The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by it on May 2016

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.

50 mg capsule: Size number 2 capsule with a Swedish orange cap and body. The capsules contain a white powder.
250 mg capsule: Size number 0 capsule with a white cap and white body. The capsules contain a 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 (2.2)
• 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 (see section 4.6).

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 (see section 4.4)

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 (see section 4.5) at approximately the same time each day, in the morning and/or evening. The capsules should be swallowed whole with water. For infants and children who cannot swallow capsules, the capsules may be opened and the content added to infant formula or juice. For additional information, see section 6.6.

4.3 Contraindications

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

Concomitant use with phenobarbital (see section 4.5).

4.4 Special warnings and precautions for use

Treatment with cholic acid should be stopped if in case of abnormal hepatocellular function, as measured by prothrombin time, hepatocellular function does not improve within 3 months of the initiation of cholic acid treatment. A concomitant decrease of urine total bile acids should be observed. Treatment should be stopped earlier if there are clear indicators of severe hepatic failure.

Familial hypertriglyceridemia
Patients with newly diagnosed, or a family history of, familial hypertriglyceridaemia may have poor absorption of cholic acid from the intestine. The cholic acid dose for patients with familial triglyceridaemia will have to be established and adjusted as necessary (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies with cholic acid and concomitantly administered medicinal products or food have been carried out.

Phenobarbital has been shown to increase the pool size and turnover of cholic acid and therefore has an antagonistic effect to the desired action of cholic acid in patients. Therefore use of phenobarbital in patients treated with cholic acid is contraindicated (see section 4.3).

Drug interactions with cholic acid mainly relate to medicinal products capable of interrupting the enterohepatic circulation of bile acids, such as the sequestering agents cholestyramine, colestipol, or colesevalem. Aluminium-based antacids have been shown to adsorb bile acids *in vitro* and may be expected to reduce the levels of cholic acid in the same manner as the bile acid sequestering agents. Should the use of a preparation containing one of these substances be necessary, it must be taken at least 5 hours before or after cholic acid.

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

Oestrogens, oral contraceptives, and clofibrate (and perhaps other lipid-lowering substances) increase hepatic cholesterol secretion, and encourage cholesterol gallstone formation and hence may counteract the effectiveness of cholic acid. Any medicinal products implicated in drug-induced cholestasis through inhibition of transporters could reduce the effectiveness of cholic acid treatment on co-administration. In these cases, serum/bile levels of cholic acid should be closely monitored and the dose adjusted accordingly.

The effect of food on the bioavailability of cholic acid has not been studied. There is a theoretical possibility that administration of food may increase cholic acid bioavailability and improve tolerability. It is recommended that cholic acid is taken with food (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited safety data from the use of cholic acid in pregnant women. Pregnancies with normal outcomes have been reported in women taking cholic acid.
The limited data from animal studies do not indicate direct reproductive toxicity (see section 5.3). The use of cholic acid may be considered during pregnancy if the doctor considers that the benefits to the patient outweigh the possible risk.

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.

Breast-feeding
There is insufficient information on the excretion of cholic acid and its metabolites in human milk. Available data in animals have shown excretion of cholic acid in milk (see section 5.3). At therapeutic doses, no effects on the breast-fed newborn infant are anticipated since the systemic exposure of the breast -feeding mother to cholic acid is negligible (see section 5.2). Cholic acid can be used during breast-feeding if the doctor considers that the benefits to the patient outweigh the possible risk.

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Cholic acid has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Adverse reactions in patients (both adults and children) receiving cholic acid are generally mild to moderate in severity; the main reactions observed are given in the table below. The events were transitory and generally did not interfere with the therapy.

Tabulated list of adverse reactions
Based on clinical trial data, adverse reactions in patients (both adults and children) receiving cholic acid are generally mild to moderate in severity and are provided in the following table.
Adverse reactions are ranked according to system organ class, using the following convention: very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).
The adverse reactions reported in the literature with an unknown frequency are also reported in the following table.

