1. NAME OF THE MEDICINAL PRODUCT

Chenodeoxycholic acid Leadiant

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 250 mg of chenodeoxycholic acid.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Size 0 capsule, 21.7 mm in length with a yellow body and orange cap, containing a white, compressed powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chenodeoxycholic acid Leadiant is indicated for the treatment of inborn errors of primary bile acid synthesis due to sterol 27 hydroxylase deficiency (presenting as cerebrotendinous xanthomatosis (CTX)) 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 experienced in the management of CTX or inborn errors of primary bile acid synthesis.

During the initiation of therapy and dose adjustment, serum cholestanol levels and/or urine bile alcohols should be monitored every 3 months till metabolic control and then annually. The lowest dose of chenodeoxycholic acid that effectively reduces the serum cholestanol and/or urine bile alcohols levels to within the normal range should be chosen. Liver function should also be monitored. Concurrent elevation of liver enzymes above normal levels may indicate overdose. After the initiation period, cholestanol, urine bile alcohols and liver function should be determined annually, at a minimum, and the dose adjusted accordingly (see section 4.4). Additional or more frequent investigations may need to be undertaken to monitor therapy during periods of fast growth, concomitant disease and pregnancy (see section 4.6).

In case of persistent lack of therapeutic response to chenodeoxycholic acid monotherapy, other treatment options should be considered.

Posology
Adults
The starting dose in adults is 750 mg/day, in three divided doses provided that it is sufficient to normalise serum cholestanol and/or urine bile alcohols. The daily dose can be subsequently increased in 250 mg increments to a maximum of 1,000 mg/ day if the serum cholestanol and/or urine bile alcohols remain elevated.

Paediatric population (1 month -18 years)
The starting dose in children is 5 mg/kg/day in three divided doses. Where the dose calculated is not a multiple of 250 mg, the nearest dose below the maximum of 15 mg/kg/day should be selected, provided that is sufficient to normalise serum cholestanol and/or urine bile alcohols.

Neonates less than one month of age
The safety and efficacy in neonates less than one month of age have not been established. Limited safety data are available (see section 4.8).

Missed dose
If a dose is missed, the patient should take the next dose at the scheduled time. A double dose should not be taken to make up for the missed dose.

Special populations
Elderly patients (≥ 65 years)
Dose adjustment is not necessary.

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

Hepatic impairment
No data are available for patients with hepatic impairment. However, these patients should be carefully monitored and the dose titrated individually.

Method of administration
Oral use.
Chenodeoxycholic acid Leadiant capsules can be taken with or without food. The hard capsules should be taken whole with sufficient water at approximately the same time each day. For infants and children who cannot swallow capsules, the capsules may be carefully opened and the content added to sodium bicarbonate solution 8.4%, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Monitoring
After the initiation period, cholestanol, urine bile alcohols and liver function should be determined annually, at a minimum, and the dose adjusted accordingly (see section 4.2). Additional or more frequent investigations may need to be undertaken to monitor therapy during periods of fast growth, concomitant disease and pregnancy (see section 4.6).

Co-administration of chenodeoxycholic acid with other medicinal products
Co-administration with ciclosporin, sirolimus, phenobarital is not recommended, see section 4.5 for further details.

Colestipol or antacid medicinal products containing aluminium hydroxide and/or smectite should be taken either 2 hours before or after taking Chenodeoxycholic acid Leadiant, see section 4.5 for further details.
Chenodeoxycholic acid Leadiant should be taken either one hour before cholestyramine or 4-6 hours after, see section 4.5 for further details.

Co-administration with oral contraceptives is not recommended, see section 4.5 for further details. Women of childbearing potential should use an effective method of contraception, see section 4.6 for further details.

4.5 Interaction with other medicinal products and other forms of interaction

In patients with CTX, no interaction studies with chenodeoxycholic acid and concomitantly administered medicinal products have been performed

Colestipol and antacid medicinal products
Chenodeoxycholic acid Leadiant should not be administered together with colestipol or antacid medicinal products containing aluminium hydroxide and/or smectite (aluminium oxide) since these preparations bind the active substance of chenodeoxycholic acid in the intestine and thus prevent its reabsorption and efficacy. If it is necessary to take a medicinal product containing one of these active substances it should be taken either 2 hours before or after taking Chenodeoxycholic acid Leadiant.

Colestyramine
Chenodeoxycholic acid Leadiant should not be administered together with colestyramine as it binds chenodeoxycholic acid in the intestine and thus prevents its reabsorption and efficacy. If it is necessary to take colestyramine, then Chenodeoxycholic acid Leadiant should be taken either one hour before colestyramine or 4-6 hours after.

