

**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**

Chenodeoxycholic acid Leadiant 250 mg hard capsules

## **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 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 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, see section 4.5 for further details.

Chenodeoxycholic acid should be taken either one hour before colestyramine 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 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.

##### Colestyramine

Chenodeoxycholic acid 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 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 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 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 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 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, 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 in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Chenodeoxycholic acid 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 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 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.

### Tabulated list of adverse reactions

Adverse reactions are ranked according to MedDRA 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 ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

MedDRA system organ class	Preferred term	Frequency
Gastrointestinal disorders	Constipation	not known
Hepatobiliary disorders	Transaminases increased	not known
	Jaundice	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.

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. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system](#) listed in [Appendix V](#).

## **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 7 $\alpha$ -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  $\geq$  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  $0.08 \pm 0.74$  and  $0.27 \pm 1.24$  in the overall population and this increase was not statistically significant. There was a statistically significant ( $p = 0.04$ ) improvement (decrease) of  $-0.31 \pm 0.48$  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 7 $\alpha$ -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 (3 $\alpha$  hydroxycholanolic 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 (3 $\alpha$ -, 7 $\beta$ -di-hydroxycholanolic 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 fetuses. 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

#### Capsule shell

Gelatin  
Titanium dioxide (E 171)  
Quinoline yellow (E 104)  
Erythrosine (E 127)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **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 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.

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).

Further information is provided at the end of the package leaflet under "information for healthcare professionals only".

#### Disposal

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

### **7. MARKETING AUTHORISATION HOLDER**

Leadiant GmbH  
Liebherrstr. 22  
80538 Munich  
Germany  
Telephone: +49 (0)89 4111 595 00  
Fax: +49 (0) 89 4111 595 25  
e-mail: [info@leadiantbiosciences.com](mailto:info@leadiantbiosciences.com)

### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/16/1110/001

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 10 April 2017  
Date of latest renewal: 09 December 2021

### **10. DATE OF REVISION OF THE TEXT**

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(S) 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(s) responsible for batch release

Pharmaloop S.L.  
C/Bolivia, no 15  
Polígono Industrial Azque  
Alcalá de Henares  
Madrid 28806  
Spain

## **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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 marketing authorisation holder (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.

**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:

<b>Description</b>	<b>Due date</b>
In order to collect long term safety and efficacy data in patients treated with chenodeoxycholic acid, the MAH will submit the results of a study deriving from a registry of patients with inborn errors of primary bile acid synthesis due to sterol 27-hydroxylase deficiency in infants, children and adolescents aged 1 month to 18 years and adults.	Study results – PSUR and annual reassessments

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Chenodeoxycholic acid Leadiant 250 mg hard capsules  
chenodeoxycholic acid

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each capsule contains 250 mg chenodeoxycholic acid.

**3. LIST OF EXCIPIENTS****4. PHARMACEUTICAL FORM AND CONTENTS**

100 hard capsules

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Leadiant GmbH  
Liebherrstr. 22  
80538 Munich  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/16/1110/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Chenodeoxycholic acid Leadiant

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC  
SN  
NN

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
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<b>BLISTER PACKS</b>
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<b>1. NAME OF THE MEDICINAL PRODUCT</b>
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Chenodeoxycholic acid Leadiant 250 mg hard capsules  
chenodeoxycholic acid

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
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Leadiant GmbH

<b>3. EXPIRY DATE</b>
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EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. OTHER</b>
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## **B. PACKAGE LEAFLET**

## **Package leaflet: Information for the user**

### **Chenodeoxycholic acid Lediart 250 mg hard capsules** chenodeoxycholic 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 or pharmacist.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

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

#### **1. What Chenodeoxycholic acid Lediart is and what it is used for**

Chenodeoxycholic acid Lediart capsules contain a substance called chenodeoxycholic acid. This substance is normally produced by the liver from cholesterol. It is a part of the bile, a fluid which helps in the digestion of fat and vitamins from food. Patients with a rare condition known as cerebrotendinous xanthomatosis (CTX) cannot produce chenodeoxycholic acid and this causes a build-up of fatty deposits in various areas of the body. This can cause damage to the affected areas.

Chenodeoxycholic acid Lediart capsules treats CTX by replacing the chenodeoxycholic acid, which prevents the build-up of the fatty deposits.

Chenodeoxycholic acid Lediart capsules can be used from the age of one month and patients with CTX will require treatment for the rest of their life.

#### **2. What you need to know before you take Chenodeoxycholic acid Lediart**

##### **Do not take Chenodeoxycholic acid Lediart**

- if you are allergic to chenodeoxycholic acid or any of the other ingredients of this medicine (listed in section 6)

##### **Warnings and precautions**

Chenodeoxycholic acid Lediart should be used under medical supervision. During your treatment, your doctor will carry out blood and urine tests to monitor your response to this medicine, and adjust your dose if necessary. More frequent tests may be needed if you are growing fast, if you are ill (if you have e.g. liver problems), or if you are pregnant. Your doctor will advise you if for any reason you have to stop treatment with Chenodeoxycholic acid Lediart.

