

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Ursofalk® 250mg / 5ml Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

5 ml (= 1 cup) of Ursofalk Suspension contains 250 mg ursodeoxycholic as the active ingredient.

Excipients with known effect:

5 ml of Ursofalk Suspension contain 7.5 mg benzoic acid, 50 mg propylene glycol and 11 mg sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension

Appearance: white, homogenous oral suspension with small air bubbles and an odour of lemon.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of primary biliary cholangitis (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 15mm in diameter. The gall bladder must be functioning despite the gallstone(s).

Paediatric population

Hepatobiliary disorders associated with cystic fibrosis in children aged 1 month to 18 years.

4.2 Posology and method of administration

There are no age restrictions on the use of Ursofalk suspension in the treatment of PBC and for the dissolution of gallstones.

The following daily dose is recommended for the various indications:

For the treatment of primary biliary cholangitis (PBC)

The daily dose depends on body weight, and is approx. 14 ± 2 mg ursodeoxycholic acid per kg of body weight.

For the first 3 months of treatment, Ursofalk suspension should be taken divided over the day. When the liver function parameters improve, the daily dose can be administered once a day in

the evening.

Body weight (kg)	Daily dose (mg/kg BW)	Cups* of Ursofalk suspension			
		first 3 months			<u>subsequently</u>
		morning	midday	evening	evening (1 x daily)
8 – 11	12 – 16	-	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{2}$
12 – 15	12 – 16	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{3}{4}$
16 – 19	13 – 16	$\frac{1}{2}$	-	$\frac{1}{2}$	1
20 – 23	13 – 15	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{2}$	1 $\frac{1}{4}$
24 – 27	13 – 16	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	1 $\frac{1}{2}$
28 – 31	14 – 16	$\frac{1}{4}$	$\frac{1}{2}$	1	1 $\frac{3}{4}$
32 – 39	12 – 16	$\frac{1}{2}$	$\frac{1}{2}$	1	2
40 – 47	13 – 16	$\frac{1}{2}$	1	1	2 $\frac{1}{2}$
48 – 62	12 – 16	1	1	1	3
63 – 80	12 – 16	1	1	2	4
81 – 95	13 – 16	1	2	2	5
96 – 115	13 – 16	2	2	2	6
Over 115		2	2	3	7

*One cup (= 5 ml oral suspension) contains 250 mg of ursodeoxycholic acid.

Ursofalk suspension should be taken in accordance with the dosage regimen given above. The oral suspension must be taken regularly.

The use of Ursofalk suspension in primary biliary cholangitis may be continued indefinitely.

For dissolution of cholesterol gallstones

Approximately 10 mg of ursodeoxycholic acid per kg of body weight daily, equivalent to:

Body weight	Cups *	equivalent to ml
5 to 7 kg	$\frac{1}{4}$	1.25
8 to 12 kg	$\frac{1}{2}$	2.50
13 to 18 kg	$\frac{3}{4}$ (= $\frac{1}{4} + \frac{1}{2}$)	3.75
19 to 25 kg	1	5.00
26 to 35 kg	1 $\frac{1}{2}$	7.50
36 to 50 kg	2	10.00
51 to 65 kg	2 $\frac{1}{2}$	12.50
66 to 80 kg	3	15.00
81 to 100 kg	4	20.00
Over 100 kg	5	25.00

*One cup (= 5 ml oral suspension) contains 250 mg of ursodeoxycholic acid.

Ursofalk suspension should be taken in the evening at bedtime. The oral suspension 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, treatment must be ended.

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 1 month to 18 years: 20 mg/kg/day in 2-3 divided doses, with a further increase to 30 mg/kg/day if necessary

Very rarely, children under 10 kg body weight are affected. In this case, a commercially available single-use syringe should be used (please note: a syringe is not provided in the pack)

Up to 10 kg body weight: Dosing 20 mg UDCA/kg/day

Measuring device: single-use 2 ml graduated syringe (**not provided**)

Body weight (kg)	Ursofalk Suspension (ml)	
	Morning	Evening
4	0.8	0.8
4.5	0.9	0.9
5	1.0	1.0
5.5	1.1	1.1
6	1.2	1.2
6.5	1.3	1.3
7	1.4	1.4
7.5	1.5	1.5
8	1.6	1.6
8.5	1.7	1.7
9	1.8	1.8
9.5	1.9	1.9
10	2.0	2.0

