Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ursofalk® 250 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250mg of ursodeoxycholic acid (UDCA) as the active substance.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.
White opaque hard gelatin capsules (size 0) containing a white compressed powder or granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Primary biliary cirrhosis (PBC) stages I – III.

For the dissolution of cholesterol gallstones in functioning gallbladders with or without prior extracorporeal shock wave lithotripsy.

Paediatric population
Hepatobiliary disorders associated with cystic fibrosis in children aged 6 to 18 years.

4.2 Posology and method of administration

There are no age restrictions on the use of Ursofalk capsules in the treatment of PBC and for the dissolution of gallstones. For patients weighing less than 47kg or patients who are unable to swallow Ursofalk capsules, Ursofalk suspension is available.

Ursofalk capsules are for oral administration.

The following daily dose is recommended for the various indications:

Primary biliary cirrhosis (PBC) stages I – III:
The daily dose depends on body weight, and ranges from 3 to 7 capsules (14 ± 2 mg UDCA per kg of body weight).

For the first 3 months of treatment, Ursofalk capsules 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)	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. Care should be taken to ensure that they are taken regularly.

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

Dissolution of Gallstones:
Adults: The usual dose is 10 – 12mg/kg/day to be taken in the evening, i.e. 750mg, daily in the evening.

Paediatric population
Both PBC and gallstones are very rare in children and adolescents and there are no adequate data on the efficacy and safety in this population. The administration of Ursofalk is based on body weight and the medical condition.

Hepatobiliary disorders associated with Cystic Fibrosis
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 BW [kg]	**Daily dose [mg/kg BW]**	**Ursofalk 250mg hard capsules**		
		Morning	**Midday**	**Evening**
20 – 29	17-25	1	--	1
30 – 39	19-25	1	1	1
40 – 49	20-25	1	1	2
50 – 59	21-25	1	2	2
60 – 69	22-25	2	2	2
70 – 79	22-25	2	2	3
80 – 89	22-25	2	3	3
90 – 99	23-25	3	3	3
100 – 109	23-25	3	3	4
>110		3	4	4

4.3 Contraindications

Ursofalk should not be used in patients with:

- Acute inflammation of the gall bladder or biliary tract
- occlusion of the biliary tract (occlusion of the common bile duct or a cystic duct)
- frequent episodes of biliary colic
- radio-opaque calcified gallstones
- impaired contractility of the gall bladder
- hypersensitivity to bile acids or any excipient of the formulation

When used in hepatobiliary disorders associated with cystic fibrosis in children aged 6 to 18 years.

- Unsuccessful portoenterostomy or without recovery of good bile flow in children with biliary atresia

4.4 Special warnings and precautions for use

Ursofalk capsules should be taken under medical supervision.

During 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 treatment of advanced stage of primary biliary cirrhosis:
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 should be reduced to 250mg daily and then gradually increased again as described in section 4.2.

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, Ursofalk should not be used.

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

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 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 UDCA in the intestine and thereby inhibit 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 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 Ursofalk capsules can reduce the absorption of ciprofloxacin.

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

UDCA 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 UDCA 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

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.

Pregnancy
There are no or limited amounts 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). 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 use reliable contraception: non-hormonal or low-oestrogen oral contraceptive measures are recommended. However, in patients taking Ursofalk 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 UDCA are very low and probably no adverse reactions are to be expected in breastfed infants.

4.7 Effects on ability to drive and use machines

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

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

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

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 the national reporting system

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4.9 Overdose

Diarrhoea may occur in cases of overdose. In general, other symptoms of overdose are unlikely because the absorption of UDCA 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/ATC code
Group: Bile acid preparations and ursodeoxycholic acid
Code: A05AA and A05AA02

UDCA is a bile acid. It affects concentration of cholesterol in bile. Furthermore, UDCA can prevent cholestasis and cellular lesions induced by biliary obstruction or bile acid administration. In addition, UDCA has a direct protective action on liver cell membranes by blocking bile acid receptors or by the incorporation of ursodeoxycholic acid into the liver cell membrane.

Cystic fibrosis - Paediatric population
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

Following oral administration, UDCA is absorbed, conjugated in the liver and excreted in bile. It is converted by bacteria to lithocholic acid and it undergoes enterohepatic recycling.

5.3 Preclinical safety data

No further relevant information other than that, which is included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate
Maize starch
Silica, colloidal anhydrous

Capsule Shell
Gelatin
Titanium dioxide (E171)
Sodium lauryl sulphate

6.2 Incompatibilities

None known.

6.3 Shelf life

5 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/Aluminium blister packs packed in cardboard cartons to contain 100 capsules (4 strips each containing 25 capsules) or 60 capsules (6 blister strips of 10 capsules).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA0573/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 November 1984

Date of last renewal: 14 November 2009

10 DATE OF REVISION OF THE TEXT

June 2022