URSOSAN FORTE®, 500 mg film-coated tablets

Ursodeoxycholic Acid (500 mg)

DESCRIPTION

Film-coated tablets.

Almost white, oblong film-coated tablets with a break line and length 17 mm. The tablet can be divided into equal halves.

COMPOSITION

Each film-coated tablet contains 500 mg of ursodeoxycholic acid.

List of excipients:

maize starch, pregelatinised starch, sodium starch glycolate A, silica colloidal anhydrous, magnesium stearate, hypromellose 6, titanium dioxide (E171), macrogol 400.

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 rapidly absorbed in in the jejunum and upper ileum through passive, and in terminal ileum active transport. The rate of absorption is generally 60–80 %. After absorption, the bile acid undergoes almost complete hepatic conjugation with the amino acids glycine and taurine and is then excreted with the bile. First-pass clearance through the liver is up to 60%.

Depending on the daily dose and underlying disorder or condition of the liver, the more hydrophilic ursodeoxycholic acid accumulates in the bile. At the same time, a relative decrease in other more lipophilic bile acids is observed.

Under the influence of intestinal bacteria, there is partial degradation to 7-ketolithocholic acid and lithocholic acid. Lithocholic acid is hepatotoxic and causes liver parenchyma damage in a number of animal species. In humans, only very small amounts are absorbed, which are sulphated in the liver and thus detoxified, before being excreted in the bile and ultimately in the faeces.

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

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
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. The tests with ursodeoxycholic acid revealed no relevant evidence of a mutagenic effect.

d) Toxicity to reproduction
In studies in rats, tail aplasia occurred after a dose of 2000 mg 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.

INDICATION

- Dissolution of cholesterol gallstones in the gallbladder. The gallstones must not show as shadows on X-ray images and should not exceed 15 mm in diameter. Gall bladder must be functioning, despite the gallstones.
- Symptomatic treatment of primary biliary cirrhosis (PBC), in patients without decompensated hepatic cirrhosis.

RECOMMENDED DOSAGE

Posology
For patients weighing less than 47 kg or patients who are unable to swallow Ursosan Forte® 500mg film-coated tablets, ursodeoxycholic acid capsules are available.

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 at bedtime. Ursosan Forte® needs to be taken regularly.

Body weight	Ursodeoxycholic acid	Number of film-coated tablets
Up to 60 kg	500 mg	1
61 – 80 kg	750 mg	1½
81 – 100 kg	1,000 mg	2
Over 100 kg	1,250 mg	2½

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. At the follow-up examinations, a check should be made to see whether calcification of the stones has occurred in the meantime. Should this be the case, the treatment must be ended.

Symptomatic treatment of primary biliary cirrhosis (PBC)
The daily dose depends on body weight and ranges from 1½ to 3½ film-coated tablets (14 ± 2 mg of ursodeoxycholic acid per kg of body weight).
For the first 3 months of treatment, Ursosan Forte® should be taken divided over the day. When the liver function parameters improve, the daily dose may be taken once daily in the evening.

Body weight	Ursosan Forte® 500 mg film-coated tablets			
	first 3 months			subsequently
	morning	midday	evening	evening (1 x daily)
47 – 62 kg	½	½	½	1½
63 – 78 kg	½	½	1	2
79 – 93 kg	½	1	1	2½
94 – 109 kg	1	1	1	3
Over 110 kg	1	1	1½	3½

The use of Ursosan Forte® mg film-coated tablets in primary biliary cirrhosis may be continued indefinitely. In patients with primary biliary cirrhosis, in rare cases the clinical symptoms may worsen at the beginning of treatment, e.g. the itching may increase. In this event, therapy should first be continued with half an Ursosan Forte® film-coated tablets or one ursodeoxycholic acid capsule (containing 250 mg of ursodeoxycholic acid) daily, and the dose then gradually increased (weekly increase of the daily dose by half a film-coated tablet or one ursodeoxycholic acid capsule) until the dose indicated in the respective dosage regimen is reached again. In this case the dose of Ursosan Forte® should be reduced to one Ursosan 250 mg capsule daily and then gradually increased again until the dose indicated in the respective dosage regimen is reached again.

Method of administration

The tablets should be swallowed whole and not chewed, with a sufficient amount of fluids. The tablets must be taken regularly.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients;
- Acute inflammation of the gallbladder or biliary tract;
- Occlusion of the biliary tract (occlusion of the common bile duct or cystic duct);
- Frequent episodes of biliary colics;
- Radio-opaque calcified gallstones;
- Impaired contractility of the gallbladder.

WARNINGS AND PRECAUTIONS

Ursosan Forte® should be administered under medical supervision.

During the treatment, it is necessary to monitor liver enzyme levels AST (SGOT), ALT (SGPT), 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 Forte® should not be used.

If used for the treatment of primary biliary cholangitis in an advanced stage:

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 Forte® dose should be reduced to one 250 mg capsule of Ursosan Forte® 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 Forte® 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 Forte® 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.

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

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

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.

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.

STATEMENT ON USAGE DURING PREGNANCY AND LACTATION

Pregnancy

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 Forte® 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 Forte® 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 (≥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
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 at temperatures not exceeding 30 °C.

SHELF-LIFE
48 months.

DOSAGE FORM AND PACKAGING AVAILABLE

PVC/PVdC and Al blister, carton.
Pack size: 50 or 100 film-coated tablets.

MANUFACTURER:
PRO.MED.CS Praha a.s.
Telčská 377/1
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Czech Republic

PRODUCT REGISTRATION HOLDER:
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