MedDRA System Organ Class	Preferred Term	Frequency
Nervous system disorders	Mild peripheral neuropathy	Common
Gastrointestinal disorders	Diarrhoea Mild nausea Mild reflux Moderate diarrhoea Reflux esophagitis	Common Common Common Common Common
Hepatobiliary disorders	Jaundice Increased serum transaminases Gallstones	Common Not known Not known
Skin and subcutaneous tissue disorders	Skin lesion Pruritus	Common Not known
General disorders and administration site conditions	Malaise	Common

Description of selected adverse reactions
Adverse reactions reported in the literature are pruritus and increased serum transaminases in one or two children treated with high doses of cholic acid; however these adverse reactions disappeared with a reduced dosage. Diarrhoea is also known to occur in cases of excessive dosing with cholic acid. Gallstones have been reported after long-term therapy

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

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 (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il).

4.9 Overdose

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

In the event of overdose the patient should be monitored and treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bile and liver therapy, bile acid preparations; ATC code: A05AA03
Mechanism of action
After administration of cholic acid a down-regulation of bile acid synthesis occurs and there is a strong decrease or almost complete disappearance of abnormal bile acids. Concurrent with the disappearance of atypical bile acid metabolites, there is a consistent reduction and normalization in serum liver enzymes. Treatment with oral cholic acid stimulates bile flow and secretion, inhibits production and

accumulation of hepatotoxic and cholestatic bile acid precursors and facilitates fat absorption without toxic side effects at therapeutic doses.

Pharmacodynamic effects

Inborn errors of primary bile acid synthesis involve congenital defects in the primary enzymes responsible for catalysing key reactions in the synthesis of cholic and chenodeoxycholic acids. The primary enzyme defects include but are not limited to:

- 3β-hydroxy-Δ^5-C_{27}-steroid oxidoreductase (3β-hydroxy-Δ^5-C_{27}-steroid dehydrogenase/isomerase or 3β-HSD or HSD3β7) deficiency
- Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency
- 2- (or α-) methylacyl-CoA racemase (AMACR) deficiency
- Cholesterol 7α-hydroxylase *(*CYP7A1) deficiency

Treatment with exogenous cholic acid is intended to replace physiological bile acid in cases of inborn errors of bile acid synthesis. Cholic acid is one of the primary bile acids in man on which essential physiological functions depend. The purpose of substituting missing cholic acid is to restore the main functions of this bile acid consisting of lipid transport in the form of mixed micelles, the activation of co-lipase and fat digestion and absorption, the absorption of fat-soluble vitamins, and the induction of bile flow, thus preventing cholestasis.

The pharmacodynamic action of cholic acid is feedback inhibition of the synthesis of toxic partial bile acid biosynthetic products that result from blockages in the normal bile acid synthetic pathway. Cholic acid down-regulates bile acid biosynthesis via activation of farnesoid X receptor, which represses transcription of the CYP7A1 gene encoding cholesterol 7α-hydroxylase, the rate-limiting enzyme of bile acid synthesis. In each of the primary bile acid deficiencies due to enzyme defects in the biosynthetic pathway, absence of primary bile acids leads to cholestasis and unregulated accumulation of toxic bile acid precursors. The rationale for cholic acid therapy is improvement of bile flow and fat absorption and restoration of a physiologic feedback inhibition on bile acid synthesis, lowering the production of toxic bile acid precursors.

Clinical efficacy and safety

Study CAC-91-10-10, (Investigation in the pathogenesis of liver disease in patients with inborn errors of bile acid metabolism) was conducted from 1992-2009 to evaluate the therapeutic efficacy and safety of cholic acid to treat patients with identified inborn errors of bile acid metabolism. The study was an open-label, single arm, non-randomized design. A total of 85 patients took part in the clinical study. Of these 85 patients, 52 presented with disorders in primary bile acid synthesis manifested as defects in the following 5 single enzymes:

- 3β-hydroxy-Δ^5-C_{27}-steroid oxidoreductase (3β-hydroxy-Δ^5-C_{27}-steroid dehydrogenase/isomerase or 3β-HSD or HSD3β7) deficiency (n=35)
- Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency (n=5)
- 2- (or α-) methylacyl-CoA racemase (AMACR) deficiency (n=1)
- Cholesterol 7α-hydroxylase *(*CYP7A1) deficiency (n=1)

A total of 79 patients received cholic acid treatment, 49 of these suffered from one of the five primary enzyme defects listed above.

