NEW ZEALAND DATA SHEET

1. URSOFALK Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ursofalk Capsule contains ursodeoxycholic acid 250mg

Ursodeoxycholic acid (UDCA) 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 UDCA is 3α, 7ß-dihydroxy-5-cholan-24-oic acid. Its CAS number is 128-13-2.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ursofalk Capsules are presented as white, opaque, hard gelatin capsules.

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

Adults and the elderly:

10 - 15mg UDCA per kg per day in two to four divided doses are recommended for PBC (primary biliary cirrhosis) and chronic cholestic liver diseases other than CF (cystic fibrosis). This dose can be approximated as follows:

For the capsule:

body weight (kg)	daily dose		Number of capsules
(capsules)	morning	noon	evening
34 – 50	2	1	-	1
51 - 65	3	1	1	1
66 – 85	4	1	1	2
86 – 110	5	1	2	2
Over 110	6	2	2	2

For CF, the general recommended dose is up to 20 mg/kg/day. This dose has been shown to improve histology in PSC patients.

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.

In patients with primary biliary cirrhosis, 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 of URSOFALK daily, and the daily dose gradually increased until the recommended daily dose has been reached.

4.3 Contraindications

URSOFALK must not be used in the presence of acute inflammation of the gall bladder and bile ducts; and obstruction of the biliary tract (common bile duct).

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.

Pre-existing radiolucent gallstones may occasionally become calcified. The clinical significance of this observation is unclear.

The effect of URSOFALK in patients with renal impairment has not been studied.

Carcinogenicity/mutagenicity and Impairment of Fertility

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 5 times the recommended maximum clinical dose of 16 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.

URSOFALK 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.

In a fertility study in Sprague-Dawley rats at oral doses up to 2700 mg/kg/day (27 times the maximum recommended human dose based on BSA), no adverse effect 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 (2.5 times the maximum recommended human dose based on BSA) and of embryolethality (resulting in a reduction in number of live foetuses) at doses ≥ 1000 mg/kg/day.

4.5 Interaction with other medicines and other forms of interaction

Some drugs, such as cholestyramine, charcoal, colestipol and certain antacids (e.g. aluminium hydroxide) bind bile acids in vitro. They could therefore have a similar effect in vivo and may interfere with the absorption of URSOFALK.

UDCA may increase the absorption of cyclosporin in transplantation and non-

transplant patients. Therefore, monitoring cyclosporin plasma concentrations are recommended.

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

4.6 Fertility, pregnancy and lactation

Fertility

No data available.

Pregnancy (Category B3)

URSOFALK has been shown to cross the placenta in rats. There was no evidence of a teratogenic effect of URSOFALK following oral administration to rats, mice or rabbits at doses of up to 4000, 1500 and 300 mg/kg/day, respectively. In one of two studies in rats, there was evidence of embryolethality, with a reduction in number of live foetuses and live births at oral doses of 2000 mg/kg/day.

There are no adequate or well-controlled studies in pregnant women. URSOFALK 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 URSOFALK.

Lactation

It is not known whether URSOFALK is excreted in human milk but small amounts of UDCA 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. The possibility of adverse reactions on the infant should be considered if URSOFALK is administered to a nursing mother. Alternatively, nursing can be discontinued.

4.7 Effects on ability to drive and use machines

No data available.

4.8 Undesirable effects

UDCA 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.

Allergic reactions have been reported in some patients.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose
Serious adverse effects are 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
The mechanism of action of UDCA in liver and cholestatic disorders has not yet been explained totally. However, UDCA alters bile acid composition, resulting in increases in the concentration of UDCA and decreases in the concentrations of the more hydrophobic and potentially toxic bile acids, cholic and chenodeoxycholic acids. UDCA 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.