More than 10 kg body weight (BW): Dosing 20-25 mg UDCA/kg/day

Measuring device: measuring cup

Body weight (kg)	Daily dose UDCA (mg/kg BW)	*Cups of Ursofalk Suspension	
		Morning	Evening
11 – 12	21-23	½	½
13 – 15	21-24	½	¾
16 – 18	21-23	¾	¾
19 – 21	21-23	¾	1
22 – 23	22-23	1	1
24 – 26	22-23	1	1¼
27 – 29	22-23	1¼	1¼
30 – 32	21-23	1¼	1½
33 – 35	21-23	1½	1½
36 – 38	21-23	1½	1¾
39 – 41	21-22	1¾	1¾
42 – 47	20-22	1¾	2

48 – 56	20-23	2¼	2¼
57 – 68	20-24	2¾	2¾
69 – 81	20-24	3¼	3¼
82 – 100	20-24	4	4
>100		4½	4½

* Conversion table:

	Ursofalk suspension	Ursodeoxycholic acid
1 cup	= 5 ml	= 250 mg
¾ cup	= 3.75 ml	= 187.5 mg
½ cup	= 2.5 ml	= 125 mg
¼ cup	= 1.25 ml	= 62.5 mg

4.3 Contraindications

Ursofalk suspension 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 1 month 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 Suspension 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 and thereafter every 3 months. Apart from allowing for identification of responders and non-responders in patients being treated for primary biliary cholangitis, this monitoring would also enable early detection of potential hepatic deterioration, particularly in patients with advanced stage primary biliary cholangitis.

When used for treatment of advanced stage of primary biliary cholangitis:

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 of Ursofalk 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 suspension should not be used.

Female patients taking Ursofalk for dissolution of gallstones should use an effective non-hormonal method of contraceptive, 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.

This medicinal product contains 7.5 mg benzoic acid in each 5 ml of suspension. Benzoic acid may increase jaundice in neonates.

This medicinal product contains 50 mg propylene glycol in each 5 ml of suspension. May induce serious adverse effects in neonates.

This medicinal product contains 11 mg sodium per 5 ml of suspension, equivalent to 0.6 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interactions with other medicinal products and other forms of interaction

Ursofalk suspension 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 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 suspension.

Ursofalk suspension 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 suspension 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.

Ursodeoxycholic acid has been shown to reduce the peak plasma concentrations (C_{max}) 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 in 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 ursodeoxycholic acid 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 ursodeoxycholic acid in pregnant women. Studies in animals have shown reproductive toxicity during the early phase of gestation (see section 5.3). Ursofalk suspension 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 ursodeoxycholic acid 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

Ursodeoxycholic acid has 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 are listed in the table below, by MedDRA system organ class and frequency. Frequencies are defined as:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ 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
<i>Gastrointestinal disorders</i>	Soft stools or diarrhoea	Severe right upper abdominal pain during treatment of PBC	Nausea, vomiting
<i>Hepatobiliary disorders</i>		Calcification of gallstones, decompensation of hepatic cirrhosis ¹	
<i>Skin and subcutaneous tissue disorders</i>		Urticaria	Pruritus

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

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 scheme:

Ireland

4.9 Overdose

Diarrhoea may occur in cases of overdose. 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 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 Preparation

ATC code: A05AA02 and A05B

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 effect of ursodeoxycholic acid 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 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.

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

Benzoic acid
Citric acid
Glycerol
Microcrystalline cellulose
Carmellose sodium
Sodium chloride
Sodium citrate 2H₂O
Sodium cyclamate
Propylene glycol
Purified water
Xylitol
Lemon flavouring

6.2 Incompatibilities

None known

6.3 Shelf life

Unopened container: 4 years

After first opening: 4 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Amber glass bottle (type III) with a child-resistant plastic screw cap (PP/PE), a PE pouring device and a 5 ml measuring cup with 4 embossed graduations: 1.25 ml, 2.5 ml, 3.75 ml and 5 ml.

Pack sizes

Bottle of 250 ml oral suspension

6.6 Special precautions for disposal and other handling

Opening the child-resistant closure:

To open the bottle, press down firmly on the cap whilst twisting it to the left.

Shake the closed bottle vigorously before each use.

No special precautions for disposal.

7. MARKETING AUTHORISATION HOLDER

Dr. Falk Pharma GmbH
Leinenweberstr. 5
79108 Freiburg
Germany

8. MARKETING AUTHORISATION NUMBER

PA 573/5/2

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th January 2011

10. DATE OF REVISION OF THE TEXT

14 November 2024