Ursofalk Kapseln Gebrauchsinformation (GI) für Malaysia
Mat.-Nr.: 1242780 (Losan Pharma)
Falk-Datumscode: MY/01.25
Laetuscode: 329
Machart: plano
Format: 300 x 200 mm
Druckfarben: (1/1) Schwarz
Grammatur: 50 g/m²
Schriftgröße/ZAB: 8pt / 9,5pt

Ursofalk® Capsules

Active Substance: ursodeoxycholic acid

Composition:
Active Substance:
One Ursofalk® capsule contains 250 mg of ursodeoxycholic acid

Other ingredients:
Maize starch, Silica colloidal anhydrous, magnesium stearate, titanium dioxide [E171], sodium dodecyl sulphate, gelatin, water.

Source of gelatin in the capsule: bovine
Source of ursodeoxycholic acid: bovine

Pharmacodynamic properties:
Pharmacotherapeutic group: Bile and liver therapy, bile acids and derivatives
ATC code: A05AA02

Small amounts of ursodeoxycholic acid are found in human bile.

After oral administration, it reduces cholesterol saturation of the bile by inhibiting cholesterol absorption in the intestine and decreasing cholesterol secretion into the bile. Presumably as a result of dispersion of the cholesterol and formation of liquid crystals, a gradual dissolution of cholesterol gallstones occurs.

According to current knowledge, the effects of ursodeoxycholic acid in hepatic and cholestatic diseases are thought to be due to a relative exchange of lipophilic, detergent-like, toxic bile acids for the hydrophilic, cytoprotective, non-toxic ursodeoxycholic acid, together with an improvement in the secretory capacity of the hepatocytes, as well as to immune-regulatory processes.

Pharmacokinetic properties:
Orally administered ursodeoxycholic acid is rapidly absorbed in the jejunum and upper ileum through passive transport and in the terminal ileum through 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-keto-lithocholic 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 genotoxicity tests with ursodeoxycholic acid were negative.

d) Toxicity to reproduction
In studies in rats, tail aplasia 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.

Indications:
- Dissolution of 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 proceeding extracorporeal shock wave lithotripsy.
- Cholestatic liver disease (e.g. compensated primary biliary cholangitis (PBC), cholestasis of pregnancy).

Contraindications:
Ursofalk® must not be used in the presence of:
- acute inflammation of the gallbladder and bile ducts.
- occlusion of the biliary tract (common bile duct).
- hypersensitivity to bile acids or to any of the excipients of the formulation listed above.

Ursofalk® should not be taken where the gallbladder cannot be visualized at X-ray, in patients with calcified or X-ray dense gallstones (non-cholesterol gallstones), disturbed contractility of the gallbladder, gallbladder filled more than half with gallstones, occlusion of ductus cysticus, frequent biliary colic.

Precaution/Warning:
Ursofalk® capsules should be taken under medical supervision.

In 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 PBC, this monitoring would also enable early detection of potential hepatic deterioration, particularly in patients with advanced stage PBC.

When used for the dissolution of cholesterol gallstones:
In order to assess therapeutic progress and for prompt 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.

Female patients taking Ursofalk® capsules for dissolution of gallstones should use an effective non-hormonal method of contraception, since hormonal contraceptives may increase biliary lithiasis.

When used for treatment of advanced stage of PBC:
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 (e.g. itching) may worsen at the beginning of treatment. In this case the dose of Ursofalk® capsules should be reduced to one Ursofalk® capsule daily and then gradually increased again as described.

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

Use during pregnancy and lactation:
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.

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. Ursofalk® capsules must not be used during pregnancy unless clearly necessary.

Women of childbearing potential
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 Ursofalk® capsules 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.

Effects on ability to drive and use machines:
Ursofalk® capsules have no or negligible influence on the ability to drive and use machines.

Side effects:
Adverse reactions observed in clinical trials and during the treatment with Ursofalk® capsules are listed in the table below, by MedDRA system organ class and frequency. Frequencies are defined as: 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) or Not known (cannot be estimated from the available data).

MedDRA system organ class	Common	Very rare	Not known
Gastrointestinal disorders	Soft stools or diarrhoea	Severe right upper abdominal pain during treatment of PBC	Nausea, vomiting
Hepatobiliary disorders		Calcification of gallstones, decompensation of hepatic cirrhosis[1]	
Skin and subcutaneous tissue disorders		Urticaria	Pruritus

[1] Observed during therapy of the advanced stages of PBC and which partially regressed after treatment was discontinued.

Drug interactions:
Ursofalk® capsules 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 reduce 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 Ursofalk® capsules.

Ursofalk® capsules can increase 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, Ursofalk® capsules can reduce the absorption of ciprofloxacin.

In a clinical study in healthy volunteers concomitant use of ursodeoxycholic acid (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 peak plasma concentrations (Cmax) and 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.

Dosage:
For dissolution of cholesterol gallstones (approx. 10mg per kg bodyweight daily):

		Time of administration
Body weight	**Daily dose**	**In the evening**
Up to 60 kg	2 capsules	2
61 – 80 kg	3 capsules	3
81 – 100 kg	4 capsules	4
Over 100 kg	5 capsules	5

The capsules should be swallowed whole with some liquid in the evening at bedtime. They must be taken regularly.

For the treatment of PBC
The daily dose depends on body weight (BW) and ranges from 3 to 7 capsules (14 ± 2 mg ursodeoxycholic acid per kg of body weight). For the first 3 months of treatment, Ursofalk® capsules should be taken in divided doses throughout the day. When the liver function parameters improve, the daily dose may be taken once daily in the evening.

Body weight (kg)	Daily dose (mg/kg BW)	Ursofalk® capsules			
		first 3 months			**subsequently**
		morning	midday	evening	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
over 110		2	2	3	7

The capsules should be swallowed whole with some liquid. They must be taken regularly.

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 event, therapy should first be continued with 1 capsule of Ursofalk® capsules daily, and the dose then gradually increased (weekly increase of the daily dose by one capsule) until the dose indicated in the respective dosage regimen is reached again.

Route and duration of administration:
Oral

Duration of treatment:
Dissolution of gallstones generally takes from 6 to 24 months to dissolve. If the gallstones have not become smaller after 12 months, do not continue treatment. The results of therapy should be monitored by ultrasonography or X-ray 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, treatment must be ended.

The use of Ursofalk® capsules in PBC may be continued indefinitely.

Symptoms and treatment of overdosage:
Following overdose, diarrhoea may occur. In general, other symptoms of overdose are unlikely, as the absorption rate of ursodeoxycholic acid decreases with increasing dosage, and therefore more substance is eliminated in the faeces.
In cases of diarrhea it is advisable to reduce the dose. If diarrhea does not subside, therapy should be discontinued.
No specific counter-measures are necessary and the consequences of diarrhoea should be treated symptomatically with restoration of fluid and electrolyte balance.

Presentation:
Capsule 250mg x 100's

Description:
White, opaque gelatin capsule (coni-snap). Size 0, containing a white, compressed powder or granules.

Shelf life:
5 years. Do not take the medicine after the expiry date.

Storage conditions:
Store at 30°C or below.

Date of first authorisation: 15.12.1986
Date of last renewal: 02.02.2024

Date of information:
January 2025

Keep medicines out of the reach of children!

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