AUSTRALIAN PRODUCT INFORMATION -URSOFALK® (Ursodeoxycholic Acid)

1. NAME OF THE MEDICINE

Ursodeoxycholic Acid

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

URSOFALK Capsule contains ursodeoxycholic acid 250 mg.

URSOFALK Suspension contains ursodeoxycholic acid 50 mg/mL.

URSOFALK Tablet contains ursodeoxycholic acid 500 mg.

For the full list of excipients, see Section 6.1 List of excipients.

Excipient with known effect:
The Ursofalk suspension contains a maximum of 7.68 g of xylitol (based on a body weight of 60 kg and a maximum dose of 20mg/kg (xylitol content/mL = 320mg/mL) which may have a laxative effect or cause diarrhoea.

3. PHARMACEUTICAL FORM

URSOFALK Capsules contain 250 mg ursodeoxycholic acid and are presented as white, opaque, hard gelatin capsules.

URSOFALK Suspension contains 50 mg/mL ursodeoxycholic acid and is presented as a white homogenous suspension containing small air bubbles and with lemon flavour.

URSOFALK Tablets contain 500 mg ursodeoxycholic acid and are presented as white, oblong tablets equipped with a double-sided breaking notch.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

URSOFALK is indicated in the treatment of chronic cholestatic liver diseases.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage for adults and the elderly:
For PBC and chronic cholestatic liver diseases other than CF and PSC, the dosage of 12 – 16 mg/kg body weight/day of ursodeoxycholic acid is recommended.

For CF-related cholestasis, the recommended dose is 20 mg/kg/day of ursodeoxycholic acid.

For PSC, the dosage of 10-15 mg/kg body weight/day of ursodeoxycholic acid is recommended. A dosage of 20 mg/kg body weight /day has also been shown to improve histology and liver function tests in PSC patients.

Dosage for children:
Data on use in children are very limited. In the few available studies, dosages used have generally been up to 15 - 20 mg/kg/day.

Administration:
For PBC patients: In the first 3 months of treatment, URSOFALK capsules, tablets or suspension should be taken in 2 to 3 doses over the day. With improvement of the liver function parameters, the daily dose may be taken as a single dose in the evening.

For other cholestatic liver diseases, URSOFALK capsules, tablets or suspension should be taken in 2 to 3 doses over the day.

For patients under 34 kg or patients who are unable to swallow URSOFALK capsules or tablets, URSOFALK suspension should be used.

The capsules and tablets should be swallowed whole with some liquid.

Care should be taken to ensure that URSOFALK is taken regularly.

In patients with PBC, there may, in rare cases, be an initial deterioration in symptoms, e.g. itching. If this is the case, therapy can be continued with 1 capsule (or ½ tablet or 5 mL suspension) of URSOFALK daily, and the daily dose gradually increased weekly until the recommended daily dose has been reached.

For PSC patients, dominant stenoses of the bile ducts should be dilated before and during treatment with URSOFALK.

4.3 CONTRAINDICATIONS

URSOFALK must not be used if there is hypersensitivity to the active ingredient or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

During the first three months of therapy, it is advisable to monitor the liver parameters of AST (SGOT), ALT (SGPT), and GGT every 4 weeks, subsequently 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 advance stage primary biliary cholangitis.

URSOFALK is not recommended in patients with dominant stenoses of the bile ducts unless the obstructed bile ducts are dilated (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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

One measuring cupful (5 mL) URSOFALK suspension contains 0.50 mmol (11.39 mg) sodium. This should be taken into consideration by patients on a controlled sodium diet.

Treatment of patients with primary sclerosing cholangitis
Long periods of high dose ursodeoxycholic acid therapy (28-30 mg/kg) in patients with primary sclerosing cholangitis may be associated with a higher rate of serious adverse events.

Use in renal impairment
The effect of ursodeoxycholic acid in patients with renal impairment has not been studied.

Use in the elderly
No data available

Paediatric Use
See section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Effects on laboratory tests
No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Some drugs, such as cholestyramine, charcoal, colestipol and certain antacids (containing aluminium hydroxide and/or smectite [aluminium oxide]) bind to 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.