Study CAC-002-01, (An open-label, single-centre, nonrandomized continuation study of cholic acid capsules in subjects with inborn errors of bile acid synthesis), was the continuation of study CAC-91-10-10 and started on 1 Jan 2010. The study followed an open-label, single arm, non-randomized design and included eligible subjects who had previously received cholic acid through CAC-91-10-10 and newly diagnosed subjects. Therapeutic efficacy and safety of cholic acid treatment in patients with inborn errors of bile acid metabolism was evaluated. A total of 41 patients took part in the clinical study and received at least one dose of cholic acid. Of these 41 patients, 29 presented with disorders in primary bile acid synthesis including Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency (n=4) and 3β-hydroxy-Δ^5-C_{27}-steroid oxidoreductase (3β-hydroxy-Δ^5-C_{27}-steroid dehydrogenase/isomerase or 3β-HSD or HSD3β7) deficiency (n=21).

In all studies, a dose of 10-15 mg/kg/day was administered.

Efficacy was demonstrated in two ways:

(a) treatment with cholic acid leads to an improvement in liver function as demonstrated by improved liver function test values,
(b) FAB-MS data demonstrated efficacy by showing that cholic acid treatment le to a suppression of the abnormal urine bile acids that initially led to the diagnosis.

Of all the patients treated in Study CAC-91-10-10, 49 patients presented with one of the five enzyme defects listed above. In this set of patients, about one quarter were below or at most 6 months of age at diagnosis, and about one third were between 7 and 36 months. On average, patients in this subgroup were 3 years at treatment start, minimum and maximum ages were 0 and 14 years, respectively.

In Study CAC-002-01, the mean age of patients at baseline was 9.0 years, with ages ranging from 0.3 to 35 years. Affected patients often present with significant comorbidities, including CNS impairment, which would not be treated by addressing the bile defect effects.

From the 49 patients with one of the five enzyme defects (listed above) treated in Study CAC-91-10-10 and included in the safety analysis, 42 had at least one pre- and one post-treatment assessment for urine bile acids, liver function tests, and height and weight and were included in the primary efficacy analysis.

Of the 52 patients (with one of the five enzyme defects listed above) that were included in Study CAC-91-10-10 during the 17-year study period, 6 died, 3 had no evidence of treatment, 4 terminated the study, 10 were lost to follow-up, and for 1 data retrieval was unsuccessful.
Of the 29 patients (with one of the three enzyme defects listed above) that were treated in Study CAC-002-01 3 patients discontinued (all due to AEs), and one patient died.

In Study CAC-91-10-10 the efficacy analysis showed that treatment with cholic acid significantly improved, i.e. decreased, urinary bile acid excretion in patients with single enzyme defects. General improvements in the degree of atypical urine bile acids were also seen in individual defect groups.

The efficacy analysis also demonstrated that treatment with cholic acid significantly improved ALT and AST values for patients stratified by single enzyme defects. Regarding primary diagnoses, shifts towards improvements in ALT and AST values were shown in individual defect groups.

In an interim analysis of Study CAC-002-01, the efficacy analysis of urinary bile acids and transaminases using the comparison from baseline to worst post-baseline value for the overall population that included both patients on cholic acid at study start and treatment naive patients showed no statistically significant changes. Similar results were shown for the height and weight analysis. Mean total bilirubin values also remained stable in the baseline to worst post-baseline value analysis.

Paediatric population
The clinical experience reported is from a patient population with disorders in primary bile acid synthesis that includes principally infants from the age of one month, children and adolescents.

5.2 Pharmacokinetic properties

Distribution and pharmacological effects of bile acids such as cholic acid are mainly limited to the enterohepatic circulation, which includes the intestine, portal vein, liver and biliary tract.

