

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Kolbam 50 mg hard capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 50 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 (black imprint “ASK001”) and body (black imprint “50mg”). The capsules contain a white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kolbam is indicated for the treatment of inborn errors in primary bile acid synthesis due to Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or α -) methylacetyl-CoA racemase (AMACR) deficiency or Cholesterol 7 α -hydroxylase (CYP7A1) deficiency in infants, children and adolescents aged 1 month to 18 years and adults.

4.2 Posology and method of administration

Treatment must be initiated and monitored by 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.

Patients should be monitored initially every 3 months during the first year then 6 monthly during the subsequent three years and annually thereafter. In case of persistent lack of therapeutic response to cholic acid monotherapy, other treatment options should be considered, see section 4.4.

During the initiation of therapy and dose adjustment, serum and urine bile acid levels should be monitored intensively by using suitable analytical techniques. The concentrations of the abnormal bile

acid metabolites synthesised subsequently 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 Kolbam. 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 suitable analytical techniques) and liver parameters should be determined annually, at a minimum, and the dose adjusted accordingly. Additional or more frequent investigations should be undertaken to monitor therapy during periods of fast growth, concomitant disease and pregnancy (see section 4.6).

Special populations

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 colesevalam. 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 7 α -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.

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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
<i>Nervous system disorders</i>	Mild peripheral neuropathy	Common
<i>Gastrointestinal disorders</i>	Diarrhoea	Common
	Mild nausea	Common
	Mild reflux	Common
	Moderate diarrhoea	Common
	Reflux esophagitis	Common
<i>Hepatobiliary disorders</i>	Jaundice	Common
	Increased serum transaminases	Not known
	Gallstones	Not known
<i>Skin and subcutaneous tissue disorders</i>	Skin lesion	Common
	Pruritus	Not known
<i>General disorders and administration site conditions</i>	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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#)

4.9 Overdose

Episodes of symptomatic overdose (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. There are several enzyme defects described in the literature. Some of the primary defects include but are not limited to:

- Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency
- 2- (or α -) methylacyl-CoA racemase (AMACR) deficiency
- Cholesterol 7 α -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 7 α -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 including the following 3 single enzymes:

- Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency (n=5)
- 2- (or α -) methylacyl-CoA racemase (AMACR) deficiency (n=1)
- Cholesterol 7 α -hydroxylase (CYP7A1) deficiency (n=1)

A total of 79 patients received cholic acid treatment, 49 of these suffered from a primary enzyme defect.

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).

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 led 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 a single enzyme defect. 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 a single enzyme defect 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 described 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 described 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.

Other information

This medicinal product has been authorised under ‘exceptional circumstances’. This means that, due to the rarity of the disease and for ethical reasons it has not been possible to obtain complete information on this medicinal product.

The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

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 re-conjugation 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 dose 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 hyperproliferation 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
Magnesium stearate

50 mg Capsule shell

Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)

Printing ink

Shellac (E904)
Propylene Glycol (E1520)
Strong Ammonia Solution (E527)
Potassium Hydroxide (E525)
Black Iron Oxide (E172)

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 30°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 immediately. 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. MARKETING AUTHORISATION HOLDER

Retrophin Europe Limited, Palmerston House, Fenian Street
Dublin 2, Ireland

8. MARKETING AUTHORISATION NUMBER

EU/1/13/895/001

9. DATE OF FIRST AUTHORISATION

20 November 2015

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>

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

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Kolbam 250 mg hard capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 250 mg of cholic acid.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

250 mg capsule: Size number 0 capsule with a white cap (black imprint “ASK002”) and white body (black imprint “250mg”). The capsules contain a white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kolbam is indicated for the treatment 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 or Cholesterol 7 α -hydroxylase (CYP7A1) deficiency in infants, children and adolescents aged 1 month to 18 years and adults.

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acid metabolites synthesised subsequently 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.

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Special populations

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Paediatric population

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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

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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.

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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).

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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 7 α -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).

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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.

