseases for which ORPHACOL is indicated, it is not expected that this proprietary medicinal product will benefit public health in this indication.

**Taking account of these points, the Committee considers that the actual benefit of ORPHACOL is substantial in the treatment of inborn errors in primary bile acid synthesis due to 3β-hydroxy-$\Delta^5$-$C_{27}$-steroid oxidoreductase deficiency or $\Delta^4$-3 oxosteroid-5β-reductase deficiency in infants, children and adolescents aged 1 month to 18 years and adults.**

**The Committee recommends inclusion on the list of medicines approved for hospital use in the indication and at the dosages in the Marketing Authorisation.**

## 010.2 Improvement in actual benefit (IAB)

The benefits of using cholic acid in the treatment of inborn errors in primary bile acid synthesis due to 3β-hydroxy-Δ5-C27-steroid oxidoreductase deficiency or $\Delta^4$-3 oxosteroid-5β-reductase deficiency as soon as they are diagnosed have been established since 1993, when the first hospital preparation was made available in France by the AP-HP and then under a temporary authorisation for named patient use since 2007. In particular, none of the 20 patients followed in France and treated with cholic acid since this date have needed liver transplant, the only other treatment option. Treatment with cholic acid allows deferring liver transplantation and improving overall symptomatology, normalising lab work results and improving histological liver lesions, with good safety. Several women treated have carried pregnancies to term and given birth to healthy children.
There is an absence of a treatment alternative, other than resorting to liver transplant, for these inborn deficiencies with fatal outcome in the early years of life without treatment. The Transparency Committee considers that the ORPHACOL proprietary medicinal products provide a major improvement in actual benefit (IAB I) in the therapeutic strategy.

## 010.3 Target population

3β-HSD and $\Delta^4$-3-oxoR deficiencies are extremely rare: international literature data have established, on the one hand, that these pathologies are strongly linked to consanguinity, and on the other hand that they are generally fatal, in the early years of life. Due to the frequent lack of reporting, an estimate of mortality is impossible.

Given the extreme rarity of these diseases and the absence of a registry, it is very difficult to give a reliable estimate of epidemiological parameters. Taking data from the cohort of patients diagnosed and followed in the Bicêtre Hospital department (Paris), we can deduce that the cumulative incidence of these two deficiencies in France is around one patient per year (20 patients in 20 years).
By taking data from the French and British cohort, the prevalence in Europe can be estimated to be less than 0.003/10,000 for 3β-HSD and around 0.0003/10,000 for $\Delta^4$-3-oxoR deficiencies. Therefore, for each deficiency respectively, the number of patients can be estimated at 100 and 15 patients for Europe in 28 countries.

Between March 2003 and January 2013, only two new cases have been diagnosed in France: one 3β-HSD deficiency and one $\Delta^4$-3-oxoR deficiency.

In France, the number of patients followed is currently 17. A population increase of one patient per year, at a maximum, can be envisaged.

# 011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

### ◗ Packaging

Appropriate for the prescription conditions as regards the indication, dosage and treatment duration.