SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cholurso 500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of ursodeoxycholic acid.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White oblong tablet (19 mm long, 8.8 mm wide) with a score line on each side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of primary biliary cirrhosis (PBC) in adult patients without decompensated cirrhosis.

- Dissolution of radiolucent cholesterol gallstones not larger than 15 mm in diameter in patients with a functioning gallbladder and for whom surgical treatment is not indicated.

4.2 Posology and method of administration

Oral route.

For patients weighing less than 47 kg or patients who are unable to swallow Cholurso 500 mg film-coated tablets, other formulations are available (suspension).

The following daily dose is recommended for the various indications:

For treatment of primary biliary cirrhosis (PBC)

Stage I-III

The daily dose is dependent on body weight and ranges from 1½ to 3½ film-coated tablets (12-16 mg ursodeoxycholic acid per kg of body weight).

During the first 3 months of treatment, Cholurso 500 mg film-coated tablets should be taken at mealtime in divided doses throughout the day. If liver function improves, the total daily dose can be taken once daily in the evening.

Body weight (kg)	Daily dose (mg/kg Body weight)	Cholurso 500 mg film-coated tablets			
		First 3 months			**Subsequently**
		Morning	Midday	Evening	evening (1 x daily)
47 – 62	12 – 16	½	½	½	1½
63 – 78	13 – 16	½	½	1	2
79 – 93	13 – 16	½	1	1	2½
94 – 109	14 – 16	1	1	1	3
Over 110		1	1	1½	3½

Stage IV:

In combination with increased serum bilirubin levels (> 40 µg/L; conjugated), only half the normal dosage should initially be given (see dosage for stages I - III), (6 - 8 mg ursodeoxycholic acid per kg body weight per day, equivalent to about 1 to 1½ Cholurso 500 mg film-coated tablets).

Thereafter, liver function should be closely monitored for several weeks (once every 2 weeks for 6 weeks). If there is no deterioration in liver function (AP, ALAT, ASAT, gamma-GT, bilirubin) and if no increased pruritus occurs, the dosage can be increased further to the usual level. However, liver function should again be closely monitored for several weeks. Once again, if there is no deterioration in liver function, the patient can be maintained at the normal dosage over the long term.

Patients with primary biliary cirrhosis (stage IV) without increased serum bilirubin levels are allowed to receive the normal starting dose immediately (see dosage stages I - III).

However, close monitoring of liver function, as described above, is likewise applicable in such cases; treatment of primary biliary cirrhosis will need to be regularly assessed on the basis of liver (laboratory) values and clinical findings.

The tablets should be swallowed whole with some liquid. Care should be taken to ensure that they are taken regularly.

Dissolution of Gallstones:

Adults: Approx. 10 mg ursodeoxycholic acid (UDCA) per kg body weight per day according to:

- up to 60 kg: 1 tablet
- 61-80 kg: 1½ tablet
- 81-100 kg: 2 tablets
- above 100 kg: 2½ tablets

The tablet should be swallowed whole with some liquid in the evening before bedtime. Care should be taken to ensure that they are taken regularly.

Based on experience to date, the duration of the dissolution process with Ursodeoxycholic acid is 6 months to 2 years, depending on the initial size of the stones. For a proper assessment of the therapeutic outcome, it is necessary, at the start of treatment, to accurately determine the size of the existing stones and subsequently to monitor them regularly, for example, every 3 to 4 months, via new X-rays and/or ultrasound scans.

In patients whose stones have not decreased in size after six months of treatment at the dosage stated, it is recommended that the biliary lithogenic index be determined via duodenal samples. If the bile has an index of > 1.0, it is unlikely that a favourable result can be obtained and it is better to consider a different form of treatment for gallstones. Treatment must be continued for 3 to 4 months after ultrasound follow-up has confirmed complete dissolution of the gallstones. Discontinuation of treatment for 3-4 weeks leads to a return of bile supersaturation and prolongs the overall duration of therapy. Discontinuation of treatment upon dissolution of the gallstones may be followed by a relapse.

Older people: There is no evidence to suggest that any alteration in the adult dose is needed but the relevant precautions should be taken into account.

4.3 Contraindications

Cholurso 500 mg film-coated tablets should not be used in patients with:

- acute inflammation of the gall bladder or biliary tract
- occlusion of the biliary tract (occlusion of the common bile duct or a cystic duct)
- frequent episodes of biliary colic
- radio-opaque calcified gallstones
- impaired contractility of the gall bladder

- hypersensitivity to active substance or hypersensitivity to peanut or soya or to any excipients listed in section 6.1

4.4 Special warnings and precautions for use

Cholurso 500 mg film-coated tablets should be taken under medical supervision.

