Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Ursofalk 500mg film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of ursodeoxycholic acid 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the symptomatic treatment of primary biliary cirrhosis (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 weighing less than 47 kg or patients who are unable to swallow Ursofalk 500mg tablets, Ursofalk 250 mg capsules are available.

<u>For the symptomatic treatment of primary biliary cirrhosis (PBC)</u>

The daily dose depends on body weight and ranges from 1½ to 3½ tablets (14 ± 2 mg of ursodeoxycholic acid per kg of body weight).
For the first 3 months of treatment, Ursofalk 500mg tablets should be taken divided over the day. When the liver function parameters improve, the daily dose may be taken once daily in the evening.

Body weight (kg)	Ursofalk 500mg tablets			
	first 3 months			**subsequently**
	morning	midday	evening	evening (1 x daily)
47 – 62	½	½	½	1½
63 – 78	½	½	1	2
79 – 93	½	1	1	2½
94 – 109	1	1	1	3

Over 110	1	1	1½	3½

The tablets should be swallowed with some liquid. They must be taken regularly.

The use of Ursofalk 500mg tablets in primary biliary cirrhosis may be continued indefinitely.

In patients with primary biliary cirrhosis, 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

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

*Children and adolescents:*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 of the excipients listed in section 6.1

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 or 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 the advanced stages of primary biliary cirrhosis:
In very rare cases decompensation of the hepatic cirrhosis has been observed; which partially regressed after the treatment 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 500mg tablets should be reduced to half a tablet Ursofalk 500mg tablets or one Ursofalk 250mg capsule 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 500mg tablets 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 500mg tablets.

Ursofalk 500mg 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 500mg tablets 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.

Ursodeoxycholic acid 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 effects 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 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.

There are no or limited data ~~on~~ 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 500mg tablets must not be used during pregnancy unless clearly necessary. 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.

According to few documented cases of breast feeding 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

Ursofalk 500mg tablets have 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 (<1/10,000), not known (cannot be estimated from the available data)

Gastrointestinal disorders:
In clinical trials, reports of soft 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.

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.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.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 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) used 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 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.

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 aplasia 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

Magnesium stearate, polysorbate 80, povidone K25, microcrystalline cellulose, silica colloidal anhydrous, crospovidone 80 , talc, hypromellose, macrogol 6000.

6.2 Incompatibilities

None known to date

6.3 Special precautions for storage

Do not store above 25 °C.

6.4 Nature and contents of container

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

Pack sizes: 50 and 100 tablets.
Not all package 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

Registration Number: 150 68 33832

The format and content of this document have been approved by the Ministry of Health in February 2016.