**Babies (less than one month of age)**

The safety and efficacy of Chenodeoxycholic acid Lediart has not been studied in babies less than one month of age.

**Other medicines and Chenodeoxycholic acid Lediart**

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

The following medicines may affect the levels of Chenodeoxycholic acid Lediart:

- ciclosporin and sirolimus (medicines used to suppress the immune system)
- phenobarbital (a medicine used for epilepsy)

If your doctor considers it necessary for you to take ciclosporin, sirolimus or phenobarbital they will closely monitor the results of blood and urine tests and adjust the dose of Chenodeoxycholic acid Lediart if necessary.

Oral contraceptives may affect the way in which Chenodeoxycholic acid Lediart works making it less effective. It is not recommended to take oral contraceptives whilst taking Chenodeoxycholic acid Lediart. Please discuss suitable contraceptive methods with your doctor.

The following medicines may reduce the effect of Chenodeoxycholic acid Lediart:

- colestyramine, colestipol (so called bile acid sequestrants)
- medicines to treat heartburn (antacids) containing aluminium hydroxide and/or smectite (aluminium oxide)

If you have to take colestyramine then take Chenodeoxycholic acid Lediart either one hour before colestyramine or 4-6 hours after.

For the colestipol or heartburn medicines, take them either 2 hours before or 2 hours after taking Chenodeoxycholic acid Lediart.

Please talk to your doctor if you are taking any of these medicines.

**Pregnancy**

It is not recommended to take Chenodeoxycholic acid Lediart during pregnancy. There might be a risk to your unborn baby. If you think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

**Breastfeeding**

It is not known if Chenodeoxycholic acid Lediart passes into breast milk. Tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding, or whether to stop taking Chenodeoxycholic acid Lediart, considering the benefit of breast-feeding the baby and the benefit of Chenodeoxycholic acid Lediart to the mother.

**Contraception in females**

Women who could become pregnant should use an effective contraceptive method whilst taking Chenodeoxycholic acid Lediart. Oral contraceptives are not recommended (see Other medicines and Chenodeoxycholic acid). Please discuss suitable contraceptive methods with your doctor.

**Driving and using machines**

Chenodeoxycholic acid Lediart is not expected to affect your ability to drive or use machines.

**3. How to take Chenodeoxycholic acid Lediart**

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The usual starting dose in adults is one 250 mg capsule three times a day. The maximum dose is one 250 mg capsule four times a day. The capsules should be swallowed whole with water at approximately the same time each day. The capsules can be taken with or without food. Your doctor may decide to increase your dose depending on how your body responds to treatment. Your doctor will tell you how many capsules you need to take, and when you should take the capsules.

#### **Use in children and adolescents (aged one month to 18 years)**

In babies, children and adolescents the dose will be calculated based on the child's weight. The starting dose will be calculated at 5 mg per kg per day. The maximum dose for children is 15 mg per kg per day. The doctor will decide how many times and when your child should receive the dose(s) to make up the total dose for the day. Your doctor may change the dose depending on how your child responds to treatment.

For babies, children and those who cannot swallow capsules and/or need to take a dose below 250 mg, a capsule may be opened and the contents mixed with 8.4% sodium bicarbonate solution. The active substance will be dissolved in the sodium bicarbonate solution and as not all the contents of the capsule will be dissolved it appears as a mixture. This mixture might be prepared and provided to you by your pharmacy. The mixture should be provided in a glass bottle and can be kept for up to 7 days. Do not refrigerate or freeze the mixture. Your doctor or pharmacist will give you instructions on how much and how often your child needs to take the mixture. The mixture contains sodium, tell your doctor if you are on a controlled sodium diet.

#### **If you take more Chenodeoxycholic acid Leadiant than you should**

Chenodeoxycholic acid Leadiant is unlikely to cause serious side effects. You should contact your doctor for advice if you or your child has taken more than the amount prescribed.

#### **If you forget to take Chenodeoxycholic acid Leadiant**

Skip the missed dose and take your next dose when you would normally take it. Do not take a double dose to make up for a forgotten dose.

#### **If you stop taking Chenodeoxycholic acid Leadiant**

This medicine is for long-term use. Do not stop taking Chenodeoxycholic acid Leadiant without first speaking with your doctor. If you stop taking this medicine your symptoms may worsen.

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.

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

- constipation
- abnormal liver tests (increased transaminases)
- yellowing of the skin and the whites of the eyes (jaundice)

#### **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 this 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 Chenodeoxycholic acid Leadiant**

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

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

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 protect the environment.

