SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ursofalk ® (Capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 hard capsule of Ursofalk® (Capsules) contains 250 mg ursodeoxycholic acid (UDCA) as the active substance.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

Appearance: white, opaque, hard gelatin capsules size 0, containing a white compressed powder or granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- For the dissolution of cholesterol gallstones in the gall bladder. The gallstones must not show as shadows on X-ray images and should not exceed 15 mm in diameter. Gall bladder function must not be significantly impaired, despite the gallstones.

- For the treatment of bile reflux gastritis.

- For the treatment of primary biliary cirrhosis (PBC) in patients without decompensated hepatic cirrhosis.

Paediatric population:

For the treatment of hepatobiliary disorder associated with cystic fibrosis in children aged 6 years to less than 18 years.

4.2 Posology and method of administration

There are no age restrictions on the use of Ursofalk® (Capsules).

The following daily dose is recommended for the various indications:

For dissolution of cholesterol gallstones

Approx. 10 mg of UDCA per kg of body weight, equivalent to:

Up to 60 kg	2 hard capsules
61-80 kg	3 hard capsules
81-100 kg	4 hard capsules
Over 100 kg	5 hard capsules

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

The time required for the dissolution of gallstones is generally 6-24 months. If there is no reduction in the size of the gallstones after 12 months, the therapy should not be continued.

The success of the treatment should be checked by means of ultrasound or X-ray examination every 6 months. At the follow-up examinations, a check should be carried out to see whether calcification of the stones has occurred in the meantime. Should this be the case, the treatment must be ended.

For the treatment of bile reflux gastritis

1 hard capsule of Ursofalk® (Capsules) should be swallowed whole with some liquid once daily in the evening before bedtime.

For the treatment of bile reflux gastritis, Ursofalk® (Capsules) should normally be taken for 10-14 days. In general, the duration of use depends on the course of the disease. The treating physician will decide on the duration of use in the individual case.

For the treatment of PBC

The daily dose depends on body weight (BW) and ranges from 3 to 7 hard capsules (14 ± 2 mg UDCA 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)	**Ursofalk® (Capsules)**			
	first 3 months			**subsequently**
	morning	midday	evening	evening (1 x daily)
47-62	1	1	1	3
63-78	1	1	2	4
79-93	1	2	2	5
94-109	2	2	2	6
over 110	2	2	3	7

The hard capsules should be swallowed whole with some liquid. Ursofalk® (Capsules) must be taken regularly.

The use of Ursofalk® (Capsules) in PBC may be continued indefinitely.

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 hard capsule of Ursofalk® (Capsules) daily, and the dose then gradually increased (weekly increase of the daily dose by one hard capsule) until the dose indicated in the respective dosage regimen is reached again.

Paediatric population:

Children with cystic fibrosis aged 6 years to less than 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® (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® (Capsules) 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 cystic duct)
- frequent episodes of biliary colic
- radio-opaque calcified gallstones
- impaired contractility of the gall bladder

Hypersensitivity to bile acids or to any of the excipients listed in section 6.1

Paediatric population
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, the liver function parameters AST (SGOT), ALT (SGPT) and ɣ- 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 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® (Capsules) should not be used.

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 (see sections 4.5 and 4.6)

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 1 capsule of Ursofalk® (Capsules) daily and then gradually increased again as described in section 4.2.

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

4.5 Interactions with other medicinal products and other forms of interaction

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 (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.

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 UDCA to induce cytochrome P450 3A enzymes. Induction by UDCA 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 UDCA 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.

There are no or limited amount 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 child-bearing 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.

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

Ursofalk® (Capsules) have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable 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 /not known (<1/10,000) (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.

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

Pharmacodynamic properties

Pharmacotherapeutic group: Bile and liver therapy, bile acids and derivatives

ATC code: A05AA02 and A05B

Small amounts of UDCA are found in human bile.

After oral administration, UDCA 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 effect of UDCA in hepatic and cholestatic diseases is thought to be due to a relative exchange of lipophilic, detergent-like, toxic bile acids for the hydrophilic, cytoprotective, non-toxic UDCA, to an improvement in the secretory capacity of the hepatocytes, and to immune-regulatory processes.

Paediatric population

Cystic fibrosis

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 disease (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

Orally administered UDCA 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, UDCA 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 UDCA 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 UDCA is 3.5-5.8 days

5.3 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 UDCA, 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 UDCA having carcinogenic potential. In vitro and in vivo genotoxicity tests with UDCA were negative.

d) Toxicity to reproduction:
In studies in rats, tail aplasia occurred after a dose of 2000 mg of UDCA 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). UDCA had no effect on fertility in rats and did not affect peri-/postnatal development of the offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

1. Gelatin
2. Silica, colloidal anhydrous
3. Magnesium stearate
4. Maize starch
5. Sodium dodecyl sulphate
6. Titanium dioxide (E 171)
7. Purified water

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

Do not use after the expiry date as stated on the carton and on the blister strips.

6.4 Special precautions for storage:

Keep medicines out of the reach and sight of children. Store below 25 °C.

6.5 Nature and contents of container

Ursofalk® (Capsules) are available in blister packs of 50 and 100 capsules.

Transparent, colourless PVC foil, welded with hot seal lacquer to aluminium foil

7. MARKETING AUTHORISATION HOLDER:

A. Menarini (Thailand) Limited, Bangkok, Thailand

Manufactured by

DR. FALK PHARMA GmbH
Freiburg im Breisgau,
Germany

8. MARKETING AUTHORISATION NUMBER(S):

1C 344/48

9. DATE OF FIRST AUTHORISATION:

23-Dec-2005

10. DATE OF REVISION OF THE TEXT:

Apr, 2025