Ursodeoxycholic acid may affect the absorption of ciclosporin in transplantation and non-transplant patients. Therefore, monitoring ciclosporin plasma concentrations are recommended and ciclosporin dose adjusted if necessary.

Ursodeoxycholic acid has been reported to decrease the absorption of ciprofloxacin in a few cases.

In a clinical study in 12 healthy volunteers with the OATP1B1*1b/*1b genotype, predicting high OATP1B1 activity, it was demonstrated that concomitant use of ursodeoxycholic acid (500mg/day) and rosuvastatin (20mg/day) resulted in a significant increase in the plasma levels of rosuvastatin. ursodeoxycholic acid increased the AUC of rosuvastatin by approximately 60%, from 145.5 ng/mL per hour to 231.9 ng/mL per hour (p=0.004).

Administration of ursodeoxycholic acid for 14 days also significantly increased total bilirubin by 139 ± 39% (p=0.003), conjugated bilirubin by 127 ± 29% (p=0.005) and unconjugated bilirubin by 151 ± 52% (p=0.004). The proposed biological mechanism for this interaction is that bilirubin and rosuvastatin are both metabolites of organic anion transporting polypeptide 1B1 (OATP1B1). OATP1B1 expression is regulated by transcription factor hepatic nuclear factor (HNF) 1α. ursodeoxycholic acid acts as an inhibitor of HNF 1α and consequently may decreased expression of OAT1B1. A dose reduction in rosuvastatin should be considered in any individuals exposed to both rosuvastatin and ursodeoxycholic acid. The clinical relevance of this interaction with regard to other statins is unknown. However, it is biologically possible that this interaction may also occur between ursodeoxycholic acid and other statins which are known substrates of OAT1B1, such as atorvastatin, fluvastatin, simvastatin acid, pitavastatin and pravastatin.

Ursodeoxycholic acid reduces the peak plasma concentrations (C_{max}) and the area under the curve (AUC) of the calcium channel blocker, nitrendipine. On the basis of this, together with a single case report of an interaction with the substance dapsone (reduction of the therapeutic effect) and *in vitro* findings, it may be assumed that ursodeoxycholic acid induces the medicinal product-metabolising enzyme cytochrome P450 3A4. Caution should therefore be exercised in cases of co-administration of medicinal products metabolised by this enzyme, and a dose adjustment may be necessary. Induction has, however, not been observed in a well-designed interaction study with budesonide which is a known cytochrome P450 3A substrate.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
In a fertility study in Sprague-Dawley rats at oral doses up to 2700 mg/kg/day (25 times the maximum recommended human dose of 20 mg/kg/day based on body surface area/BSA), no adverse effects on male or female fertility or pregnancy outcome were observed. However, in an oral fertility study in Wistar rats, there was evidence of a reduction in female mating behaviour at doses ≥ 250 mg/kg/day (2 times the maximum recommended human dose based on BSA) and of embryolethality (resulting in a reduction in number of live fetuses) at doses ≥ 1000 mg/kg/day (9 times the maximum recommended human dose based on BSA). Human data on fertility effects following treatment with ursodeoxycholic acid are not available.

Use in pregnancy (Category B3)
Ursodeoxycholic acid has been shown to cross the placenta in rats. Animal studies have provided evidence of a teratogenic effect of ursodeoxycholic acid during the early phase of gestation. In studies in rats, tail malformations occurred after an oral dose of 2000 mg per kg of body weight (18 times the maximum recommended human dose based on body surface area/BSA). In one of two studies in rats, there was evidence of embryolethality, with a reduction in number of live fetuses and live births at oral doses of 2000 mg/kg/day. In studies in rabbits, embryotoxic effects from an oral dose of 100 mg per kg of body weight were found (2 times the maximum recommended human dose). No teratogenic effects were found in the study of ursodeoxycholic acid following oral administration to mice or rabbits at doses of up to 1500 and 300 mg/kg/day, respectively (at least 5 times the maximum recommended human dose).

There are no adequate or well-controlled studies in pregnant women during the first trimester. Therefore, ursodeoxycholic acid should not be used during the first three months of

pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with ursodeoxycholic acid.