5.2 Pharmacokinetic properties
UDCA occurs naturally in the body. After oral administration of a single 500 mg dose of UDCA to healthy volunteers, peak plasma concentrations were 7 to 16 µM. Tmax 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 UDCA from the portal vein by the liver ranges from 50 – 70%. UDCA 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 UDCA 500 mg with 14C tracer, 30 – 44% of the dose was excreted in faeces in the first three days as UDCA (2 – 4%), lithocholic acid (37%) and 7-ketolithocholic acid (5%).

The biological half-life of orally administered UDCA is 3.5 - 5.8 days.

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

5.3 Preclinical safety data

Primary Biliary Cirrhosis

Five pivotal randomised, double-blind control studies examined the efficacy of ursodeoxycholic acid in the treatment of primary biliary cirrhosis. All 5 trials were of at least 2 years follow-up. Four of the five studies used a dosage in the range of 10 – 15 mg/kg/day; the fifth trial used a significantly lower dose of 7.7 + 0.2 mg/kg/day.
Significant improvement in some or all biochemical tests of liver function was shown in subjects given UDCA during the treatment period. Symptom improvement or improvement in histology were not consistently reported with UDCA but longer survival without liver transplantation was reported in two long term studies. One of the studies reported that the efficacy of UDCA in patients with primary biliary cirrhosis 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 UDCA 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, UDCA had no effect on time to treatment failure and survival, without liver transplantation. Serum bilirubin, ALP and AST improved, but UDCA was not associated with a significant improvement in symptoms or histological score.
In three smaller randomised, double-blind, placebo-controlled studies, UDCA 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 UDCA. These trials used UDCA doses ranging from 10 – 15 mg/kg/day.

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.

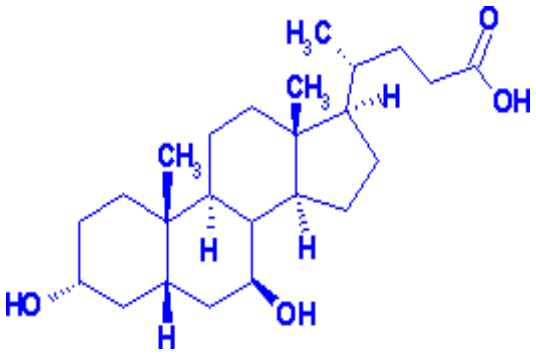
One double-blind, placebo-controlled, study randomised 55 patients with CF to UDCA 900 mg/day or placebo for one year. In addition, taurine supplements or placebo were randomly assigned. Efficacy was assessed by improvements in clinically relevant and nutritional parameters, and liver biochemistry. After one year, the UDCA 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 UDCA group.

In a dose comparison study, UDCA 20 mg/kg/day for 12 months resulted in a more pronounced improvement in GGT and ALT compared to UDCA 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 UDCA improves quality of life, histology, or survival is unknown.

6. PHARMACEUTICAL PARTICULARS

Chemical structure



Ursodeoxycholic Acid

6.1 List of excipients

Ursofalk capsules contains the following excipients: ethanol, purified water, maize starch, colloidal silicon dioxide, magnesium stearate, gelatin and titanium dioxide.

6.2 Incompatibilities

No data available.

6.3 Shelf life

5 years from date of manufacture stored at or below 25°C.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

It is supplied in clear PVC blister strips of aluminium foil backing packed in cardboard cartons. Each carton contains 100 capsules.

6.6 Special precautions for disposal and other handling

No data available.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Name and Address of Marketing Authorisation Holder

Orphan Australia Pty Ltd
34-36 Chandos Street
St Leonards NSW 2065
Australia

Name and Address of Agent in New Zealand
Pharmacy Retailing Limited trading as Healthcare Logistics (on behalf of Orphan Australia Pty Ltd)
58 Richard Pearse Drive Airport Oaks
Auckland New Zealand

9. DATE OF FIRST APPROVAL
25 June 2015

10. DATE OF REVISION OF THE TEXT
April 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections revised	Update to the SPC-style format