Ciclosporin and sirolimus
Ciclosporin has been shown to reduce the synthesis of chenodeoxycholic acid by inhibition of CYP27A1 and increasing the activity of HMG CoA reductase. A similar effect on CYP27A1, albeit at higher doses, is also seen with sirolimus. Co-administration of Chenodeoxycholic acid Leadiant with ciclosporin or sirolimus should be avoided. If administration of ciclosporin or sirolimus is considered necessary, serum and urine bile alcohol levels should be closely monitored and the Chenodeoxycholic acid Leadiant dose adjusted accordingly.

Phenobarbital
Concomitant administration of chenodeoxycholic acid with phenobarbital increases HMG CoA reductase and thus counteracts one of the pharmacodynamics effects of chenodeoxycholic acid in CTX. If administration of phenobarbital is considered necessary, serum and urine bile alcohol levels should be closely monitored and the Chenodeoxycholic acid Leadiant dose adjusted accordingly.

Oral contraceptives
The administration of oral contraceptives reduces the pool size of chenodeoxycholic acid. Oral contraceptives therefore may worsen the underlying deficiency and counteract the effectiveness of Chenodeoxycholic acid Leadiant in CTX. Co-administration with oral contraceptives is not recommended.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use an effective method of contraception. The use of oral contraceptives is not recommended in patients taking Chenodeoxycholic acid Leadiant, see section 4.5 for further details.

Pregnancy
Patients with CTX and high cholestanol have been shown to have adverse outcomes during pregnancy. Two intrauterine deaths in a mother with CTX have been reported in the literature. Two pregnancies in mothers with CTX resulted in premature infants with evidence of intrauterine growth retardation also reported in the literature. There are no or limited amount of data from the use of Chenodeoxycholic acid Leadiant in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Chenodeoxycholic acid Leadiant is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
It is unknown whether chenodeoxycholic acid/metabolites are excreted in human milk.

A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Chenodeoxycholic acid Leadiant therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman

Fertility
Chenodeoxycholic acid is an endogenous bile acid used for replacement therapy and it is anticipated to have no effects on fertility at therapeutic doses.

4.7 Effects on ability to drive and use machines

Chenodeoxycholic acid Leadiant 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 chenodeoxycholic acid are generally mild to moderate in severity; the main reactions observed are given in the table below. The events were transitory and did not interfere with the therapy.

Tabulated list of adverse reactions
Adverse reactions are ranked according to MedDRA 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), not known (cannot be estimated from the available data).

MedDRA system organ class	Preferred term	Frequency
Gastrointestinal disorders	Constipation	not known
Hepatobiliary disorders	Hepatic adverse reactions	not known

Description of selected adverse reactions
In two non-interventional studies with chenodeoxycholic acid a total of three adverse reactions were reported in three out of 63 patients (safety population). The three adverse reactions were all non-serious. One case of mild intermittent constipation occurred in an adult and another instance occurred in a child. One case of hepatic adverse reactions occurred in a two week old infant diagnosed with CTX and is discussed in the section below.

Paediatric population
In two-non interventional studies with chenodeoxycholic acid, a total of 14 paediatric patients with CTX were treated with chenodeoxycholic acid : 1 infant (0 to < 2 years), 6 children (2 to < 12 years) and 7 adolescents (12 to < 18 years). All paediatric patients received 15 mg/kg/day as their starting dose.

The only infant enrolled presented with raised liver function tests within six weeks of treatment start. The infant's liver function normalised upon temporarily stopping treatment with chenodeoxycholic acid. Chenodeoxycholic acid supplementation was re-started and maintained at a lower dose of 5 mg/kg/day with no further complications.

This case of hepatic adverse reactions in an infant presented with multiple confounders, such as concomitant parechovirus infection, co-administration of medicinal products known to affect liver function (acyclovir and phenobarbital) and presence of hyperbilirubinemia at birth.

The presented safety information for hepatic adverse reactions is derived from paediatric patients. Due to the rarity of CTX, the available literature is not sufficient to detect a difference in the safety of chenodeoxycholic acid within paediatric age groups or between paediatric patients and adults.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health..gov.il

4.9 Overdose

The potential for harm from overdose is considered extremely low, as accumulation of chenodeoxycholic acid is unlikely due to an efficient endogenous mechanism of elimination and excretion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bile and liver therapy, bile acids and derivatives, ATC code: A05AA01

Mechanism of action
Exogenous chenodeoxycholic acid is used as replacement therapy to restore the feedback inhibition lost due to the deficiency/absence of endogenous chenodeoxycholic acid. In CTX, a defect in the CYP27A1 gene results in a deficient mitochondrial sterol 27-hydroxylase enzyme. This deficiency blocks the synthesis of primary bile acids via the classical (neutral pathway) and the alternative (acidic) pathway. However, cholic acid is still formed via an alternate microsomal pathway. The net result is a total bile acid pool that is severely deficient in chenodeoxycholic acid but relatively enriched with cholic acid.