In women with Intrahepatic Cholestasis of Pregnancy (ICP) ursodeoxycholic acid reduces pruritus when given in the second or third trimesters of pregnancy. Data are insufficient to determine the effect of ursodeoxycholic acid on neonatal outcomes.

Use in lactation
It is not known whether ursodeoxycholic acid is excreted in human milk, but small amounts of ursodeoxycholic acid or its metabolites were excreted in milk of lactating rats following oral administration of 30 mg/kg. In an oral peri-postnatal study in rats, there was a slight transient reduction in postnatal body weight gain of pups at 2000 mg/kg/day (18 times the maximum recommended human dose based on body surface area/BSA).

According to few documented cases of breast feeding women, ursodeoxycholic acid was secreted in the breast milk levels of lactating mothers. The possibility of adverse reactions on the infant should be considered if ursodeoxycholic acid is administered to a nursing mother. Alternatively, breastfeeding can be discontinued.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of this registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Ursodeoxycholic acid is generally well tolerated with few side effects. Diarrhoea is the main reported side effect. The incidence of diarrhoea in controlled studies was up to 3%.

Some patients may experience increased pruritus in the early weeks of treatment. In such cases a dose reduction, and thereafter a slow (weekly) increase of dose to the recommended dose, may help.

Severe right upper abdominal pain has occurred during the treatment of PBC (≤1 in 10,000 patients). During advanced stages of PBC, in very rare cases (≤1 in 10,000 patients), decompensation of hepatic cirrhosis has been observed, which partially regressed after the treatment was discontinued.

Calcification of gallstones can occur in ≤1 in 10,000 patients.

Allergic reactions have been reported in some patients. Urticaria can occur in ≤1 in 10,000 patients).

Other adverse reactions reported include increased cholestasis, nausea, vomiting and sleep disturbance.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Diarrhoea may occur in cases of overdosage. If diarrhoea occurs, the dose must be reduced and in cases of persistent diarrhoea, the therapy should be discontinued. No specific counter-measures are necessary and the consequence of diarrhoea should be treated symptomatically with restoration of fluid and electrolyte balance.

In general, other symptoms of overdosage are unlikely because the absorption of ursodeoxycholic acid decreases with increasing dose and therefore more is excreted with the faeces.

Serious adverse effects are also unlikely to occur in overdosage. However, liver function should be monitored. If necessary, ion-exchange resins may be used to bind bile acids in the intestines.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action
The mechanism of action of ursodeoxycholic acid in liver and cholestatic disorders has not yet been explained totally. However, ursodeoxycholic acid alters bile acid composition, resulting in increases in the concentration of ursodeoxycholic acid and decreases in the concentrations of the more hydrophobic and potentially toxic bile acids, cholic and chenodeoxycholic acids. ursodeoxycholic acid also has a choleretic effect, resulting in increased bile acid output and bile flow. There is some evidence for immunological effects, including a reduction of abnormal expression of HLA Class I antigens on hepatocytes and a suppression of immunoglobulin and cytokine production.

CLINICAL TRIALS
Primary Biliary Cholangitis
Primary biliary cholangitis (PBC) is an autoimmune disease of the liver marked by the gradual destruction and eventual disappearance of the bile duct epithelial cells. The sustained loss of intralobular bile ducts causes the signs and symptoms of cholestasis, and eventually results in cirrhosis and liver failure. Eight pivotal randomised, controlled studies examined the efficacy of ursodeoxycholic acid in the treatment of primary biliary cholangitis (PBC). All 8 trials were of at least 2 years follow-up. Seven of the eight studies used a dosage in the range of 12 – 16 mg/kg/day; the eighth trial used a significantly lower dose of 7.7 $\pm$ 0.2 mg/kg/day. Significant improvement in some or all biochemical tests of liver function was shown in subjects given ursodeoxycholic acid during the treatment period. Symptom improvement or improvement in histology were not consistently reported with ursodeoxycholic acid but longer survival without liver transplantation was reported in two long term studies. One of the studies reported that the efficacy of ursodeoxycholic acid in

patients with PBC was greater in patients with less advanced disease (entry bilirubin < 2mg/dL; histological stage I or II) compared to patients with more advanced disease.

