1. NAME OF THE MEDICINAL PRODUCT

CHOLBAM 50 mg

CHOLBAM 250 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 50 mg of cholic acid.

Each hard capsule contains 250 mg of cholic acid.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

CHOLBAM is available in two capsule strengths:

•50 mg capsule: Swedish Orange size 2 hard gelatin capsule with cap imprinted with “50mg” and body imprinted with “ASK001”. The capsules contain a white to off-white powder.

•250 mg capsule: White opaque size 0 hard gelatin capsule with a cap imprinted with “250mg” and body imprinted with “ASK002”. The capsules contain a white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Cholbam is indicated for the treatment in infants, children, adolescents aged 1 month to 18 years and adults of inborn errors in primary bile acid synthesis due to Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency,
- 2- (or α-) methylacyl-CoA racemase (AMACR) deficiency
- Cholesterol 7α -hydroxylase (CYP7A1) deficiency
- 3β-hydroxy-5-C27-steroid oxidoreductase deficiency (also known as 3β-hydroxy-5-C27-steroid dehydrogenase/isomerase or 3β-HSD or HSD3β7.

4.2 Posology and method of administration

Treatment must be initiated and monitored by physicians, including paediatricians, experienced in the management of the specific deficiencies.

Posology

The recommended dosage for cholic acid in the treatment of inborn errors of primary bile acid synthesis is 10-15 mg/kg per day, either as a single daily dose or in divided doses, for both adult and paediatric patients. The dose should be subsequently titrated to the desired effect but should not exceed a maximum of 15mg/kg/day.

Where the dose calculated is not a multiple of 50, the nearest dose below the maximum of 15mg/kg/day should be selected, provided that is sufficient to suppress urinary bile acids. If not, the next higher dose should be selected.
The recommended dosage in patients with concomitant familial hypertriglyceridemia is 11 to 17 mg/kg once daily or in two divided doses and is adjusted based on clinical response.
• Monitor AST, ALT, GGT, alkaline phosphatase, bilirubin and INR every month for the first

3 months, every 3 months for the next 9 months, every 6 months during the next three years and annually thereafter. Administer the lowest dose that effectively maintains liver function
• Discontinue CHOLBAM if liver function does not improve within 3 months of starting treatment, if complete biliary obstruction develops, or if there are persistent clinical or laboratory indicators of worsening liver function or cholestasis; continue to monitor liver function and consider restarting a lower dose when parameters return to baseline.

During the initiation of therapy and dose adjustment, serum and urine bile acid levels should be monitored intensively using gas chromatography-mass spectrometry (GC-MS) or equivalent technology coupled to mass spectrometry. The concentrations of the abnormal bile acid metabolites synthesised subesquently should be determined. 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 Cholic acid FGK. The dose should be adjusted accordingly, as described above.

Liver parameters should also be monitored. Concurrent elevation of serum gamma glutamyltransferase (Gamma GT), 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 Gamma GT is not elevated and if serum bile acid levels are falling or in the normal range.

After the initiation period, serum and 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

Special populations

Patients with familial hypertriglyceridaemia
Patients with newly diagnosed or a family history of familial hypertriglyceridaemia are expected to poorly absorb cholic acid from the intestine. The cholic acid dose for patients with familial hypertriglyceridaemia will have to be established and adjusted as necessary, an elevated dose may be required in order to suppress urinary bile acids.

Paediatric population
The safety and efficacy of cholic acid in neonates less than one month of age has not been established. No data are available.

Elderly patients (older than 65 years)
The safety and efficacy of cholic acid in elderly patients has not been established. No data available.

Renal impairment
No data are available for patients with renal impairment. However, these patients should be carefully monitored and the dose of cholic acid titrated individually.

Hepatic impairment
The majority of patients with inborn errors of bile acid metabolism presented with some degree of hepatic impairment at the time of diagnosis; in most patients, the hepatic impairment improved or resolved with treatment. The dose of cholic acid should be adjusted individually.

No data regarding cholic acid treatment are available in patients with inborn errors of bile acid metabolism with hepatic impairment unrelated to their primary disease. In the absence of clinical experience in such patients population, no recommendations on dosage adjustment can be made. Patients with hepatic impairment unrelated to their primary disease who are treated with cholic acid are monitored closely.