During the first 3 months of treatment, liver function parameters AST (SGOT), ALT (SGPT) and γ-GT should be monitored by the physician every 4 weeks, thereafter every 3 months. Apart from allowing for identification of responders and non-responders in patients being treated for primary biliary cirrhosis, this monitoring would also enable early detection of potential hepatic deterioration, particularly in patients with advanced stage primary biliary cirrhosis.

When used for dissolution of cholesterol gallstones:

In order to assess therapeutic progress and for timely detection of any calcification of the gallstones, depending on stone size, the gall bladder should be visualised (oral cholecystography) with overview and occlusion views in standing and supine positions (ultrasound control) 6-10 months after the beginning of treatment.

If the gall bladder cannot be visualised on X-ray images, or in cases of calcified gallstones, impaired contractility of the gall bladder or frequent episodes of biliary colic, Cholurso 500 mg film-coated tablets should not be used.

Female patients taking Cholurso 500 mg film-coated tablets for dissolution of gallstones should use an effective non-hormonal method of contraception, since hormonal contraceptives may increase biliary lithiasis (see section 4.5. and 4.6.).

When used for treatment of advanced stage of primary biliary cirrhosis:

In very rare cases decompensation of hepatic cirrhosis has been observed, which partially regressed after the treatment was discontinued.

In patients with PBC, in rare cases the clinical symptoms may worsen at the beginning of treatment, e.g. the itching may increase. In this case the dose of Cholurso should be reduced to one Cholurso 250 mg film-coated tablet daily and then gradually increased again as described in section 4.2.

If diarrhoea occurs, the dose must be reduced and in cases of persistent diarrhoea, the therapy should be discontinued.

Ursodeoxycholic acid must not be used at doses beyond 20 mg/kg/day regarding the potential higher risk of treatment failures found in patients with primary sclerosing cholangitis.

Soya lecithin:

This medicine contains soya lecithin.

If a patient is hypersensitive to peanut or soya, Cholurso 500 mg film-coated tablets should not be used.

4.5 Interaction with other medicinal products and other forms of interaction

Cholurso 500 mg film-coated tablets should not be administered concomitantly with colestyramine, colestipol or antacids containing aluminium hydroxide and/or smectite (aluminium oxide), because these preparations bind ursodeoxycholic acid in the intestine and thereby inhibit its absorption and efficacy. Should the use of a preparation containing one of these substances be necessary, it must be taken at least 2 hours before or after Cholurso 500 mg film-coated tablets.

Cholurso 500 mg film-coated tablets can affect the absorption of ciclosporin from the intestine. In patients receiving ciclosporin treatment, blood concentrations of this substance should therefore be checked by the physician and the ciclosporin dose adjusted if necessary.

In isolated cases Cholurso 500 mg film-coated tablets can reduce the absorption of ciprofloxacin.

In a clinical study in healthy volunteers concomitant use of UDCA (500 mg/day) and rosuvastatin (20 mg/day) resulted in slightly elevated plasma levels of rosuvastatin. The clinical relevance of this interaction also with regard to other statins is unknown.

Ursodeoxycholic acid has been shown to reduce the plasma peak concentrations (Cmax) and the area under the curve (AUC) of the calcium antagonist nitrendipine in healthy volunteers. Close monitoring of the outcome of concurrent use of nitrendipine and ursodeoxycholic acid is recommended. An increase of the dose of nitrendipine may be necessary.

An interaction with a reduction of the therapeutic effect of dapsone was also reported.

These observations together with in vitro findings could indicate a potential for ursodeoxycholic acid to induce cytochrome P450 3A enzymes. Induction has, however, not been observed in a well-designed interaction study with budesonide, which is a known cytochrome P450 3A substrate.

Oestrogenic hormones and blood cholesterol lowering agents such as clofibrate increase hepatic cholesterol secretion and may therefore encourage biliary lithiasis, which is a counter –effect to ursodeoxycholic acid used for dissolution of gallstones.

4.6 Fertility, pregnancy and lactation

Animal studies did not show an influence of ursodeoxycholic acid on fertility (see section 5.3). Human data on fertility effects following treatment with ursodeoxycholic acid are not available.

There are no or limited amounts of data from the use of ursodeoxycholic acid in pregnant women. studies in animals have shown reproductive toxicity during the early phase of gestation (see section 5.3). Cholurso 500 mg film-coated tablets must not be used during pregnancy unless clearly necessary. Women of childbearing potential should be treated only if they are using reliable contraception; non-hormonal or low-oestrogen oral contraceptive measures are recommended. However, in patients taking Cholurso 500 mg film-coated tablets for dissolution of gallstones, effective non-hormonal contraception should be used, since hormonal oral contraceptives may increase biliary lithiasis.

The possibility of a pregnancy must be excluded before beginning treatment.

According to few documented cases of breastfeeding women milk levels of ursodeoxycholic acid are very low and probably no adverse reactions are to be expected in breastfed infants.