Orally administered cholic acid is absorbed by passive diffusion along the length of the gastrointestinal tract. Once absorbed, exogenous cholic acid will enter into the body's bile acid pool and will undergo multiple cycles of enterohepatic circulation. Cholic acid will pass to the liver in the portal blood, in which it is moderately bound to albumin. In the liver, cholic acid is extracted from portal blood by multiple mechanisms, including passive diffusion and transporters. Within the liver,

cholic acid is amidated in species-specific proportions, with glycine and/or taurine, into a more hydrophilic, conjugated form. Conjugated cholic acid is secreted into bile and will pass into the small intestine where, in association with other components of bile, it will perform its principal digestive function. Conjugated cholic acid is absorbed in the ileum via transporters , passed back to the liver and enters another cycle of enterohepatic circulation.

Any conjugated cholic acid not absorbed in the ileum will pass into the lower intestine where it may be subject to bacterial metabolism, principally deconjugation and 7-dehydroxylation. Deconjugated cholic acid and deoxycholic acid, the product of 7-dehydroxylation, are passively absorbed in the lower intestine and carried back to the liver in portal blood, where reconjugation will take place. In this manner the vast majority of the bile acid pool is conserved and will cycle multiple times during feeding. Any cholic acid not absorbed will be excreted in the faeces, either unchanged or following dehydroxylation via bacterial metabolism.

5.3 preclinical safety data

No formal preclinical safety studies have been conducted however data in the literature reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

There are a limited number of studies that have demonstrated that cholic acid administered orally for up to 26 weeks at doses significantly greater than the therapeutic dose, was well tolerated in animals with no mortalities, no effects on bodyweight or food consumption and no evidence of significant macroscopic or microscopic findings in the liver. In repeated dose studies, frequently reported effects of cholic acid have included decreased body weight, diarrhoea and liver damage with elevated transaminases although are considered to be associated with the pharmacological effects of bile acid metabolism. Increased liver weight and gallstones have been reported in repeated dose studies in which cholic acid was co-administered with cholesterol.

Slightly increased blood pressure was evident in rats after 30 days of cholic acid at approximately 4 fold therapeutic doses with increased vasoconstrictor responses to noradrenaline, together with decreased levels of aldosterone and increased corticosterone, but no adverse clinical signs were observed.

Cholic acid is not mutagenic, however co-administration of cholic acid with known carcinogens has shown increased tumour formation compared to the known carcinogen alone. This has led to the identification of cholic acid as a tumour promoter, considered to be via the hyperprofileration of colorectal epithelium in the presence of secondary bile acids.

Administration of a single dose of cholic acid intravenously to pregnant ewes in late gestation demonstrated systemic exposure of cholic acid in the foetus with no effect on either the mother or the foetuses other than an increase in early deliveries. The relevance of animal data with regards to cholic acid therapy safety is uncertain due to the known high inter-animal variability of bile acid homeostasis. Biliary bile alcohols and bile acids show remarkable structural diversity across animal species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Silicified microcrystalline cellulose (Prosolv SMCC 90)
Magnesium stearate

50 mg Capsule shell
Gelatin

Titanium dioxide (E171)
Red iron oxide (E172)

250 mg Capsule shell
Gelatin
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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

6.4 Special precautions for storage

Do not store above 25°C.
Store in original package in order to protect from light.

6.5 Nature and contents of container

White 185 ml HDPE bottle induction-sealed with a 38 mm white, child-resistant closure consisting of a HDPE grooved screw cap and induction seal (cardboard, wax and aluminium foil) liner.
Pack sizes: 90 capsules.

6.6 Special precautions for disposal

Use in the paediatric 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.

7. MANUFACTURER

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

8. MARKETING AUTHORISATION HOLDER

Megapharm LTD, POBox 519, Hod Hasharon, Israel

9. MARKETING AUTHORISATION NUMBER(S)

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10. DATE OF REVISION OF THE TEXT

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