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

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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
<i>Nervous system disorders</i>	Mild peripheral neuropathy	Common
<i>Gastrointestinal disorders</i>	Diarrhoea	Common
	Mild nausea	Common
	Mild reflux	Common
	Moderate diarrhoea	Common
	Reflux esophagitis	Common
<i>Hepatobiliary disorders</i>	Jaundice	Common
	Increased serum transaminases	Not known
	Gallstones	Not known
<i>Skin and subcutaneous tissue disorders</i>	Skin lesion	Common
	Pruritus	Not known
<i>General disorders and administration site conditions</i>	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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#)

4.9 Overdose

Episodes of symptomatic overdose (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. There are several enzyme defects described in the literature. Some of the primary defects include but are not limited to:

- Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency
- 2- (or α -) methylacyl-CoA racemase (AMACR) deficiency
- Cholesterol 7 α -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 7 α -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 including the following 3 single enzymes:

- Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency (n=5)
- 2- (or α -) methylacyl-CoA racemase (AMACR) deficiency (n=1)
- Cholesterol 7 α -hydroxylase (CYP7A1) deficiency (n=1)

A total of 79 patients received cholic acid treatment, 49 of these suffered from a primary enzyme defect.

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).

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

Efficacy was demonstrated in two ways:

- (c) treatment with cholic acid leads to an improvement in liver function as demonstrated by improved liver function test values,
- (d) FAB-MS data demonstrated efficacy by showing that cholic acid treatment led 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 a single enzyme defect. In this set of patients, about one quarter were below or at most 6 months of age at diagnosis, and about one third approximately a quarter 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 a single enzyme defect 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 described 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 described above that were treated in Study CAC-002-01 A total of 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.

Other information

This medicinal product has been authorised under ‘exceptional circumstances’. This means that, due to the rarity of the disease and for ethical reasons it has not been possible to obtain complete information on this medicinal product.

The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

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 re-conjugation 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 dose 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 hyperproliferation 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
Magnesium stearate

250 mg Capsule shell

Gelatin
Titanium dioxide (E171)

Printing ink

Shellac (E904)
Propylene Glycol (E1520)
Strong Ammonia Solution (E527)
Potassium Hydroxide (E525)
Black Iron Oxide (E172)

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 30°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 immediately. 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. MARKETING AUTHORISATION HOLDER

Retrophin Europe Limited, Palmerston House, Fenian Street
Dublin 2, Ireland

8. MARKETING AUTHORISATION NUMBER

EU/1/13/895/002

9. DATE OF FIRST AUTHORISATION

20 November 2015

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>

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

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Patheon France
40 boulevard de champaret
38300 Bourgoin-Jallieu

France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic Safety Update Reports

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

• Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

• Additional risk minimisation measures

Prior to launch in each Member State, the MAH shall agree the final educational material with the competent authority in that Member State. The MAH shall ensure that at launch all physicians expected to prescribe the product are provided with information on the correct and safe use of the product.

The physician's educational material should contain the following key elements:

- Summary of product characteristics
- Information on:
 - Calculation of the correct dose and the need to instruct caregivers on how to administer the product correctly
 - Symptoms and signs of an overdose and the management of this

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

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

Description	Due date
To monitor the long term safety and efficacy in patients treated with Kolbam from a patient registry for which details are reflected in the risk management plan. The registry will monitor accumulating data on efficacy and safety in the treatment of inborn errors in primary bile acid synthesis in infants, children, adolescents and adults due to Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX), 2- (or α -) methylacyl-CoA racemase (AMACR) and Cholesterol 7 α -hydroxylase (CYP7A1) deficiencies. Reports on recruitment progress of the registry will be submitted with PSURs and Annual Re-assessments. Progress and results from the registry will form the basis of the annual reassessments of the benefit/risk profile of Kolbam.	- PSURs - Annual Re-assessments

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kolbam 50 mg hard capsules
cholic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 50 mg cholic acid

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule.
90 capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in original package in order to protect from light.
Use within 3 months of opening.

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

Return any unused medicine to your pharmacist for disposal

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Retrophin Europe Limited, Palmerston House, Fenian Street
Dublin 2, Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/13/895/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kolbam 50 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Kolbam 50 mg hard capsules
cholic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 50 mg cholic acid

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule
90 capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in original package in order to protect from light.
Use within 3 months of opening.