4.7 Effects on ability to drive and use machines

Cholurso 500 mg film-coated tablets has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The evaluation of undesirable effects is based on the following frequency data:

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 / Not known (< 1/10,000 /cannot be estimated from available data)

Gastrointestinal disorders:

Common: pasty stools or diarrhoea (reported from clinical trials).

Very rare: severe right upper abdominal pain (during the treatment of primary biliary cirrhosis).

Frequency not known: vomiting.

Hepatobiliary disorders:

Very rare: calcification of gallstones, decompensation of hepatic cirrhosis (during therapy of the advanced stages of primary biliary cirrhosis), which partially regressed after the treatment was discontinued.

Frequency not known: increase of the serologic levels of alkaline phosphatase, γ-GT and bilirubin (in patients with an advanced stage of PBC).

Skin and subcutaneous tissue disorders:

Very rare: urticaria.

Not known: an exacerbation of pruritus (upon the beginning of UDCA administration in patients with cirrhosis).

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Diarrhoea may occur in cases of overdose. In general, other symptoms of overdose are unlikely because the absorption of ursodeoxycholic acid decreases with increasing dose and therefore more is excreted with the faeces.

No specific counter-measures are necessary and the consequences of diarrhoea should be treated symptomatically with restoration of fluid and electrolyte balance.

Additional information on special populations:

Long-term, high-dose ursodeoxycholic acid therapy (28-30 mg/kg/day) in patients with primary sclerosing cholangitis (off-label use) was associated with higher rates of serious adverse events.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: A05AA02, Bile Acid Preparations

Bile acids are the most important components of bile and play a role in stimulating bile production. Bile acids are also important to keep cholesterol dissolved in bile. In healthy individuals, the ratio between cholesterol concentrations and bile acids in the gallbladder is such that cholesterol is kept dissolved for most of the day. Thus, no gallstones can form (bile is non-lithogenic). In patients with cholesterol stones in the gallbladder, this ratio has altered and the bile is supersaturated with cholesterol (bile is lithogenic). After some time, this may cause precipitation of cholesterol crystals and the formation of gallstones. Ursodeoxycholic acid can convert lithogenic bile into non-lithogenic bile and also gradually dissolve cholesterol gallstones.

Studies into the effect of ursodeoxycholic acid on cholestasis in patients with impaired biliary drainage and on clinical symptoms in patients with biliary cirrhosis have shown a rapid decline in cholestatic symptoms in the blood (as measured by increased levels of alkaline phosphatase (AP), gamma-GT and bilirubin) and pruritus, as well as decreased fatigue in most patients.

5.2 Pharmacokinetic properties

Ursodeoxycholic acid occurs naturally in the body. When given orally it is rapidly and completely absorbed. It is 96-98% bound to plasma proteins and efficiently extracted by the liver and excreted in the bile as glycine and taurine conjugates. In the intestine some of the conjugates are deconjugated and reabsorbed. The conjugates may also be dehydroxylated to lithocholic acid, part of which is absorbed, sulphated by the liver and excreted via the biliary tract.

5.3 Preclinical safety data

a) Acute toxicity

Acute toxicity studies in animals have not revealed any toxic damage.

b) Chronic toxicity

Subchronic toxicity studies in monkeys showed hepatotoxic effects in the groups given high doses, including functional changes (e.g. liver enzyme changes) and morphological changes such as bile duct proliferation, portal inflammatory foci and hepatocellular necrosis. These toxic effects are most likely attributable to lithocholic acid, a metabolite of ursodeoxycholic acid, which in monkeys – unlike humans – is not detoxified. Clinical experience confirms that the described hepatotoxic effects are of no apparent relevance in humans.

c) Carcinogenic and mutagenic potential

Two-year studies in mice and rats revealed no evidence of carcinogenic potential.

In vitro and in vivo genetic toxicology tests with ursodeoxycholic acid were negative.

d) Toxicity to reproduction

In studies in rats, tail malformations occurred after a dose of 2000 mg of ursodeoxycholic acid per kg of body weight. In rabbits, no teratogenic effects were found, although there were embryotoxic effects (from a dose of 100 mg per kg of body weight). Ursodeoxycholic acid had no effect on fertility in rats and did not affect peri-/post-natal development of the offspring.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Maize starch, sodium laurilsulfate, povidone (E1201), colloidal anhydrous silica, magnesium stearate.

Film-coat

Lecithin (Soya) (E322), polyethylene glycol (E1521), polyvinyl alcohol (E1203), talc (E553b), titanium dioxide (E171).

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

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

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

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6, avenue de l'Europe,

BP 51,

78401 CHATOU Cedex

FRANCE

8 MARKETING AUTHORISATION NUMBER(S)

PL 19549/0004

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