

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ursosan 250 mg, hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 250 mg ursodeoxycholic acid (UDCA) as the active substance.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

White, hard gelatin capsules (size 0) containing (almost) white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the dissolution of gallstones in the gallbladder. The gallstones should not cause shadows on an X-ray and should not be larger than 15 mm in diameter. The gallbladder must function despite the gallstones.

For treatment of reflux gastritis (bilious reflux).

For the symptomatic treatment of primary biliary cholangitis (PBC), provided there is no worsening of liver cirrhosis.

Pediatric population

For the treatment of hepatobiliary disorders related to cystic fibrosis in children between 6 years and 18 years of age.

4.2 Dosage and method of administration

There are no age restrictions for using Ursosan. Ursosan is suitable for patients with a body weight of 47 kg or more.

The following daily dosage is recommended for the different indications:

For dissolving cholesterol stones

Approximately 10 mg ursodeoxycholic acid per kg body weight, corresponding to:

up to 60 kg	61	2 hard capsules
to 80 kg	81 to 100	3 hard capsules
kg above 100 kg		4 hard capsules
		5 hard capsules

The hard capsules should be swallowed with water in the evening before going to bed without chewing.

The capsules should be taken regularly.

The duration of resolution of gallstones is generally 6 to 24 months. If there is no reduction in gallstones after 12 months, treatment should not be continued.

The result of the treatment should be checked ultrasound or radiographically every 6 months. During follow-up examinations it should also be checked whether calcification of the stones has occurred in the meantime. If this is the case, treatment should be stopped.

Behandeling van refluxgastritis (gallige reflux).

Take 1 hard capsule of Ursosan once a day, in the evening before going to bed, swallowed whole with water.

To treat reflux gastritis (bilious reflux), Ursosan should be taken for 10 - 14 days. In general, the duration of treatment corresponds to the course of the disease. The doctor on duty decides on specifics during the duration of the treatment.

For symptomatic treatment of primary biliary cholangitis (PBC): The daily dosage depends on body weight and

ranges from 3 to 7 hard capsules (14 ± 2 mg ursodeoxycholic acid per kg body weight).

During the first 3 months of treatment, Ursosan should be taken throughout the day. If the liver values improve, the daily dosage can be reduced to once a day in the evening.

Body weight (kg)	Daily dose (mg/kg/BW)	Ursosan 250 mg, hard capsules			
		first 3 months			thereafter
		'in the morning	at noon	'in the evening	'in the evening (1 x daily)
47–62	12 -16	1	1	1	3
63–78	13 -16	1	1	2	4
79–93	13 -16	1	2	2	5
94–109	14 -16	2	2	2	6
above 110	-	2	2	3	7

The hard capsules should be swallowed unchewed with liquid. Make sure the tablets are taken regularly.

The use of Ursosan in case of PBC can be continued indefinitely.

It is possible that early in the treatment of patients with primary biliary cholangitis, clinical symptoms may worsen, for example increased pruritus. If this is the case, therapy should be continued with 1 hard capsule of Ursosan per day and therapy can be continued gradually (increasing the daily dose by 1 hard capsule per week) until the planned dose in the respective dosing schedule is reached.

Pediatric population Children with

cystic fibrosis between 6 and 18 years of age

20 mg/kg/day in 2–3 divided doses, with further increases to 30 mg/kg/day if necessary.

Body weight (kg)	Ursosan 250 mg, hard capsules		
	in the morning at noon		'in the evening
20–29	1	-	1
30–39	1	1	1
40–49	1	1	2
50–59	1	2	2
60–69	2	2	2
70–79	2	2	3

80–89	2	3	3
90–99	3	3	3
100–109	3	3	4
above 110	3	4	4

4.3 Contraindications

Ursosan should not be used in patients with:

- acute inflammation of the gallbladder and bile ducts; - closure of the bile ducts (occlusion of the common bile duct or a cystic duct); - frequent attacks of biliary colic; - calcified gallstones visible on an X-ray;
- reduced contraction of the gallbladder; - hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pediatric population

Failed Kasai surgery or insufficient restoration of proper bile drainage in children with biliar atresia.

4.4 Special warnings and precautions for use

Ursosan should be used under medical supervision.

During the first three months of treatment, the liver function values AST (SGOT), ALT (SGPT) and γ -GT should be checked by the doctor every 4 weeks, thereafter every 3 months.

In addition to distinguishing between responders and non-responders treated for primary biliary cholangitis, this monitoring also allows early detection of potential deterioration of liver function, especially in patients with advanced primary biliary cholangitis.