Method of administration
It is recommended that cholic acid is taken with food at approximately the same time each day, in the morning and/or evening. The capsules should be swallowed whole with water.
Use in the pediatric population.
For infants and children who cannot swallow capsules, the capsule may be opened gently and the contents mixed with food. For young infants the contents may be mixed with infant formula, expressed breast milk or fruit puree and for infants and children under 6 years, mixed with soft food such as mashed potatoes or apple puree. The mixture should be administered immediately after preparation. Mixing of the capsule contents is designed to mask any unpleasant taste which results from the capsules being opened but no data on the compatibility or palatability are available. The capsule contents will remain as fine granules in the milk or food.

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

5. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 16.1

6. WARNINGS AND PRECAUTIONS

6.1 Exacerbation of Liver Impairment

In clinical trials, evidence of liver impairment was present before treatment with CHOLBAM in approximately 86% (44/51) of patients with bile acid synthesis disorders due to SEDs and in approximately 50% (14/28) of patients with PDs including Zellweger spectrum disorders. Five of the patients (3SED and 2 PD) with liver impairment at baseline experienced worsening serum transaminases, elevated bilirubin values, or worsening cholestasis on liver biopsy following treatment. Five additional patients (2 SED and 3 PD) who did not have baseline cholestasis experienced exacerbation of their liver disease while on treatment. In patients with cirrhosis, cases of severe hepatotoxicity have also been observed following postmarket use of CHOLBAM. Exacerbation of liver impairment by CHOLBAM in these patients cannot be ruled out.

Six patients with SEDs underwent liver transplant, including four patients diagnosed with AKR1D1 deficiency, one with 3β-HSD deficiency, and one with CYP7A1 deficiency.

Concurrent elevations of serum GGT and ALT may indicate CHOLBAM overdose.

Monitor liver function and discontinue CHOLBAM in patients who develop worsening of liver function while on treatment. Discontinue treatment with CHOLBAM at any time if there are clinical or laboratory indicators of worsening liver function or cholestasis.

7. ADVERSE REACTIONS

The following clinically significant adverse reaction is described elsewhere in the labeling:

- Exacerbation of Liver Impairment

7.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical safety experience with CHOLBAM consists of:

- Trial 1: a non-randomized, open-label, single-arm trial of 50 patients with bile acid synthesis disorders due to SEDs and 29 patients with PDs including Zellweger spectrum disorders. Safety data are available over the 18 years of the trial.
- Trial 2: an extension trial of 12 new patients (10 SED and 2 PD) along with 31 (21 SED and 10 PD) patients who rolled over from Trial 1. Safety data are available for 3 years and 11 months of treatment.

Adverse events were not collected systematically in either of these trials. Most patients received an oral dose of 10 to 15 mg/kg/day of CHOLBAM.

Deaths

In Trial 1, among the 50 patients with SEDs, 5 patients aged 1 year or less died, which included three patients originally diagnosed with AKR1D1 deficiency, one with 3β-HSD deficiency and one with CYP7A1 deficiency. The cause of death was attributed to progression of underlying liver disease in every patient.

Two additional patients in Trial 1 (1 SED and 1 PD) died who had been off study medication for more than one year with the cause of death most likely being a progression of underlying liver disease. Of the patients who died with disease progression, laboratory testing showed abnormal serum transaminases, bilirubin, or cholestasis on liver biopsy suggesting worsening of their underlying cholestasis.

In Trial 2, among the 31 patients with SED, two patients (1 new patient and 1 who rolled over from Trial 1) died. The cause of death in both cases was unrelated to their primary treatment or progression of their underlying liver disease.

Worsening of Liver Impairment

Seven patients in Trial 1 (4 SED and 3 PD) and 3 patients in Trial 2 (1 SED and 2 PD) experienced worsening serum transaminases, elevated bilirubin values, or worsening cholestasis on liver biopsy during treatment.

Common Adverse Reactions

There were 12 adverse reactions reported across 9 patients in the trials, with diarrhea being the most common reaction in approximately 2% of the patient population. All other adverse reactions represented 1% of the patient population. The breakdown by trial follows:

Table 1: Most Common Adverse Reactions in Trials 1 and 2

Adverse Reactions	Trial 1	Trial 2*	Overall n (%)
Diarrhea	1	2*	3 (2)
Reflux Esophagitis	1	0	1 (1)
Malaise	1	0	1 (1)
Jaundice	1	0	1 (1)
Skin lesion	1	0	1 (1)
Nausea	0	1*	1 (1)
Abdominal Pain	0	1*	1 (1)
Intestinal Polyp	0	1*	1 (1)
Urinary Tract Infection	0	1*	1 (1)
Peripheral Neuropathy	0	1	1 (1)

*Adverse reactions that occurred in new patients

Only one of the reactions (peripheral neuropathy) resulted in discontinuation of medication for a patient in Trial 2. An additional five SED patients (3 from Trial 1 and 2 from Trial 2) and 1 PD patient (Trial 1) discontinued medication and withdrew from the study due to a worsening of their primary disease.