## **6. Contents of the pack and other information**

### **What Chenodeoxycholic acid Leadiant contains**

- The active substance is chenodeoxycholic acid. Each capsule contains 250 mg of chenodeoxycholic acid.
- The other ingredients are:  
Capsule contents: maize starch, magnesium stearate, silica colloidal anhydrous,  
Capsule shell: gelatin, titanium dioxide (E 171), quinoline yellow (E 104), erythrosine (E 127)

### **What Chenodeoxycholic acid Leadiant looks like and contents of the pack**

Chenodeoxycholic acid Leadiant is provided as size 0 hard capsules which are 21.7 mm in length. The capsules consist of a yellow body and an orange cap containing a white compressed powder.

Chenodeoxycholic acid Leadiant is available in blister packs containing 100 hard capsules.

### **Marketing Authorisation Holder**

Leadiant GmbH  
Liebherrstr. 22  
80538 Munich  
Germany  
e-mail: [info@leadiantbiosciences.com](mailto:info@leadiantbiosciences.com)

### **Manufacturer**

Pharmaloop S.L.  
C/Bolivia, no 15 Polígono Industrial Azque  
Alcalá de Henares  
Madrid 28806  
Spain

**This leaflet was last revised in**

### **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.

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## Information for healthcare professionals only

### *Preparation of chenodeoxycholic acid suspension*

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

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

Stir the mixture until all the powder is in suspension. Take care to scrape any powder from the side of the bowl into the mixture and stir (for about 5 minutes) to make sure that there are no lumps. The mixture is ready when there are no visible lumps or powder.

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 by 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 then stable for up to 7 days.

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.

A pharmacy label should be placed on the bottle and include the patient's name, dosing instructions, use by date, name of medicinal product and any other required information to be in compliance with local pharmacy regulations.

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

*Dose calculation (children 1-11 years, adolescents 12-18 years and adults) chenodeoxycholic acid **10 mg/mL** suspension*

Daily dose:	(Weight in kg) x (Dose in mg/kg) = Daily dose in mg
Divided dose*	$\frac{\text{Daily dose in mg}}{\text{Dose frequency}}$ = Divided dose in mg
Volume to administer:	$\frac{\text{Divided dose in mg} \times 1 \text{ ml}}{10 \text{ mg}}$ = Amount of suspension to give
Example:	<p><b>10 kg</b> patient on a dose of <b>15 mg/kg</b> of chenodeoxycholic acid.</p> <p>The total daily dose =  <math>10 \text{ kg} \times 15 \text{ mg/kg} = 150 \text{ mg}</math></p> <p>The divided dose when given three times a day =  <math>\frac{150 \text{ mg}}{3} = 50 \text{ mg}</math></p> <p>The corresponding amount of suspension to give =  <math>\frac{50 \text{ mg} \times 1 \text{ ml}}{10 \text{ mg}} = 5 \text{ ml}</math></p>
*number of divided doses dependant on advice from doctor.	

*Dose calculation (infants 1 month-11 months) chenodeoxycholic acid **5 mg/mL** suspension*

Daily dose:	(Weight in kg) x (Dose in mg/kg) = Daily dose in mg
Divided dose*	$\frac{\text{Daily dose in mg}}{\text{Dose frequency}}$ = Divided dose in mg
Volume to administer:	$\frac{\text{Divided dose in mg} \times 1 \text{ ml}}{5 \text{ mg}}$ = Amount of suspension to give
Example:	<p><b>3 kg</b> patient on a dose of <b>5 mg/kg</b> of chenodeoxycholic acid.</p> <p>The total daily dose =  <math>3 \text{ kg} \times 5 \text{ mg/kg} = 15 \text{ mg}</math></p> <p>The divided dose when given three times a day =  <math>\frac{15 \text{ mg}}{3} = 5 \text{ mg}</math></p> <p>The corresponding amount of suspension to give =  <math>\frac{5 \text{ mg} \times 1 \text{ ml}}{5 \text{ mg}} = 1 \text{ ml}</math></p>
*number of divided doses dependant on advice from doctor.	

**ANNEX IV**  
**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS**  
**OF THE MARKETING AUTHORISATION(S)**

## **Scientific conclusions**

Taking into account the PRAC Assessment Report on the PSUR(s) for chenodeoxycholic acid (inborn error in primary bile acid synthesis, xanthomatosis - centrally authorised products only), the scientific conclusions of PRAC are as follows:

In view of available cumulative data on hepatic adverse reactions from the literature and spontaneous reports and in view of a plausible mechanism of action, the PRAC considers a causal relationship between chenodeoxycholic acid and increased transaminases and jaundice is at least a reasonable possibility.

The PRAC concluded that the product information of products containing chenodeoxycholic acid should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

## **Grounds for the variation to the terms of the marketing authorisation(s)**

On the basis of the scientific conclusions for chenodeoxycholic acid (inborn error in primary bile acid synthesis, xanthomatosis - centrally authorised products only) the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing chenodeoxycholic acid (inborn error in primary bile acid synthesis, xanthomatosis - centrally authorised products only) is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.