Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Proursan 500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of ursodeoxycholic acid (UDCA) as the active ingredient.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Almost white, oblong film-coated tablets with a break line on each side, length 17 mm and width 9 mm. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For dissolution of cholesterol gallstones of the gall bladder. The gallstones must not produce any shadows on the radiograph and should not be of a greater diameter than 15 mm, and the gall bladder, despite the gallstone(s), must be functioning.
For symptomatic treatment of primary biliary cholangitis (PBC), as long as there is no decompensated cirrhosis of the liver.

Paediatric population
For treatment of hepatobiliary disorders associated with cystic fibrosis in children aged 6 to 18 years.

4.2 Posology and method of administration

Proursan is suitable for patients with body weight of 47 kg and over. For patients weighing less than 47 kg or patients who are unable to swallow Proursan other formulations containing ursodeoxycholic acid might be available.

Posology

The following daily dosage is recommended for the various indications:

For the dissolution of cholesterol gallstones
Approx. 10 mg of ursodeoxycholic acid per kg of body weight corresponding to:

up to 60 kg	1 film-coated tablet
61 to 80 kg	1 ½ film-coated tablets
81 to 100 kg	2 film-coated tablets
over 100 kg	2 ½ film-coated tablets

The film-coated tablets should be taken in the evening before bedtime.

The time required for dissolution of gallstones is likely to range from 6 to 24 months. In case there is no reduction in gallstones after 12 months, the therapy should not be continued.
The success of treatment should be checked sonographically or radiographically every 6 months. It should also be observed during follow-up examinations whether in the meantime there has been any calcification of the stones. If this is the case, the treatment should be ended.

For symptomatic treatment of primary biliary cholangitis (PBC)
The daily dose depends on the body weight and ranges from 1 ½ to 3 ½ film-coated tablets (14 ± 2 mg of ursodeoxycholic acid per kg of body weight).

For the first 3 months of treatment Proursan should be taken divided over the day. With improvement of the liver values, the daily dose may be taken once daily in the evening.

Body weight (kg)		Proursan 500 mg film-coated tablets			
		first 3 months			**subsequent**
		morning	midday	evening	evening (1 × daily)
47–62		½	½	½	1 ½
63–78		½	½	1	2
79–93		½	1	1	2 ½
94–109		1	1	1	3
over 110		1	1	1 ½	3 ½

The use of Proursan in PBC may be continued indefinitely.

It is possible that at the beginning of treatment in patients with primary biliary cholangitis the clinical symptoms worsen, e.g. an aggravation of itching occurs. If this is the case, the therapy is to be continued with ½ film-coated tablets of Proursan per day and the therapy gradually (increase in the daily dose by ½ film-coated tablets per week) carried on, until the dose planned in the respective dosage plan is reached again.

Paediatric population
Children with cystic fibrosis aged 6 to 18 years
20 mg/kg/day in 2–3 divided doses, with a further increase to 30 mg/kg/day if necessary.

Body weight (kg)	Proursan 500 mg film-coated tablets		
	morning	midday	evening
20–29	½	-	½
30–39	½	½	½
40–49	½	½	1
50–59	½	1	1
60–69	1	1	1
70–79	1	1	1½
80–89	1	1½	1½

90–99	1½	1½	1½
100–109	1½	1½	2
over 110	1½	2	2

Proursan is not suitable for children under 6 years due to the pharmaceutical form and strength of the presentation.

Method of administration

The film-coated tablets should be swallowed unchewed with some liquid.
The tablets have to be taken regularly.

4.3 Contraindications

Proursan should not be used in patients with:
- acute inflammation of the gall bladder and the biliary tract,
- occlusion of the biliary tract (occlusion of the common bile duct or a cystic duct),
- frequent episodes of biliary colic,
- radioopaque calcified gallstones,
- impaired contractility of the gall bladder,
- hypersensitivity to bile acids or to any of the excipients listed in section 6.1.

Paediatric population
- unsuccessful portoenterostomy or without recovery of good bile flow in children with biliary atresia.

4.4 Special warnings and precautions for use

Proursan should be taken under medical supervision.

Proursan is suitable for patients with body weight of 47 kg and over. For patients weighing less than 47 kg or patients who are unable to swallow Proursan other formulations containing ursodeoxycholic acid might be available.

During the first three 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 cholangitis, this monitoring would also enable early detection of potential hepatic deterioration, particularly in patients with advanced stage primary biliary cholangitis.

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, Proursan should not be used.

Female patients taking Proursan for dissolution of gallstones should use an effective non-hormonal method of contraception, since hormonal contraceptives may increase biliary lithiasis (see sections 4.5 and 4.6).

When used for treatment of advanced stage of primary biliary cholangitis
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 Proursan should be reduced to ½ tablet Proursan 500 mg 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.

