

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ursofalk® 500

Film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One **Ursofalk 500** film-coated tablet contains 500 mg 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 break line on both sides. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

There are no age restrictions on the use of Ursofalk 500mg tablets. For patients who are unable to swallow Ursofalk 500mg tablets, Ursofalk 250mg capsules are available.

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 500mg 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)	Ursofalk 500mg 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 500mg tablets 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 half an Ursofalk 500mg tablet or one Ursofalk 250mg capsule daily, and the dose then gradually increased (weekly increase of the daily dose by half a tablet or one Ursofalk 250 mg capsule) until the dose indicated in the respective dosage regimen is reached again.

Special population

Older people: There is no evidence to suggest that any alteration in the adult dose is needed but the relevant precautions should be taken into account.

Paediatric population: The indication is very rare in children and adolescents. Therefore, there are no adequate data on the efficacy and safety in this population.

The administration of Ursofalk 500mg film-coated tablets is based on body weight and the medical condition.

4.3 Contraindications

Ursofalk 500mg 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

4.4 Special warnings and precautions for use

Ursofalk 500mg 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 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 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 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 to the recommended dose 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 Interaction with other medicinal products and other forms of interaction

Ursofalk 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 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 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 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 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 in some cases.

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 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.

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 ($\geq 1/10$)

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 ($< 1/10,000$), 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

¹Observed 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

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 was associated with higher rates of serious adverse events.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group/ATC code

ATC code: A05AA02 and A05B

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

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 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 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 genetic toxicology tests with UDCA were negative. The tests with UDCA 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). UDCA 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

Cellulose microcrystalline, povidone K 25, crospovidone, talc, hypromellose, magnesium stearate, silica colloidal anhydrous, polysorbate 80, macrogol 6000.

6.2 Incompatibilities

None known to date.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

Transparent, colourless PVC/PVDC foil, 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. MANUFACTURER

Dr. Falk Pharma GmbH, Leinenweberstr. 5, 79108 Freiburg, Germany.

8. REGISTRATION HOLDER

Rafa Laboratories Ltd., POB 405, Jerusalem 9100301, Israel.

Registration Number: 150-68-33832

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