In CTX, deficiency of chenodeoxycholic acid causes a lack of feedback of cholesterol 7α- hydroxylase (CYP7A1) and HMG CoA reductase, causing increased production of atypical bile acids, bile alcohols and cholestanol that lead to the pathological consequences of the condition. Exogenous replacement with chenodeoxycholic acid inhibits CYP7A1 (via nuclear receptor, FXR) and HMG CoA reductase, thus restoring the feedback inhibition.

The primary pharmacodynamic effects of chenodeoxycholic acid are:

1. Reduced production of cholesterol: reduces serum cholestanol (action on HMG CoA reductase).
2. Reduced production of cholestanol: reduces serum cholestanol (action on HMG CoA reductase and CYP7A1).
3. Reduced production of atypical bile alcohols and bile acids: through restoration of feedback inhibition of primary bile acid synthesis (action on CYP7A1)

Clinical efficacy and safety
Efficacy and safety was studied in two retrospective trials in two centres in Europe. The mean age of the patient population in the pivotal study was younger at 25.8 years than the supporting study population at 35 years which also reflected the level of disability present in the two cohorts prior to treatment start, with the supporting study having a higher disability score at baseline.

In the pivotal study CDCA-STUK-15-001 treatment of CTX patients with chenodeoxycholic acid 750-1,000 mg/day in adults or 5-15 mg/kg/day in infants and children was associated with statistically significant decreases in mean serum levels of cholestanol from baseline to post-baseline in the overall population and in the two subgroups of patients aged < 21 years or ≥ 21 years at first treatment. Urinary bile level alcohol levels decreased. Neurological disability scale scores (Rankin and EDSS) stabilised or improved by the clinical current visit in 84.6% and 76.9% of patients respectively. Mean Rankin and EDSS scores showed a very small increase (worsening) from baseline to clinical current visit at 0.08 ± 0.74 and 0.27 ± 1.24 in the overall population and this increase was not statistically significant. There was a statistically significant (p = 0.04) improvement (decrease) of -0.31 ± 0.48 in the mean Rankin score for the < 21 years of age subgroup.

Disease signs and symptoms resolved, improved or stabilised in a majority of patients over the course of the study. Diarrhoea disappeared in 100% (23/23 patients) of the patients who had this symptom at baseline. There was a resolution, improvement or stabilisation in 88.9% (16/18) of patients with cognitive impairment. Epilepsy resolved in 100% (3/3 patients) and polyneuropathy stabilised or improved in 100% (11/11). Pyramidal dysfunction improved or stabilised in 60% (10/15) and cerebellar dysfunction in 88.7% (12/14). Psychiatric impairment resolved, improved or stabilised in 85.7% (6/7) of patients. However, parkinsonian symptoms, a rare disease manifestation/association that occurred in only 2 patients during the course of the study, did not respond.

In the supportive study CDCA-STRCH-CR-14-001 treatment of CTX patients with chenodeoxycholic acid 750 mg/day given for a median duration of 5.75 years was associated with statistically significant decreases in mean serum levels of cholestanol from baseline to any post-baseline visit. The mean levels of 7α-hydroxy-4-cholesten-3one significantly decreased from baseline to post-baseline visits 1 and 2. Vitamin D and PTH levels decreased from baseline to both post-treatment visits and mean pyruvate levels decrease from baseline to the first post-treatment visit. Rankin and EDSS scores remained stable in 61.5% and 50% of patients respectively, however there was an overall worsening of the mean score from baseline. Increases in bone mineral density (Z-score) were observed at lumbar spine at both post-treatment visits and at total hip at post-treatment at post-treatment visit 2. Signs and symptoms of the disease remained stable in most of the patients. Diarrhoea improved or disappeared in 64.3% of the patients who had this symptom present at baseline.

None of the patients had treatment-related adverse events and chenodeoxycholic acid exhibited a satisfactory safety profile in relation to routine safety laboratory parameters (haematology and clinical chemistry).

5.2 Pharmacokinetic properties

Data exists only in the adult population.
Chenodeoxycholic acid is an endogenous bile acid in humans, which is tightly regulated by its secretion into bile via exporter pumps and detoxification by sulfation. In addition to sulfation, bile acid can also be detoxified through glucuronidation.