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

Return any unused medicine to your pharmacist for disposal

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Retrophin Europe Limited, Palmerston House, Fenian Street
Dublin 2, Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/13/895/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kolbam 250 mg hard capsules
cholic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 250 mg cholic acid

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule.
90 capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in original package in order to protect from light.
Use within 3 months of opening.

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

Return any unused medicine to your pharmacist for disposal

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Retrophin Europe Limited, Palmerston House, Fenian Street
Dublin 2, Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/13/895/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kolbam 250 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Kolbam 250 mg hard capsules
cholic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 250 mg cholic acid

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule
90 capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in original package in order to protect from light.
Use within 3 months of opening.

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

Return any unused medicine to your pharmacist for disposal

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Retrophin Europe Limited, Palmerston House, Fenian Street
Dublin 2, Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/13/895/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Kolbam 50 mg hard capsules Kolbam 250 mg hard capsules cholic acid

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

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

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

What is in this leaflet

1. What Kolbam is and what it is used for
2. What you need to know before you use Kolbam
3. How to use Kolbam
4. Possible side effects
5. How to store Kolbam
6. Contents of the pack and other information

1. WHAT KOLBAM IS AND WHAT IT IS USED FOR

Kolbam contains a substance called cholic acid.

In the body cholic acid is naturally produced in the liver and is part of the bile, a fluid that helps digestion and absorbs fat and vitamins from the food. Cholic acid also promotes normal growth of children. Patients with certain types of conditions known as inborn errors of bile synthesis cannot produce cholic acid and bile normally, which leads to the production and build-up of abnormal substances that are potentially damaging to the liver.

Kolbam is used to treat these 'inborn errors of bile acid synthesis'. By replacing the missing cholic acid it stimulates the production of normal bile and helps prevent the build-up of the abnormal substances in the liver. In growing infants, treatment with cholic acid helps with the normal development of the liver and bile circulation system.

Kolbam can be used from the age of one month and patients affected by these conditions will need treatment for the rest of their life.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE KOLBAM

Do not take Kolbam

- If you are allergic to cholic acid or to any of the other ingredients of this medicine (listed in section 6).
- If you are taking phenobarbital (a medicine used for epilepsy). See under 'Other medicines and Kolbam'.

Warnings and precautions

During your treatment, your doctor will carry out various blood and urine tests at different times to see how your body is handling this medicine and to help work out the dose that you need. More frequent tests will be needed if you are growing fast, if you are ill or if you are pregnant.

If you have a condition called familial hypertriglyceridaemia, your doctor may have to increase your dose of cholic acid.

Your doctor will advise you if for any reason you have to stop treatment with cholic acid.

Children

Cholic acid has not been studied for safety and effectiveness in babies under one month of age.

Elderly

Cholic acid has not been studied for safety and effectiveness in people over 65 years of age.

Other medicines and Kolbam

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

Phenobarbital may stop cholic acid from working. Do not take any phenobarbital while you are on cholic acid. See above under 'Do not take Kolbam'.

Ciclosporin may affect the levels of cholic acid. If your doctor considers it necessary that you keep taking ciclosporin, he will closely monitor the levels of bile acids in your blood and urine and adjust the dose of cholic acid accordingly.

Medicines for lowering cholesterol levels in the blood, such as cholestyramine or colestipol and certain antacids which contain aluminium (e.g. indigestion relief products) may affect the absorption of cholic acid. Your doctor will advise you to take cholic acid at least 5 hours before or after taking the other medicine.

These are some of the medicines that may affect the way in which Kolbam works:

- oestrogen,
- oral contraceptives,
- lipid-lowering medicines such as clofibrate

These increase cholesterol production in the liver and as a result prevent cholic acid from working properly.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

The use of cholic acid may be considered during pregnancy if your doctor considers that the benefits to you outweigh any possible risk. Ask your doctor for advice.