The development of symptomatic cholelithiasis requiring cholecystectomy has been reported in a single patient with 3β-HSD deficiency.

7.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of CHOLBAM. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their relative frequency or to establish a causal relationship to CHOLBAM exposure:

- *Gastrointestinal disorders*: discomfort and distention, emesis, constipation

- *General disorders and administrative site conditions*: pyrexia/fever
- *Skin and subcutaneous tissue disorders*: rash

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

8. DRUG INTERACTIONS

8.1 Effects of Other Drugs on CHOLBAM

Drug interactions with CHOLBAM mainly relate to agents capable of interrupting the enterohepatic circulation of bile acids.

Inhibitors of Bile Acid Transporters
Avoid concomitant use of inhibitors of the bile salt efflux pump (BSEP) such as cyclosporine. Concomitant medications that inhibit canalicular membrane bile acid transporters such as the BSEP may exacerbate accumulation of conjugated bile salts in the liver and result in clinical symptoms. If concomitant use is deemed necessary, monitoring of serum transaminases and bilirubin is recommended.

Bile Acid Binding Resins
Bile acid binding resins such as cholestyramine, colestipol, or colesevelam adsorb and reduce bile acid absorption and may reduce the efficacy of CHOLBAM. Should the use of a preparation containing a bile acid binding resin be necessary, it must be taken at least 5 hours before or after cholic acid.

Aluminum-Based Antacids
Aluminum-based antacids have been shown to adsorb bile acids *in vitro* and can reduce the availability of CHOLBAM. Should the use of a preparation containing an aluminum-based antacid be necessary, it must be taken at least 5 hours before or after cholic acid.

9. USE IN SPECIFIC POPULATIONS

9.1 Pregnancy

Risk Summary
No studies in pregnant women or animal reproduction studies have been conducted with CHOLBAM. Limited published case reports discuss pregnancies in women taking cholic acid for 3β-HSD deficiency resulting in healthy infants. These reports may not adequately inform the presence or absence of drug-associated risk with the use of CHOLBAM during pregnancy.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

9.2 Lactation

Risk Summary

Endogenous cholic acid is present in human milk. Clinical lactation studies have not been conducted to assess the presence of CHOLBAM in human milk, the effects of CHOLBAM on the breastfed infant, or

the effects of CHOLBAM on milk production. There are no animal lactation data and no data from case reports available in the published literature. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CHOLBAM and any potential adverse effects on the breastfed infant from CHOLBAM or from the underlying maternal condition.

9.3 Geriatric Use

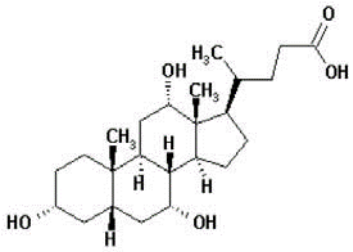
Clinical studies of CHOLBAM did not include any patients aged 65 years and over. It is not known if elderly patients respond differently from younger patients.

10. OVERDOSAGE

Concurrent elevations of serum GGT and ALT may indicate CHOLBAM overdose. If an overdose is suspected, discontinue CHOLBAM and treat symptoms. Continue to monitor laboratory parameters of liver function and consider restarting at a lower dose when the parameters return to baseline.

11. DESCRIPTION

Cholic acid is a bile acid produced by the liver where it is synthesized from cholesterol. The chemical formula is $C_{24}H_{40}O_5$, the molecular weight is 408.57 and the chemical structure is:



Cholic acid is a white to off-white powder. It is practically insoluble in water and in 0.1 M HCl at 20°C and is sparingly soluble in 0.1 M NaOH at 20°C. It is soluble in glacial acetic acid, alcohols, and acetone. A saturated solution in water at 20°C has a pH of 4.4.

CHOLBAM capsules contain 50 mg or 250 mg of cholic acid as the active ingredient in size 2 Swedish orange or size 0 white opaque gelatin capsules, respectively. Inactive ingredients in CHOLBAM include silicified microcrystalline cellulose, magnesium stearate, and hard gelatin capsules. The size 2 shells contain gelatin, red iron oxide and titanium dioxide, and the size 0 shells contain gelatin and titanium dioxide. CHOLBAM is administered orally.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cholic acid is a primary bile acid synthesized from cholesterol in the liver. In bile acid synthesis disorders due to SEDs in the biosynthetic pathway, and in PDs including Zellweger spectrum disorders, deficiency of primary bile acids leads to unregulated accumulation of intermediate bile acids and cholestasis. Bile acids facilitate fat digestion and absorption by forming mixed micelles and facilitate absorption of fat-soluble vitamins in the intestine.

