SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CHOLURSO 250 mg, film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ursodeoxycholic acid ……..…… 250 mg

For one tablet.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Concave-shaped white tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Primary biliary cirrhosis.
- Primary sclerosing cholangitis.
- Chronic cholestasis of cystic fibrosis.
- Progressive familial intrahepatic cholestasis type III.
- Symptomatic cholestasis of pregnancy.
- Biliary lithiasis of LPAC syndrome (Low Phospholipid Associated Cholelithiasis).
- Symptomatic cholesterol biliary lithiasis in a non sclero-atrophic gallbladder with normal wall in symptomatic patients with a contraindication to surgery.

4.2. Posology and method of administration

Oral route.

Cholestasis

- Primary biliary cirrhosis: 13 to 15 mg/kg/day.
- Primary sclerosing cholangitis: 15 to 20 mg/kg/day. Do not exceed 20 mg/kg/day.
- Chronic cholestasis of cystic fibrosis: 20 to 30 mg/kg/day.
- Genetic cholestasis: 20 to 30 mg/kg/day.

The starting dose is about 13 to 15 mg/kg/day. It is recommended to gradually increase the dose stepwise to achieve the optimal dose after 4 to 8 weeks of treatment without exceeding 20 mg/kg/day in primary sclerosing cholangitis (see section 4.4).

Cholestasis of pregnancy

10 to 20 mg/kg/day, as continuous treatment until delivery. The maximum daily dosage in cholestasis of pregnancy should not exceed 1000 mg/day, divided in 2 doses in the morning and evening at meals time.

Cholesterol biliary lithiasis

The recommended dosage is about 5 to 10 mg/kg/day, depending on the patient's weight.

It is recommended to take the treatment once a day in the evening or in two divided doses in the morning and in the evening.

4.3. Contraindications

This drug must not be used in the following cases:
- acute cholecystitis,
- cholangitis,

• bile duct obstruction,
• sclero-atrophic gallbladder,
• hypersensitivity to the active substance or one of the excipients.

4.4. Special warnings and precautions for use

In one clinical trial, high-dose UDCA (28-30 mg/kg/day) compared to placebo resulted in a higher risk of cumulative treatment failures (death, transplantation, varices, cirrhosis) in patients with Primary Sclerosing Cholangitis at an advanced stage. Such failures were not observed at lower dosages. Consequently, the maximum recommended dose of 20 mg/kg/day should not be exceeded.

When cholestyramine is combined for pruritus treatment, it will be necessary to comply with an interval of at least 4 hours between cholestyramine intake and that of ursodeoxycholic acid (see section 4.5).

During the first 3 months of treatment, liver function tests (AST, ALT, Gamma GT) should be monitored every 4 weeks and then every 3 months. In addition to the identification of responders and non responders, this monitoring will enable early detection of a possible deterioration of liver function, particularly in patients with PBC on treatment at an advanced stage of the disease.

It is recommended to reduce the dosage in case of diarrhea occurrence.

In cholesterol biliary lithiasis: the efficacy of treatment should be checked by ultrasound. In the absence of efficacy at the end of a sixth month period, treatment discontinuation is advised.

4.5. Interaction with other medicinal products and other forms of interaction

Association not recommended

Cholestyramine

Decrease the effect of bile acids that are bound by cholestyramine and eliminated. Cholestyramine intake should be separated from that of ursodeoxycholic acid for a time interval of 4 hours (see section 4.4).

Association to consider

Cyclosporine

Risk of changes in blood levels of cyclosporine.

4.6. Pregnancy and lactation

Pregnancy

Due to the limited clinical data on exposure during the first trimester of pregnancy, the use of ursodeoxycholic acid may be envisaged when the absence of treatment compromises the hepatic prognosis. During the second and third quarters, the use of ursodeoxycholic acid is possible due to many more clinical data.

Breast-feeding

There are very few published data on ursodeoxycholic acid and breast-feeding, but no events were reported to date in a small number of breastfed children. Use during lactation may be envisaged.

4.7. Effects on ability to drive and use machines

No effect on ability to drive or use machines has been observed.

4.8. Undesirable effects

Side effects are listed below, listed by organ class and frequency. Frequencies are defined as 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) including isolated reports. The frequent and very frequent effects have generally been described in clinical trials. The rare and very rare undesirable effects are generally notified spontaneously once the product has been marketed.

Gastrointestinal disorders

Common: pasty stools, diarrhea.
Very rare: right upper quadrant pain during the treatment of primary biliary cirrhosis.

Hepatobiliary disorders

Very rare: calcified gallstones, liver cirrhosis decompensation partially regressive on treatment discontinuation in case of initiation of treatment of primary biliary cirrhosis at an advanced stage (see section 4.4).