When used to dissolve cholesterol stones

In order to assess the therapeutic progression of the dissolution of gallstones and to timely identify any calcification of the stones, the gallbladder should be visualized, depending on the size of the stones, 6 to 10 months after the start of treatment (oral cholecystography). with overall images and images of contraction in standing and lying positions (ultrasound control).

If the gallbladder cannot be visualized on X-rays, or in case of calcified stones, reduced contractility of the gallbladder or frequent attacks of biliary colic, Ursosan should not be used.

Female patients taking Ursosan for dissolution of gallstones should use an effective non-hormonal method of contraception, because hormonal contraceptives cause biliary lithiasis can strengthen (see sections 4.5 and 4.6).

When used to treat advanced primary biliary cholangitis

In very rare cases, reduction in liver cirrhosis has been observed, which partially resolved after discontinuation of treatment.

In patients with PBC, in rare cases, clinical symptoms may worsen at the beginning of treatment, for example increased itching. In this case, the dose of Ursosan should be reduced to one Ursosan capsule of 250 mg per day and then gradually increased as described in section 4.2.

If diarrhea occurs, the dosage should be reduced. In case of persistent diarrhea, treatment should be discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

Ursosan should not be used simultaneously with cholestyramine, colestipol or antacids based on aluminum hydroxide and/or smectite (aluminium oxide), because these substances bind ursodeoxycholic acid in the intestine and therefore reduce absorption and effectiveness. If the use of such a medicine is necessary, it should be taken at least 2 hours before or after using Ursosan.

Ursosan may affect the absorption of cyclosporine in the intestines. In patients treated with cyclosporine, blood levels of cyclosporine should be monitored and the cyclosporine dosage adjusted if necessary.

In isolated cases, Ursosan may reduce the absorption of ciprofloxacin.

In a clinical study in healthy volunteers, the concomitant use of UDCA (500 mg/day) and rosuvastatin (20 mg/day) resulted in slightly increased plasma levels of rosuvastatin. The clinical significance of this interaction, also with regard to other statins, is not known.

Ursodeoxycholic acid has been shown to reduce the peak plasma concentration (C_{max}) and area under the curve (AUC) of the calcium channel blocker nitrendipine in healthy volunteers. Close monitoring of the outcome of the concomitant use of nitrendipine and ursodeoxycholic acid is advised. An increase in nitrendipine dosage may be necessary. An interaction with the reduced therapeutic effect of dapsone has also been found.

These observations, together with in vitro results, may indicate that ursodeoxycholic acid may induce cytochrome P450 3A enzymes. However, this was not demonstrated in a clinical study with budesonide, a known cytochrome P450 3A substrate.

Estrogens and blood cholesterol-lowering agents, such as clofibrate, may increase hepatic cholesterol excretion and promote biliary lithiasis, which is the opposite effect of using ursodeoxycholic acid to dissolve gallstones.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data on the use of ursodeoxycholic acid in pregnant women. In Reproductive toxicity has been observed in animal studies, particularly during early gestation (see section 5.3). Ursosan should not be used during pregnancy unless clearly necessary.

Women of childbearing potential should only be treated if they use reliable contraception: non-hormonal contraception or oral contraception with low estrogen dosage is recommended. However, effective non-hormonal contraception should be used in patients taking Ursosan for dissolution of gallstones as hormonal oral contraceptives may increase biliary lithiasis.

Before starting treatment, a possible pregnancy should be excluded.

Breastfeeding

According to a number of documented cases in breastfeeding women, ursodeoxycholic acid levels in breast milk are very low and no side effects are expected in breastfed children.

Fertility Animal

studies showed no influence of ursodeoxycholic acid (UDCA) on fertility (see section 5.3). No data are available on fertility in humans after treatment with ursodeoxycholic acid.

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 Side effects

The assessment of adverse reactions 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 the available data)

Gastrointestinal disorders

In clinical trials, reports of sticky stools or diarrhea during treatment with ursodeoxycholic acid were common.

Very rarely, severe right upper abdominal pain has been reported during the treatment of primary biliary cholangitis.

Hepatobiliary disorders

During treatment with ursodeoxycholic acid, calcification of gallstones may occur in very rare cases.

During the treatment of advanced stages of primary biliary cholangitis, in very rare cases, decrease in liver cirrhosis was observed, which partially resolved after discontinuation of treatment.

Subcutaneous or skin disorders

In very rare cases, urticaria can occur.

Reporting suspected side effects It is

important to report suspected side effects after authorization of the medicinal product. In this way, the benefit-risk balance of the medicine can be continuously monitored. Healthcare professionals are requested to report all suspected side effects via the Dutch Side Effects Center Lareb. Website: www.lareb.nl

4.9 Overdose

In case of overdose, diarrhea may occur. In general, other symptoms of overdose unlikely because the absorption of ursodeoxycholic acid decreases with increasing dosage and therefore more is excreted in the feces.

