



**Australian Government**  

---

**Department of Health and Ageing**  
**Therapeutic Goods Administration**

**Australian Public Assessment Report**  
**for**  
**Ursodeoxycholic acid**

**Proprietary Product Name: Urso/Ursofalk**

**Submission No: PM-2008-03582-3-1**

**Sponsor: Orphan Australia Pty Ltd**



***July 2010***

## Contents

<b>I.</b>	<b>Introduction to Product Submission</b> .....	<b>3</b>
	Submission Details.....	3
	Product Background.....	3
	Regulatory Status.....	5
	Product Information.....	5
<b>II.</b>	<b>Quality Findings</b> .....	<b>5</b>
	Drug Substance (active ingredient).....	5
	Drug Product.....	5
	Quality Summary and Conclusions.....	5
<b>III.</b>	<b>Nonclinical Findings</b> .....	<b>5</b>
	Nonclinical Summary and Conclusions.....	5
<b>IV.</b>	<b>Clinical Findings</b> .....	<b>5</b>
	Introduction.....	5
	Clinical Summary and Conclusions.....	6
<b>V.</b>	<b>Pharmacovigilance Findings</b> .....	<b>6</b>
<b>VI.</b>	<b>Overall Conclusion and Risk/Benefit Assessment</b> .....	<b>6</b>
	Quality.....	6
	Nonclinical.....	6
	Clinical.....	6
	Risk-Benefit Analysis.....	11
	Outcome.....	13
	<b>Attachment 1. Product Information</b> .....	<b>14</b>

## **I. Introduction to Product Submission**

### **Submission Details**

<i>Type of Submission</i>	Extension of Indications and Change of Dosage
<i>Decision:</i>	Amendment of the dose range of UDCA for primary sclerosing cholangitis – application withdrawn Amendment of the dose regimen of UDCA for primary sclerosing cholangitis, primary biliary cirrhosis and cystic fibrosis-related cholestasis – approved Extension of indications to include use in patients with intrahepatic cholestasis of pregnancy - rejected
<i>Date of Decision:</i>	16 February 2010
<i>Active ingredient(s):</i>	Ursodeoxycholic acid
<i>Product Name(s):</i>	Urso, Ursofalk
<i>Sponsor's Name and Address:</i>	Orphan Australia Pty Ltd 300 Frankston-Dandenong Road Dandenong Vic 3175
<i>Dose form(s):</i>	Capsules and liquid
<i>Strength(s):</i>	250 mg capsules and 250 mg/5 mL oral liquid
<i>Container(s):</i>	Capsules: blister pack Liquid: glass bottle
<i>Pack size(s):</i>	Capsules: 100 Liquid: 1
<i>Approved Therapeutic use:</i>	the treatment of chronic cholestatic liver diseases.
<i>Route(s) of administration:</i>	Oral
<i>Dosage:</i>	Varies with treatment and is the subject of this AusPAR
<i>ARTG Numbers:</i>	66042, 75484, 116741, 116751

### **Product Background**

The sponsors submitted an application to vary the dosage regimen of the Urso and Ursofalk trade names containing ursodeoxycholic acid in the treatment of chronic cholestatic liver disease and add the new indication of intrahepatic cholestasis of pregnancy. The sponsor has submitted clinical study reports and published papers to support these proposed changes.

Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are the most common chronic cholestatic liver diseases (CCLD) with an unknown aetiology. The mechanism of action of ursodeoxycholic acid (UDCA) in liver and cholestatic disorders is not yet fully understood. Pharmacodynamic studies have shown that exogenous UDCA alters the bile acid composition which results in an increase in UDCA concentration and a decrease in the concentration of toxic hydrophobic bile acids, namely cholic and chenodeoxycholic acids. It also appears that UDCA has a choleric effect which increases bile acid output and bile flow from the liver. Thus in CCLD, treatment with UDCA helps to re-establish bile acid homeostasis.

The natural history of PBC leads to the destruction of interlobular bile ducts which then progresses to ductopenia with granulomatous tissue stenosis of the bile duct lumen. Progressive cirrhosis and

liver failure are the end stages of this disease. Both PBC and PSC are rare diseases which affect men and women. More than 90% of PBC patients are female, usually between 40 and 60 years. For PSC patients, most are diagnosed between 25 and 45 years, with twice as many men as women being affected. But - in contrast to PBC – children might also be affected. PSC is often associated with cancers such as cholangiocarcinoma and colorectal cancer. Several observational studies have implicated a disordered immune response as a factor in the development of these conditions. There appears to be an abnormal expression of human leukocyte antigen (HLA) class I antigens on hepatocytes and the suppression of immunoglobulin and cytokine production. For example, it has been observed in patients with PBC that there is often associated Reynaud's phenomenon, CREST syndrome, sicca syndrome, Type I diabetes and immune globulin A (IgA) deficiency. Further adding weight to this disordered immune hypothesis is that immune globulin G (IgG) anti-mitochondrial antibodies are detected in >90% of patients with PBC in contrast to other forms of liver disease where these rarely are detected.

Currently, the Australian pregnancy classification for UDCA is B3. UDCA has been shown to cross the placenta in rats with teratogenic effects during the early phase of gestation. In reproductive toxicity studies involving rats, teratogenic effects with tail malformations occurred at the very high dose of 2,000 mg/kg of body weight (bw) (this dose corresponds to 14g UDCA/day in a subject with a 70 kg bw). In addition, there was evidence of embryo lethality, with a reduction in the number of live fetuses and live births at oral doses of 2,000 mg/kg/day. Studies in rabbits showed embryo toxic effects from a dose of 100 mg/kg of bodyweight. There were no teratogenic effects found in the study of UDCA administered to mice or rabbits at doses of up to 1,500 and 300 mg/kg/day respectively. Ursosalk is not recommended during the first three months of pregnancy, or for women planning to become pregnant. There are no medications currently indicated for intrahepatic cholestasis of pregnancy (ICP) in Australia. Cholestyramine resin which has a classification of B2 has been given for this condition; however its safety of use by pregnant women has not been established. Cholestyramine binds to bile acid in the gut and does not cross the placenta.