You can continue to breast-feed your baby whilst being treated with cholic acid, as levels in breast milk are considered too low to harm your baby.

Driving and using machines

This medicine is not expected to affect your ability to drive or use machines.

3. HOW TO TAKE KOLBAM

Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure.

The recommended dose is based on your body weight (10-15 mg per kg) taken either as a single dose, once a day, or divided into two doses, one in the morning and one in the evening. Your doctor will tell you how many capsules you need to take, and when you should take the capsules.

It is recommended that the capsules are taken with food, as this may help to make the cholic acid more effective, and also reduces the likelihood of diarrhoea.

Use in children

For babies and children who cannot swallow capsules, open the capsule by gently twisting it and add the contents to infant formula, expressed breast milk or fruit puree in a suitable clean container. The mixture should be given immediately after preparation.

This mixing of the capsule contents with food should mask any unpleasant taste of the medicine. The capsule contents will remain as fine granules in the milk or food.

It is important to give the full content of the capsule to the baby or young child where whole capsules cannot be given. Try to ensure that if any of the dose is spat out or refused, it is given again.

Use in adults

Swallow each capsule whole with water, either just before or just after food. Do not chew the capsule. Do not take more capsules than your doctor has advised you.

If you take more Kolbam than you should

Cholic acid is unlikely to cause serious side effects but you should contact your doctor for advice if you or your child have taken more than the amount prescribed.

If you forget to take Kolbam

Take the next dose as soon as you remember, as long as it is more than 12 hours until the next dose. Never take a double dose to make up for a forgotten dose.

If you stop taking Kolbam

This medicine is intended for long-term use. If you stop taking it the abnormal substances in your bile may build up again to the levels before treatment was started, potentially causing damage to your liver.

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

4. POSSIBLE SIDE EFFECTS

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

Common side effects (may affect up to 1 in 10 people)

- heartburn (gastric reflux)
- diarrhoea
- feeling out of sorts (malaise)
- yellowing of the skin (jaundice)
- skin lesions
- sickness (mild nausea)
- feeling of pins and needles (mild peripheral neuropathy)

Side effects of unknown frequency (cannot be estimated from the available data):

- Increase liver enzymes (serum transaminases)
- Gallstones
- Slight tingling (Pruritis)

Reporting of side effects

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

5. HOW TO STORE KOLBAM

Keep this medicine out of the sight and reach of children.

Do not use after the expiry date which is stated on the carton and bottle label after “EXP” The expiry date refers to the last day of that month.

Do not store above 30°C.

Store in the original package in order to protect from light. Use within 3 months of opening

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Kolbam contains

- The active substance is cholic acid.
Kolbam 50 mg: Each capsule contains 50 mg of cholic acid.
Kolbam 250 mg: Each capsule contains 250 mg of cholic acid.
- The other ingredients are:

Capsule content:

- Silicified microcrystalline cellulose

- Magnesium stearate

Capsule shell:

- Gelatin
- Titanium dioxide (E171)

Kolbam 50 mg also contains Red iron oxide (E172)

Printing ink

- Shellac (E904)
- Propylene Glycol (E1520)
- Strong Ammonia Solution (E527)
- Potassium Hydroxide (E525)
- Black Iron Oxide (E172)

What Kolbam looks like and contents of the pack

Kolbam is provided as hard capsules. Each capsule contains a white powder. The 50 mg capsules are orange (black imprint “ASK001” and “50mg”). The 250 mg capsules are white (black imprint “ASK002” and “250mg”).

Packs containing 90 capsules.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

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Manufacturer

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France

This leaflet was last revised in DDmonthYYYY.

This medicine has been authorised under ‘exceptional circumstances’. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.

The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information

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

ANNEX IV

**CONCLUSIONS ON THE GRANTING OF THE MARKETING AUTHORISATION UNDER
EXCEPTIONAL CIRCUMSTANCES PRESENTED BY THE EUROPEAN MEDICINES
AGENCY**

Conclusions presented by the European Medicines Agency on:

- **Marketing authorisation under exceptional circumstances**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the marketing authorisation under exceptional circumstances as further explained in the European Public Assessment Report.