Primary Sclerosing Cholangitis
Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterised by inflammation, fibrosis, and destruction of the large intra- and extra-hepatic bile ducts. One pivotal randomised, double-blind placebo-controlled study examines the efficacy of ursodeoxycholic acid in the treatment of PSC in 105 patients over 2 years. The dosage used was in the range of 13 – 15 mg/kg/day. Irrespective of initial histological stage, ursodeoxycholic acid had no effect on time to treatment failure and survival, without liver transplantation. Serum bilirubin, ALP and AST improved, but ursodeoxycholic acid was not associated with a significant improvement in symptoms or histological score.

In three smaller randomised, double-blind, placebo-controlled studies, ursodeoxycholic acid similarly showed significant improvement in liver biochemistry (in 2 of the studies) when compared to placebo, but did not significantly improve symptom scores. One study found significant improvement in some liver histological features in the patients treated with ursodeoxycholic acid. These trials used ursodeoxycholic acid doses ranging from 10 – 15 mg/kg/day.

In a small randomised, double-blind, placebo-controlled study, 20 mg/kg/day ursodeoxycholic acid treatment in PSC patients showed improvement in liver biochemistry when compared to placebo. Histological progression was significantly reduced in the ursodeoxycholic acid-treated group compared to the placebo-treated group.

Cystic fibrosis-related cholestasis
Cystic fibrosis (CF) is a hereditary disease with multiorgan involvement. Clinical liver disease is rare although many patients may have biochemical evidence of cirrhosis.

One double-blind, placebo-controlled, study randomised 55 patients with CF-related cholestasis to ursodeoxycholic acid 900 mg/day or placebo for one year. In addition, taurine supplements or placebo were randomly assigned. Efficacy was assessed by improvements in clinically relevant and nutritional parameters, and liver biochemistry. After one year, the ursodeoxycholic acid group had significant improvement in GGT and 5'-nucleosidase but not AST or ALT. However, there was a deterioration of overall clinical condition, as measured by the Shwachman-Kulcycki score in those receiving placebo compared to the ursodeoxycholic acid group.

In a dose comparison study, ursodeoxycholic acid 20 mg/kg/day for 12 months resulted in a more pronounced improvement in GGT and ALT compared to ursodeoxycholic acid 10 mg/kg/day. Improvements in AST and ALP were comparable. Although this study suggested a possible benefit with higher drug doses in resolving liver biochemistry, whether ursodeoxycholic acid improves quality of life, histology, or survival is unknown.

5.2 PHARMACOKINETIC PROPERTIES

Ursodeoxycholic acid occurs naturally in the body. After oral administration of a single 500 mg dose of ursodeoxycholic acid to healthy volunteers, peak plasma concentrations were 2.7 to 6.3 μg/mL. T_{max} occurs at 60 minutes and a second peak plasma concentration occurs at 180 minutes. After oral administration of 250 mg, 500 mg, 1000 mg and 2000 mg single

doses, respective absorption rates were 60.3%, 47.7%, 30.7% and 20.7% based on recovery from bile within 24 hours in patients with external biliary drainage.

In plasma, protein binding is 96 – 98%.

First pass extraction of ursodeoxycholic acid from the portal vein by the liver ranges from 50 – 70%. ursodeoxycholic acid is conjugated to glycine and taurine and then excreted into bile and passes to the small bowel. In the intestine, some conjugates are deconjugated and reabsorbed in the terminal ileum. Conjugates may also be dehydroxylated to lithocholic acid, part of which is absorbed, sulphated by the liver and excreted by the biliary tract. In healthy volunteers given ursodeoxycholic acid 500 mg with ^{14}C tracer, 30 – 44% of the dose was excreted in faeces in the first three days as ursodeoxycholic acid (2 – 4%), lithocholic acid (37%) and 7-ketolithocholic acid (5%).

The biological half-life, obtained by radioactive labelling, of orally administered ursodeoxycholic acid is 3.5 - 5.8 days due to the effective enterohepatic circulation of ursodeoxycholic acid in the body.