Endogenous bile acids including cholic acid enhance bile flow and provide the physiologic feedback inhibition of bile acid synthesis. The mechanism of action of cholic acid has not been fully established; however, it is known that cholic acid and its conjugates are endogenous ligands of the nuclear receptor, farnesoid X receptor (FXR). FXR regulates enzymes and transporters that are involved in bile acid synthesis and in the enterohepatic circulation to maintain bile acid homeostasis under normal physiologic conditions.

12.2 Pharmacokinetics

Orally administered cholic acid is subject to the same metabolic pathway as endogenous cholic acid.

Cholic acid is absorbed by passive diffusion along the length of the gastrointestinal tract. Once absorbed, cholic acid enters into the body's bile acid pool and undergoes enterohepatic circulation mainly in conjugated forms.

In the liver, cholic acid is conjugated with glycine or taurine by bile acid-CoA synthetase and bile acid-CoA:amino acid N-acyltransferase. Conjugated cholic acid is actively secreted into bile by the BSEP, and then released into the small intestines, along with other components of bile.

Conjugated cholic acid is mostly re-absorbed in the ileum mainly by the apical-sodium-dependent-bile acid transporter, passed back to the liver by transporters including sodium-taurocholate cotransporting polypeptide and organic anion transport protein and enters another cycle of enterohepatic circulation. Any conjugated cholic acid not absorbed in the ileum passes into the colon where deconjugation and 7-dehydroxylation are mediated by bacteria to form cholic acid and deoxycholic acid, which may be re-absorbed in the colon or excreted in the feces. The loss of cholic acid is compensated by de-novo synthesis of cholic acids from cholesterol to maintain the bile acid pool in healthy subjects.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, genetic toxicology, and nonclinical fertility studies have not been performed with cholic acid.

13.2 Animal Toxicology and/or Pharmacology

In the $PEX2^{-/-}$ mouse model of peroxisomal disorders, feeding with a combination of cholic acid and ursodeoxycholic acid normalized C24 bile acid concentrations in bile to that of untreated control animals. Although growth was only mildly improved, there was near complete normalization of stool fat content, resolution of steatorrhea, and improved survival. Bile acid feeding reduced the number of cholestatic deposits in bile ducts and alleviated cholangitis but exacerbated the degree of hepatic steatosis and mitochondrial and cellular damage in the peroxisome-deficient livers of these animals.

14. CLINICAL STUDIES

14.1 Bile Acid Synthesis Disorders due to Single Enzyme Defects

The effectiveness of CHOLBAM at dosages of 10 to 15 mg/kg per day in patients with SEDs was assessed in:

- Trial 1: a non-randomized, open-label, single-arm trial in 50 patients over an 18-year period
- Trial 2: an extension trial of 12 new patients along with 21 patients who rolled over from Trial 1 (n=33 total). Efficacy data are available for 21 months of treatment.
- A published case series of 15 patients with SEDs and 3 patients with PDs.

Enrollment criteria in Trials 1 and 2 were based on abnormal urinary bile acid by Fast Atom Bombardment ionization-Mass Spectrometry (FAB-MS).

Pre- and post-treatment liver biopsies were performed in a limited number of patients. Documentation of adherence to treatment, concomitant medications, and response to treatment were incomplete in Trial 1. Additional interventions in some patients included supplementation with fat-soluble vitamins, as dictated by the patient's clinical signs and symptoms.

Trials 1 and 2

On average, patients were 4 years of age at the start of cholic acid treatment (range three weeks to 36 years). The majority of patients were treated for an average of 310 weeks (6 years). Patient ages at the end of treatment ranged from 19 to 36 years.

These trials were carried out over many years, and data are not available on all patients. Thirty-nine patients in Trial 1 and 5 new patients in Trial 2 received at least one dose of CHOLBAM and had sufficient data available to assess baseline liver function and effects of CHOLBAM treatment. A responder analysis was performed to determine the response to treatment with CHOLBAM.