4.5 Interaction with other medicinal products and other forms of interaction

Proursan should not be administered concomitantly with cholestyramine, 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 active substances be necessary, it must be taken at least 2 hours before or after Proursan.
Ursodeoxycholic acid 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, ursodeoxycholic acid 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 (C^{max}) 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

Pregnancy
There are no or limited amount of data from the use of UDCA in pregnant women. Studies in animals have shown reproductive toxicity during the early phase of gestation (see section 5.3). Proursan must not be used during pregnancy unless clearly necessary.

Women of childbearing potential should be treated only if they use reliable contraception: non-hormonal or low-oestrogen oral contraceptive measures are recommended. However, in patients taking Proursan 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.

Breastfeeding
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.

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

4.7 Effects on ability to drive and use machines

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

Gastrointestinal disorders
In clinical trials, reports of pasty stools or diarrhoea during ursodeoxycholic acid therapy were common.
Very rarely, severe right upper abdominal pain has occurred during the treatment of primary biliary cholangitis.

Hepatobiliary disorders
During treatment with ursodeoxycholic acid, calcification of gallstones can occur in very rare cases.
During therapy of the advanced stages of primary biliary cholangitis, in very rare cases decompensation of hepatic cirrhosis has been observed, which partially regressed after the treatment was discontinued.

Skin and subcutaneous tissue disorders
Very rarely, urticaria can occur.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website:www.hpra.ie; e-mail:medsafety@hpra.ie.

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 UDCA 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

Pharmacotherapeutic group: bile and liver therapy; bile acid preparations, ATC code: A05AA02.

Ursodeoxycholic acid is found in small amounts in human gall.
Upon oral administration, it induces a decline in cholesterol saturation of the gall bladder through blocking of cholesterol resorption in the intestine and decline in cholesterol secretion to the gall. A gradual decomposition of cholesterol gallstones is presumably achieved through dispersion of cholesterol and forming of liquid crystals.
The effect of ursodeoxycholic acid in liver and cholestatic diseases is, according to current knowledge, based on relative exchange of lipophilic, detergent-type, toxic bile acids for hydrophilic, cytoprotective, non-toxic ursodeoxycholic acid, improvement of the secretory performance of liver cells and immunoregulative processes.

Paediatric population
Cystic fibrosis
From clinical reports long-term experience up to 10 years and more is available with UDCA treatment in paediatric patients suffering from cystic fibrosis associated hepatobiliary disorders (CFAHD). There is evidence that treatment with UDCA can decrease bile duct proliferation, halt progression of histological damage and even reverse hepatobiliary changes if given at early stage of CFAHD. Treatment with UDCA should be started as soon as the diagnosis of CFAHD is made in order to optimise treatment effectiveness.

5.2 Pharmacokinetic properties

Orally administered ursodeoxycholic acid is resorbed fast in the jejunum and upper ileum through passive, and in terminal ileum active transport. The resorption rate generally amounts to 60–80%. Upon resorption the bile acid conjugates almost completely with the glycine and taurine amino acids in the liver and then biliary excretion follows. The first-pass-clearance through liver amounts up to 60%.

Depending on the daily dose and the underlying disease or the liver condition, the more hydrophilic ursodeoxycholic acid accumulates in the gall. Concurrently, a relative reduction of the other, more lipophilic bile acids takes place.

In the intestine, a partial bacterial degradation to 7-keto-lithocholic acid and lithocholic acid takes place. The lithocholic acid is liver-toxic and induces liver parenchymal damage in a range of animal species. In humans, it is resorbed only to a very minor extent. This fraction is sulphated by the liver and thus detoxicated and then, again, biliary and subsequently fecal excretion follow.
The biological half-life of ursodeoxycholic acid is around 3.5 to 5.8 days.

5.3 Preclinical safety data

Acute toxicity
Studies conducted on animals concerning acute toxicity did not indicate any toxic damage.

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.

Carcinogenic and mutagenic potential
Long-term studies in mice and rats revealed no evidence of ursodeoxycholic acid having carcinogenic potential.
*In vitro*and *in vivo* genetic toxicology tests with ursodeoxycholic acid were negative.

Toxicity to reproduction
In studies in rats, tail malformations occurred after a dose of 2,000 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-/postnatal development of the offspring.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Maize starch
Maize starch, pregelatinised
Sodium starch glycolate A (E468)
Silica colloidal anhydrous (E551)
Magnesium stearate (E470b)

Tablet coating
Hypromellose 6 (E464)
Titanium dioxide (E171)
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC-PVDC/Al blister in a cardboard box.
Pack size: 10, 20, 30, 40, 50, 60, 80, 90 or 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

PRO.MED.CS Praha a.s.
Telcska 377/1
Michle
Prague 4
140 00
Czech Republic

8 MARKETING AUTHORISATION NUMBER

PA2179/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 9th May 2023

10 DATE OF REVISION OF THE TEXT

October 2022