Skin and subcutaneous tissue disorders

Very rare: urticaria.

4.9. Overdose

In case of overdose, diarrhea may be observed. While increasing dose, the absorption of ursodeoxycholic acid decreases and its fecal excretion increases. The occurrence of other symptoms is unlikely.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamics properties

Pharmacotherapeutic group: Drugs based on bile acid (A: digestive system and metabolism), ATC code: A05AA02.

Ursodeoxycholic acid is a bile acid naturally present in very small quantities in humans. Unlike endogenous bile acids (chenodeoxycholic, cholic, deoxycholic and lithocholic acid), ursodeoxycholic acid is very hydrophilic and devoid of detergent properties.

Ursodeoxycholic acid has an effect on the enterohepatic circulation of endogenous bile acids: increase in biliary secretion, inhibition of their active reabsorption by the intestine, reducing their blood concentration.

Oral administration of ursodeoxycholic acid in humans alters the composition of bile acids in bile, ursodeoxycholic acid becomes the principal bile acid and replaces endogenous hydrophobic bile acids potentially toxic to hepatocytes and cholangiocytes, facilitating their elimination.

By changing the composition of bile and bile hydrophobic salts, ursodeoxycholic acid protects hepatocytes and cholangiocytes of the cytotoxicity of endogenous bile acids and inhibits hepatocytes apoptosis. These effects, demonstrated experimentally, may contribute to explain the preventive role of ursodeoxycholic acid on the development of fibrosis, especially in primary biliary cirrhosis.

In primary biliary cirrhosis, UDCA reduces serum levels of AST, ALT, GGT, bilirubin, alkaline phosphatase and LDL cholesterol and exerts a protective effect on the disease outcome when administered early.

In primary sclerosing cholangitis, UDCA reduces serum levels of AST, ALT, GGT, bilirubin, alkaline phosphatase with no proven effect on disease progression.

In chronic cholestasis of cystic fibrosis, UDCA reduces serum levels of AST, ALT, GGT and alkaline phosphatase.

In cholestasis of pregnancy, UDCA reduces serum levels of AST, ALT, bilirubin and total bile acids and allows regression of pruritus.

In progressive familial intrahepatic cholestasis type III and in LPAC syndrome, UDCA reduces serum levels of GGT and of bile acids. These diseases are often caused by mutations in the ABCB4 gene encoding the canalicular phospholipid transporter ABCB4/MDR3.

5.2. Pharmacokinetic properties

Ursodeoxycholic acid is absorbed passively in the small intestine. Its absorption depends on the dissolution by solubilization in mixed micelles of endogenous bile acids. The first-pass hepatic extraction is 50% to 60%. In the liver, ursodeoxycholic acid is conjugated with glycine and taurine. For intakes of 10 to 15 mg/kg/day, ursodeoxycholic acid represents 50% to 70% of all circulating bile acids.

The half-life is about 3 to 5 days.

Ursodeoxycholic acid is mainly excreted in feces, the kidney is a minor pathway of elimination.

5.3. Preclinical safety data

Studies of acute administration in three animal species (rat, mouse, dog) did not reveal any unexpected effect. Subacute and chronic toxicity studies have been conducted in rats and monkeys. In both species, hepatotoxicity with functional and morphological changes was observed at doses well above those used therapeutically.

The data obtained in *in vitro* and *in vivo* studies did not reveal any mutagenic, genotoxic or carcinogenic potential.

As part of the non-clinical studies of reproduction and fertility (rat, mouse, rabbit), effects were observed at doses very much higher than the doses recommended in therapeutics and prove without relevant meaning to clinical practice.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core

Corn starch, sodium laurilsulfate, povidone, colloidal anhydrous silica, magnesium stearate.

Film-coat

Lecithin, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide.

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

3 years.

6.4. Special precautions for storage

No special storage conditions.

6.5. Nature and contents of container

20, 30, 50 or 60 tablets in blister packs (PVC/PVDC/Aluminium).

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

LABORATOIRES MAYOLY SPINDLER
6, Avenue de l'Europe – BP 51
78401 CHATOU CEDEX - France

8. MARKETING AUTHORISATION NUMBER(S)

- 34 009 219 059 4 6: 20 tablets in blister packs (PVC/PVDC/Aluminium)
- 34 009 219 060 2 8: 30 tablets in blister packs (PVC/PVDC/Aluminium)
- 34 009 219 061 9 6: 50 tablets in blister packs (PVC/PVDC/Aluminium)
- 34 009 219 062 5 7: 60 tablets in blister packs (PVC/PVDC/Aluminium)

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10 November 2011.

10. DATE OF REVISION OF THE TEXT

May 2012.

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

List I.