Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ursofalk 500mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One Ursofalk 500mg film-coated tablet contains 500mg of ursodeoxycholic acid (UDCA) as the active substance.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets
Appearance: white, oval, biconvex film-coated tablets with a breakline on both sides.
The tablet may be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of primary biliary cirrhosis (PBC), provided there is no decompensated hepatic cirrhosis.

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. The gall bladder must be functioning despite the gallstone(s).

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 tablets in the treatment of PBC and for the dissolution of radiolucent gallstones. For patients weighing less than 47 kg or patients who are unable to swallow Ursofalk tablets, Ursofalk capsules and suspension are available.

The following daily dose is recommended for the various indications:

For the treatment of primary biliary cirrhosis (PBC)
The daily dose depends on body weight and ranges from 1½ to 3½ tablets (14 ± 2 mg of UDCA per kg of body weight).

For the first 3 months of treatment, Ursofalk tablets 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)	Film-coated tablets			
		first 3 months			subsequently
		morning	midday	evening	evening (1 x daily)
47 – 62	12 – 16	½	½	½	1½
63 – 78	13 – 16	½	½	1	2
79 – 93	13 – 16	½	1	1	2½
94 – 109	14 - 16	1	1	1	3
Over 110		1	1	1½	3½

The tablets should be swallowed with some liquid. The tablets should not be crushed or chewed. Care should be taken to ensure that they are taken regularly.

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

For dissolution of cholesterol gallstones
Approximately 10 mg of UDCA per kg of body weight, equivalent to:
up to 60 kg 1 tablet
61-80 kg 1½ tablets
81-100 kg 2 tablets
over 100 kg 2½ tablets

The tablets should be swallowed with some liquid in the evening at bedtime. The tablets should not be crushed or chewed.

The tablets must be taken regularly.

The time required for 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 made 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 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 UDCA (mg/kg BW)**	**Ursofalk 500mg Film-coated Tablets**		
		Morning	**Midday**	**Evening**
20 – 29	17-25	½	--	½
30 – 39	19-25	½	½	½
40 – 49	20-25	½	½	1
50 – 59	21-25	½	1	1
60 – 69	22-25	1	1	1
70 – 79	22-25	1	1	1½
80 – 89	22-25	1	1½	1½
90 – 99	23-25	1½	1½	1½
100 – 109	23-25	1½	1½	2
>110		1½	2	2

4.3 Contraindications

Ursofalk tablets 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 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 biliar**y** atresia

4.4 Special warnings and precautions for use

Ursofalk tablets 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 primary biliary cirrhosis, this monitoring would also enable early detection of potential hepatic deterioration, particularly in patients with advanced stage primary biliary cirrhosis.

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 tablets 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 tablets 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. .

Ursofalk tablets 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 tablets 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 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 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 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 ursodeoxycholic acid 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 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 ursodeoxycholic acid, calcification of gallstones can occur in very rare cases.
During therapy of the advanced stages of primary biliary cirrhosis, 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 ursodeoxycholic acid therapy were common.
Very rarely, severe right upper abdominal pain has occurred during the treatment of primary biliary cirrhosis.

Skin and subcutaneaous 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: HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2. Tel: +353 1 6764971 Fax: +353 1 6762517 Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

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
Code: A05AA02

Small amounts of UDCA 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 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 ursodeoxycholic acid, to an improvement in the secretory capacity of the hepatocytes, and to immune-regulatory processes.

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

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, 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 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 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 malformations 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-/post-natal development of the offspring.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Magnesium stearate
Polysorbate 80
Povidone K25
Cellulose, microcrystalline
Silica, colloidal anhydrous
Crospovidone (type A)
Talc

Coating:
Hypromellose
Macrogol 6000
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Transparent, colourless PVC/PVDC film, welded with hot seal lacquer to aluminium foil.

Pack sizes:
Packs of 50 and 100 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Dr. Falk Pharma GmbH
Leinenweberstrasse 5
79108 Freiburg
Germany

8 MARKETING AUTHORISATION NUMBER

PA0573/005/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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November 2015