Chenodeoxycholic acid given orally is absorbed in the small intestine. Reabsorption is not complete. A small portion of chenodeoxycholic acid is excreted with faeces.

After reabsorption in the intestine, the bile acid is nearly completely conjugated to the amino acids glycine and taurine and then excreted again in the bile.

In the intestine chenodeoxycholic acid and its glycine or taurine conjugate are decomposed by bacteria. Deconjugation results in the free bile acid, oxidation in the 7-keto-lithocholic acid and lithocholic acid (3α hydroxycholanic acid) is formed by elimination of the 7-hydroxy group. Whereas 7-keto-lithocholic acid can be formed partially in the colon and also in the liver to chenodeoxycholic acid and ursodeoxycholic acid (3α-, 7ß-di-hydroxycholanic acid), lithocholic acid is absorbed to a small extent only and is thus largely lost with faeces.

Biological half-life of chenodeoxycholic acid is about 4 days.

Reabsorption of chenodeoxycholic acid is variable (29% - 84%). After treatment with chenodeoxycholic acid, the endogenous synthesis of the primary bile acids, cholic acid and chenodeoxycholic acid, is inhibited.

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 conventional studies of single dose toxicity, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Rodent and primate toxicity species lack efficient-sulfating capacity for conjugation of lithocholic acid, and therefore have shown hepatotoxicity. In contrast, Lithocholic acid sulfate conjugation in humans prevents the overt hepatotoxicity, as seen in animal toxicity species after repeat dosing.

Reproduction toxicity
Developmental toxicity studies in rats, hamsters and primates showed an absence of teratogenic effects. In rhesus monkey and baboon studies it was demonstrated that chenodeoxycholic acid dose to pregnant animals (at 5-120 mg/kg/day for rhesus monkey; at 18-38 mg/kg/day for baboons) produced liver pathology in the developing foetus. Pathological effects on adrenal glands and kidneys were also seen in rhesus monkey foetuses. Maternal effects in the rhesus monkeys, but not baboons, included diarrhoea, emesis, weight loss and reduction in food consumption.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Maize starch
Magnesium stearate
Silica, colloidal anhydrous
Water

Capsule shell
Gelatin
Titanium dioxide
Quinoline yellow
Erythrosine

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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

6.4 Special precautions for storage

Do not store above 25˚C

6.5 Nature and contents of container

Capsules are packed in polyvinyl chloride (PVC) blisters sealed with aluminium foil and packed in cardboard boxes.
Pack size: 100 hard capsules

6.6 Special precautions for disposal and other handling

Patients who are unable to swallow capsules
For children (1 year to 11 years)*, adolescents* (12 years to 18 years) *and adults* who cannot swallow capsules and/or need to take a dose below 250 mg, the capsule may be opened, the contents of added to 25 mL of sodium bicarbonate solution 8.4% (1 mmol/mL) and mixed to produce a suspension containing chenodeoxycholic acid 10 mg/mL.

For infants (1 month to 11 months) the capsule may be opened, the contents added to 50 mL of sodium bicarbonate solution 8.4% (1 mmol/mL) and mixed to produce a suspension containing chenodeoxycholic acid 5 mg/mL.

The active substance itself will be dissolved in the sodium bicarbonate solution and it appears as a suspension because not all components of the capsule contents will be dissolved. The suspension is formed quite easily and is ready when there are no visible lumps or powder left.

The suspension produced contains 22.9 mg of sodium per mL, which needs to be taken into consideration by patients on a controlled sodium diet.

It is recommended that this suspension is prepared at the pharmacy and instructions given to the parent on how to administer the suspension.

The suspension should be stored in a glass bottle. Do not refrigerate or freeze. The suspension is stable for up to 7 days at ambient temperature and humidity.

The pharmacy should provide oral dose syringes of appropriate volume and grading for administering the suspension. The correct volumes should preferably be marked on the oral syringe.

The physician should provide information on the dose to be received according to the weight of the child. The dose range in paediatric patients (1 month to 18 years) is 5-15 mg/kg per day (see section 4.2).

Disposal
Any unused product or waste material should be disposed of in accordance with national requirements.

7. MANUFACTURER

PHARMALOOP S.L. C/Bolivia, no 15, Polígono Industrial Azque, Alcalá de Henares, Madrid 28806, Spain for Leadiant Biosciences Limited, UK.

8. REGISTRATION HOLDER

MBI Pharma Ltd.
P.O.B.5061
Kadima
Israel

9. MARKETING AUTHORISATION NUMBERS

159-45-35040-00

Revised in November 2021 according to MOH guidelines.