Response to CHOLBAM treatment was assessed by the following laboratory criteria:

(1) ALT or AST values reduced to less than 50 U/L, or baseline levels reduced by 80%;
(2) total bilirubin values reduced to less than or equal to 1 mg/dL; and
(3) no evidence of cholestasis on liver biopsy;

and the following clinical criteria:

(1) body weight increased by 10% or stable at greater than the 50th percentile; and
(2) survival for greater than 3 years on treatment or alive at the end of Trial 2.

CHOLBAM responders were defined as patients who either:

(1) met at least two laboratory criteria and were alive at the last follow-up; or
(2) met at least one laboratory criteria, had increased body weight, and were alive at the last follow-up.

Overall, 28 of 44 patients (64%) were responders. The breakdown by defect type is as follows:

Table 2: Response to CHOLBAM Treatment by Type of Single Enzyme Defect

Single Enzyme Defect	Responders/Number Treated (%)
3□-HSD	22/37 (59%)
AKR1D1	3/4 (75%)
CTX	2/2 (100%)
AMACR	1/1 (100%)
CYP7A1	N/A*
Smith-Lemli-Opitz	N/A*

* N/A indicates no evaluable patients in the defect subgroup are represented.

Among SED responsive patients, 45% of the responders met the two clinical criteria plus 1 to 3 laboratory criteria and 55% met the weight criteria.

Only six patients had pre- and post-treatment liver biopsies in Trial 1. Where biopsies were available, pre-treatment biopsies showed varying degrees of inflammation, bridging fibrosis, and giant cell formation. Post-treatment biopsies generally showed reduced or absent inflammation and reduced or absent giant cell formation. Fibrosis remained but did not progress.

It is difficult to evaluate long term survival in patients with SEDs since there is little natural history survival data for comparison. Overall, 41 of 62 (67%) patients with SEDs survived greater than 3 years from trial entry. Thirteen of these 41 patients (32%) survived for 10 to 24 years on treatment.

Four patients in Trial 1 underwent liver transplant, including two patients diagnosed with AKR1D1 deficiency, one with 3β-HSD deficiency, and one with CYP7A1 deficiency and two patients in Trial 2, both with AKR1D1.

CHOLBAM's effects on extrahepatic manifestations of SEDs, such as neurologic symptoms have not been established.

Case Series

A published report of a case series described 15 patients with SEDs; thirteen were diagnosed with 3β-HSD deficiency and two with AKR1D1 deficiency by mass spectrometry and gene sequencing. All patients were treated with cholic acid with a median duration of treatment of 12.4 years (range 5.6 to 15 years). Therapy started at a median age of 3.9 years (range 0.3 to 13.1 years). The mean dose at the start of cholic acid treatment was 13 mg/kg and the mean dose at last follow up was 6 mg/kg. Eight patients were initially treated with oral ursodeoxycholic acid prior to receiving a diagnosis of bile acid synthesis defect, after which they were switched to cholic acid. Initial signs and symptoms included jaundice, hepatosplenomegaly, steatorrhea, or symptoms related to deficiency of a fat-soluble vitamin (K, D or E).

Of the 8 patients who received ursodeoxycholic acid initially, the six with 3β-HSD deficiency demonstrated mild clinical improvement. Following treatment with cholic acid, all patients experienced resolution of their pre-existing jaundice and steatorrhea, and all but one experienced resolution of hepatosplenomegaly. Weight and height improved, and sexual maturation progressed normally in all patients. Liver biopsies were performed in 14 patients after at least 5 years of cholic acid treatment and all showed resolution of cholestasis. In one patient with 3β-HSD deficiency, biliary bile acid analysis while on cholic acid therapy showed enrichment of the bile with cholic acid.

15. HOW SUPPLIED/STORAGE AND HANDLING

15.1 List of excipients

Capsule content

Silicified microcrystalline cellulose (Prosolv SMCC 90)

Magnesium stearate

50 mg Capsule shell

Gelatin

Red iron oxide (E172)

Titanium dioxide (E171)

250 mg Capsule shell

Gelatin

Titanium dioxide (E171)

15.2 Shelf life

The expiry date of the product is indicated on the packaging materials.

Once the bottle is opened, the medicinal product must be used within 3 months.

15.3 Special precautions for storage

Do not store above 25°C.

Store in original package in order to protect from light.

16. MANUFACTURER

Pantheon Pharmaceuticals Inc. 2110 East Galbraith Rd, Cincinnati. OH 45237, USA

17. MARKETING AUTHORISATION HOLDER

Megapharm LTD, Hatidhar St. 15, Ra'anana, Israel.

18. MARKETING AUTHORISATION NUMBER(S)

155-88-34268, 155-89-34270

Revised on November 2022 according to the IL MOH guidelines.