No specific countermeasures are required. The consequences of diarrhea should be treated symptomatically with restoration of fluid and electrolyte balance.

Additional information for 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 frequencies of serious adverse events.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: biliary and hepatic therapy; bile acid preparations, ATC code: A05AA02 and A05B.

Ursodeoxycholic acid occurs in small amounts in human bile.

After oral administration, it induces a decrease in cholesterol saturation of the gallbladder by blocking cholesterol resorption in the intestines and decreasing cholesterol excretion in the bile. Gradual breakdown of cholesterol stones is probably achieved by dispersion of cholesterol and the formation of liquid crystals.

The effect of ursodeoxycholic acid in hepatic and cholestatic diseases is, according to current knowledge, based on relative exchange of lipophilic, detergent-like, toxic bile acids for hydrophilic, cutoprotective, non-toxic ursodeoxycholic acid, an improvement in the secretory performance of liver cells and immunoregulatory processes.

Pediatric patients

Cystic fibrosis

Clinical reports are available based on more than 10 years of practical experience with UDCA treatments of pediatric patients suffering from cystic fibrosis associated with hepatobiliary disorders (CFAHD). There is evidence that treatment with UDCA can reduce proliferation, halt the progression of histological damage and even reverse hepatobiliary disease when administered early in CFAHD. Treatment with UDCA should be initiated as soon as possible once CFAHD is diagnosed to optimize treatment effectiveness.

5.2 Pharmacokinetic properties

After oral administration, ursodeoxycholic acid is rapidly released into the jejunum and the first part of the ileum absorbed by passive transport, and in the last part of the ileum by active transport. The resorption rate is generally 60-80%. After resorption, bile acid takes up virtually all glycine and taurine amino acids in the liver, followed by biliary excretion. During the first round of clearance by the liver, the resorption rate is 60%. Depending on the daily dosage and the underlying disease or liver disease, more hydrophilic ursodeoxycholic acid accumulates in the bile. At the same time, a relative decrease in the other, more lipophilic bile acids takes place.

A partial bacterial breakdown into 7-keto lithocholic acid and lithocholic acid takes place in the intestines. Lithocholic acid is liver toxic and induces parenchymatous liver damage in a number of animal species. In humans it is only absorbed to a very small extent. It is sulfated by the liver and thus detoxified, after which biliary and subsequent fecal excretion can take place again.

The biological half-life of ursodeoxycholic acid is approximately 3.5 to 5.8 days.

5.3 Data from the preclinical safety study

Acute Toxicity

Studies conducted on animals regarding acute toxicity have not shown any toxic damage.

Chronic Toxicity:

Subchronic toxicity studies in monkeys demonstrated hepatotoxic effects in groups receiving high doses, including functional changes (e.g. liver enzyme changes) and morphological changes such as bile duct proliferation, portal inflammation and hepatocellular necrosis. These toxic effects are most likely due to lithocholic acid, a metabolite of ursodeoxycholic acid, which is not detoxified in monkeys - unlike in humans.

Clinical experience confirms that the described hepatotoxic effects have no obvious relevance in humans.

Carcinogenic and mutagenic potential

Long-term studies in mice and rats showed no evidence of carcinogenic potential of ursodeoxycholic acid.

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

Reproductive toxicity

In studies in rats, tail malformations occurred at a dose of 2,000 mg ursodeoxycholic acid per kg body weight. No teratogenic effects were found in rabbits, although there were embryotoxic effects (from a dose of 100 mg per kg body weight).

Ursodeoxycholic acid had no effect on the fertility of rats and did not affect the peri- and postnatal development of the offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Corn starch
- Pregelatinized corn starch
- Anhydrous colloidal silica (E551)
- Magnesium stearate (E470b)
- Gelatine (E441)
- Titanium dioxide (E171)

6.2 Incompatibilities

Does not apply.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of the packaging

PVC/PVdC and Al blister pack, box Pack
size: 10, 20, 30, 40, 50, 60, 80, 90 or 100 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other instructions

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

PRO.MED.CS Praha a.s.

Telýská 377/1

Michle, 140 00 Prague 4

Czech Republic

8. MARKETING AUTHORIZATION NUMBER(S).

RVG 120431

**9. DATE OF FIRST GRANT OF THE AUTHORIZATION/RENEWAL OF
THE PERMIT**

Date of first granting of the permit: March 13, 2018

Date of last renewal: January 4, 2023

10. DATE OF REVISION OF THE TEXT

Last partial change concerns section 9: May 19, 2022