In patients with severe liver disease, renal excretion becomes a major route for elimination of bile acids.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Ursodeoxycholic acid was not genotoxic in the following studies: gene mutation assays (*in vitro* Ames test, gene mutation assay at the TK locus in mouse lymphoma L5178Y cells), assays of chromosome aberrations (analysis of chromosome aberrations in Chinese hamster bone marrow and in spermatogonia of mice, and micronucleus test in hamsters) and assay of sister chromatid exchanges in cultured human lymphocytes.

Carcinogenicity
In two 24-month oral carcinogenicity studies in mice, ursodeoxycholic acid at doses up to 1000 mg/kg/day was not tumourigenic. Based on body surface area (BSA), this dose represents 4 times the recommended maximum clinical dose of 20 mg/kg/day. In two 2-year oral carcinogenicity studies in rats, ursodeoxycholic acid at doses up to 300 mg/kg/day (3 times the recommended maximum human dose based on BSA) was not tumourigenic.

In 103-week oral carcinogenicity studies of lithocholic acid, a metabolite of ursodeoxycholic acid, doses up to 250 mg/kg/day in mice and 500 mg/kg/day in rats did not produce any tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

URSOFALK Capsule contains the following excipients: maize starch, colloidal anhydrous silica, magnesium stearate, gelatine, titanium dioxide, sodium lauryl sulfate and purified water.

URSOFALK Suspension contains the following excipients: benzoic acid, purified water, xylitol, glycerol, Avicel RC-591, propylene glycol, sodium citrate dihydrate, sodium cyclamate, citric acid, sodium chloride and lemon flavour (PHL 134488).

URSOFALK Tablet contains the following excipients: magnesium stearate, polysorbate 80, povidone, microcrystalline cellulose, colloidal anhydrous silica, crospovidone, purified talc, hypromellose and macrogol 6000.

6.2 INCOMPATIBILITIES

Refer to Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australia Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.
Do not use URSOFALK Suspension after 4 months of opening the bottle.

6.5 NATURE AND CONTENTS OF CONTAINER

URSOFALK Capsules are supplied in clear PVC blister strips of aluminium foil backing packed in cardboard cartons. Each carton contains 60 or 100 capsules. Not all pack sizes are currently marketed in Australia.

URSOFALK Suspension is available in amber glass bottles of 250 mL and is supplied with a calibrated measuring cup.

URSOFALK Tablets are supplied in clear PVC/PVDC/Al blister strips packed in cardboard cartons. Each carton contains 50 or 100 tablets. Starter packs of 25 tablets are also available. Not all pack sizes are currently marketed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

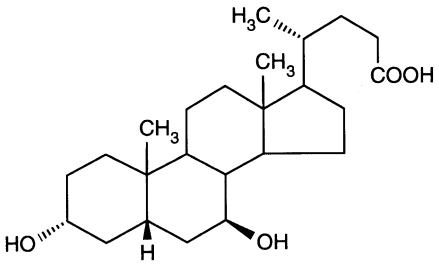
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Ursodeoxycholic acid is a white or almost white powder. It is practically insoluble in water, readily soluble in alcohol, sparingly soluble in acetone, in chloroform and in ether. It melts at 200 - 204ºC. The IUPAC chemical name of ursodeoxycholic acid is 3α, 7ß-dihydroxy-5-cholan-24-oic acid.

Chemical Structure

The chemical structure of ursodeoxycholic acid is as follows:



CAS number: 128-13-2

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4

8. SPONSOR

Dr Falk Pharma Australia Pty Ltd
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www.drfalkpharma.com.au

9. DATE OF FIRST APPROVAL

URSOFALK Capsules 250 mg: 24 May 1999
URSOFALK Suspension 50 mg/mL: 1 August 2000
URSOFALK Tablets 500 mg: 6 October 2016

10. DATE OF REVISION

14 November 2025

URSOFALK® is a registered trademark of Dr. Falk Pharma GmbH, Germany

Summary table of changes

Section changed	Summary of new information
6.1	Correction to ingredient number for lemon flavour