URSOSAN® 250 MG HARD CAPSULES

Ursodeoxycholic Acid (250 mg)

DESCRIPTION
Hard capsule.
White, hard gelatin capsules containing white or almost white powder.

COMPOSITION
Each capsule contains 250 mg of ursodeoxycholic acid.

List of excipients:
Maize starch, Maize starch, pregelatinised, Silica colloidal anhydrous, Magnesium stearate, Titanium dioxide and Gelatin.

PHARMACODYNAMICS
Pharmacotherapeutic group: Bile and liver therapy; bile acids and derivatives. ATC Code: A05AA02.

Ursodeoxycholic acid is found in small amounts in human bile.
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.

PHARMACOKINETICS
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.

INDICATION
- Dissolution of symptomatic, radiolucent cholesterol gallstones in the gallbladder less than 15 mm in diameter. The gallstones must be radiolucent, and the gallbladder function must be intact; dissolution of gallstones with or without preceding extracorporeal shock wave lithotripsy.
- Cholestatic liver disease (e.g. compensated primary biliary cirrhosis, cholestasis of pregnancy).

RECOMMENDED DOSAGE
Posology

Dissolution of cholesterol gallstones
The recommended dose in adult patients dependent on the body weight (10 mg/kg/day).
The total daily dose should be administered as one single dose, in the evening before going to bed. Ursosan® needs to be taken regularly.

Body weight	Ursodeoxycholic acid	Number of capsules
Up to 60 kg	500 mg	2
61–80 kg	750 mg	3
81–100 kg	1,000 mg	4
Over 100 kg	1,250 mg	5

The time required for dissolution of gallstones is generally 6 to 24 months, depending on stone size and composition. If there is no reduction in the size of the gallstones after 12 months, the therapy should not be continued. The success of treatment should be checked sonographically or radiographically every 6 months.

Cholestatic liver disease
The daily dose depends on the body weight and usually is 10-15 mg/kg/day (i.e. 2-6 capsules) taken in 2-3 divided doses.

Body weight	Ursodeoxycholic acid	Number of capsules	Time of administration **morning**	Time of administration **midday**	Time of administration **evening**
34 - 50 kg	500 mg	2	1	-	1
51 - 65 kg	750 mg	3	1	1	1
66 - 85 kg	1,000 mg	4	1	1	2
86 - 110 kg	1,250 mg	5	1	2	2
Over 110 kg	1,500 mg	6	2	2	2

Method of administration
The capsules should be swallowed whole and not chewed, with a sufficient amount of fluids.

CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients;
- Acute inflammation of the gallbladder or bile ducts;
- Occlusion of extrahepatic bile ducts (choledochus duct or cystic duct);
- Frequent episodes of biliary colics;
- Radiopaque calcified gallstones;
- Impaired contractility of the gallbladder.

WARNING AND PRECAUTION
URSOSAN® should be administered under medical supervision.
During the treatment, it is necessary to monitor liver enzyme levels (AST, ALT, γ-GT): during the first 3 months of treatment, they should be monitored every 4 weeks, thereafter every 3 months. Besides determining whether patients treated for primary biliary cholangitis respond to the treatment or not, this monitoring could allow timely detection of a potential risk of hepatic damage, especially in patients with primary biliary cholangitis in an advanced stage.

If used for dissolution of cholesterol gallstones:

In order to assess therapeutic progress and for timely detection of any calcification of the gallstones, oral cholecystography with radiographs in standing and supine positions or ultrasound control should be performed 6–10 months after the beginning of treatment (depending on stone size).

If the gallbladder cannot be visualised on X-ray images, or in cases of calcified gallstones, impaired contractility of the gallbladder or frequent episodes of biliary colic, Ursosan® should not be used.

Female patients taking Ursosan® for dissolution of gallstones should use an efficient non-hormonal contraception method as hormonal anticonception may increase the risk of biliary lithiasis.

<u>If used for the treatment of primary biliary cholangitis in an advanced stage:</u>
Decompensation of liver cirrhosis was observed in very rare cases, which partially subsided after discontinuation of the therapy.

In rare cases, clinical symptoms of the disease may worsen in patients with PBC, for example, the pruritus may worsen. In such a case the Ursosan® dose should be reduced to one 250 mg capsule of Ursosan® daily and then the dose should be gradually increased again by one capsule weekly until the originally prescribed dose is reached.

If diarrhoea occurs, the dose must be reduced. If diarrhoea persists, the therapy needs to be stopped.

INTERACTIONS WITH OTHER MEDICAMENTS
Ursosan® should not be administered concomitantly with cholestyramine, colestipol or antacids containing aluminium hydroxide and/or smectite (aluminium oxide) as these products 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 Ursosan®.

Ursosan® can affect the absorption of cyclosporine from the intestine. In patients concurrently receiving this substance, concentrations of cyclosporine should therefore be checked and its dose adjusted if necessary.

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

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

The ursodeoxycholic acid was demonstrated to decrease the maximum plasma concentration (C_{max}) and the area under the curve (AUC) of nitrendipine, a calcium antagonist in healthy volunteers. It is recommended to carefully monitor the result of concurrent administration of nitrendipine and ursodeoxycholic acid. The nitrendipine dose may need to be increased. A decreased therapeutic effect of dapsone was observed. This observation, together with *in vitro* findings, indicated the potential of ursodeoxycholic acid to induce cytochrome P450 3A enzymes. However, no induction was observed in a well-designed study of an interaction with budesonide, a known cytochrome P450 3A substrate.

Oestrogens and blood cholesterol lowering agents such as clofibrate increase cholesterol secretion in the liver and may thus support the formation of biliary concrements, which is an opposite effect than the effect of ursodeoxycholic acid used to dissolve gallstones.

STATEMENT ON USAGE DURING PREGNANCY AND LACTATION
<u>Pregnancy</u>

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. Ursosan® 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 Ursosan® 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.

Lactation
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 ursodeoxycholic acid on fertility. Human data on fertility effects following treatment with ursodeoxycholic acid are not available.

ADVERSE EFFECTS / UNDESIRABLE EFFECTS
The evaluation of undesirable effects is based on the following frequency data: very common, common, uncommon, rare, very rare, not known.

Gastrointestinal disorders
Common: Pasty stools or diarrhoea were observed in clinical trials during the therapy.
Very rare: Severe right upper abdominal pain (in patients with primary biliary cholangitis).

Hepatobiliary disorders
Very rare: Calcification of gallstones, decompensation of liver cirrhosis (in patients with primary biliary cholangitis in an advanced stage), which partially subsided after the treatment was discontinued.

Skin and subcutaneous tissue disorders
Very rare: Urticaria (mainly at the beginning of the therapy).

OVERDOSAGE
Diarrhoea may occur in overdose with UDCA. In this case, the dose must be reduced, and if diarrhoea persist, the treatment must be discontinued.
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. If diarrhoeic stools occur, these should be treated symptomatically with fluids and electrolytes.

Additional information for special patient groups
Long-term treatment with high doses of UDCA (28–30 mg/kg/day) in patients with primary sclerosing cholangitis (off-label use) has been associated with an increased incidence of serious adverse reactions.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Ursodeoxycholic acid has no or negligible influence on the ability to drive and use machines.

STORAGE CONDITION
Store below 30°C.

SHELF-LIFE
36 months.

DOSAGE FORM AND PACKAGING AVAILABLE
PVC/PVdC and Al blister, carton.
Pack size: 30, 50 or 100 capsules.

MANUFACTURER:
PRO.MED.CS Praha a.s.
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Czech Republic

PRODUCT REGISTRATION HOLDER:
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