The sponsor commented that UDCA is considered first-line therapy in ICP according to the *Australian Therapeutic Guidelines, Gastrointestinal 2006*. In the *Australian Therapeutic Guidelines, Dermatology, Revised Feb 2009*, it states, "Mild cholestasis usually responds to bland antipruritic emollients, such as sorbolene cream or 0.5% menthol and 0.5% phenol in aqueous cream. The treatment of choice for severe cases is ursodeoxycholic acid..."

The current approved indication for Urso and Ursosalk in Australia is for the treatment of chronic cholestatic liver diseases, which include PBC, PSC and cystic fibrosis (CF)-related cholestasis. The approved dosage in adults for chronic cholestatic liver disease (other than CF) and primary biliary cirrhosis is 10-15mg/kg/day in 2-4 divided doses. In CF-related cholestasis the dose is up to 20mg/kg/day in 2-4 divided doses.

The purpose of this submission is for the following changes:

1. To allow for once daily dosing as an alternative to 2-4 divided doses in the treatment of PBC.
2. To increase the dose of UDCA from 10-15 mg/kg/day to 12-16 mg/kg/day for treatment of PBC.
3. To increase the dose range of UDCA from 10-15 mg/kg/day for PSC and from 20 mg/kg/day for cystic fibrosis related cholestasis to 20-30 mg/kg/ day.
4. To add a new patient group – patients with intrahepatic cholestasis of pregnancy (ICP) with a daily dose of 12-16 mg/kg/day.

5. To change the currently approved 2-4 divided doses per day to 2-3 divided doses per day for approved indications (PSC and CF-related cholestasis)

The preparation and publication of an AusPAR for the first three purposes, that is, a change in dosage, is at the discretion of the TGA. The fourth purpose in this case the addition of a new patient group is, effectively, an extension of indications and this type of submission requires an AusPAR to be produced. The products Urso and Ursolfalk will be referred to as Ursolfalk for the remainder of this document.

## **Regulatory Status**

Ursolfalk was first approved for registration in Australia on 19 May 1999.

For the change in dose range and inclusion of once daily dosing of Ursolfalk for the treatment of PBC, a similar application has been approved in Austria, Czech Republic, Cyprus, Estonia, Germany, Hungary, Lithuania, Latvia, Slovakia, Slovenia and Switzerland.

In the European Union (EU) Ursolfalk is approved for:

- Dissolution of radiolucent gallstones of <15mm in diameter, composed primarily of cholesterol in patients with functioning gall bladder.
- Symptomatic treatment of PBC provided there is no decompensated hepatic cirrhosis.

## **Product Information**

The approved product information (PI) current at the time this AusPAR was prepared is at Attachment 1.

## **II. Quality Findings**

### **Drug Substance (active ingredient)**

The active ingredient in Ursolfalk is ursodeoxycholic acid (UDCA).

### **Drug Product**

The composition of Ursolfalk capsule is as follows: ursodeoxycholic acid 250mg, maize starch, colloidal silicon dioxide, magnesium stearate, gelatine, titanium dioxide, sodium lauryl sulphate and purified water. The oral liquid contains UDCA 250mg/5mL in a suspension with benzoic acid, purified water, xylitol, glycerol, microcrystalline cellulose, carmellose sodium, propylene glycol, sodium citrate, sodium cyclamate, anhydrous citric acid, sodium chloride and lemon flavouring (Giovaudan 87017).

### **Quality Summary and Conclusions**

There is no requirement for a quality evaluation in an application of this type.

## **III. Nonclinical Findings**

### **Nonclinical Summary and Conclusions**

There is no requirement for a nonclinical evaluation in an application of this type.

## **IV. Clinical Findings**

### **Introduction**

The clinical submission included two studies;

- A pharmacokinetic (PK) study to support UCDA given once daily
- A safety and efficacy study to support treatment of patients with ICP

The remainder of the clinical content of the submission consisted of published papers in support of the variations in dosage and the addition of a new patient group. The following is a summary of the submitted published data:

- For PBC: to vary the dose range – 6 published efficacy studies, 5 published long term survival studies, 2 combined analyses studies and 1 meta-analysis submitted.
- For PBC: to support once daily dosage – (using the current lower dose range of 10-15 mg/kg/day) 3 published studies.
- For PSC and CF-related cholestasis: to vary dose range – 2 published efficacy studies submitted for PSC and 3 published efficacy studies for CF.
- To add ICP as new patient group – in addition to the full study report, 19 published studies, 5 case reports and 2 review publications submitted.
- Change in divided doses from 2-4 to 2-3 times daily – 3 published studies submitted.

## **Clinical Summary and Conclusions**

Following evaluation of the submitted clinical data and comments by the sponsor, the outcome of the evaluation was summarised by the Delegate (see VI below).

### **V. Pharmacovigilance Findings**

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

### **VI. Overall Conclusion and Risk/Benefit Assessment**

The submission was summarised in the following Delegate's overview and recommendations:

#### **Quality**

There is no requirement for a quality evaluation in an application of this type.

#### **Nonclinical**

There is no requirement for a nonclinical evaluation in an application of this type.

#### **Clinical**

##### **Pharmacology**

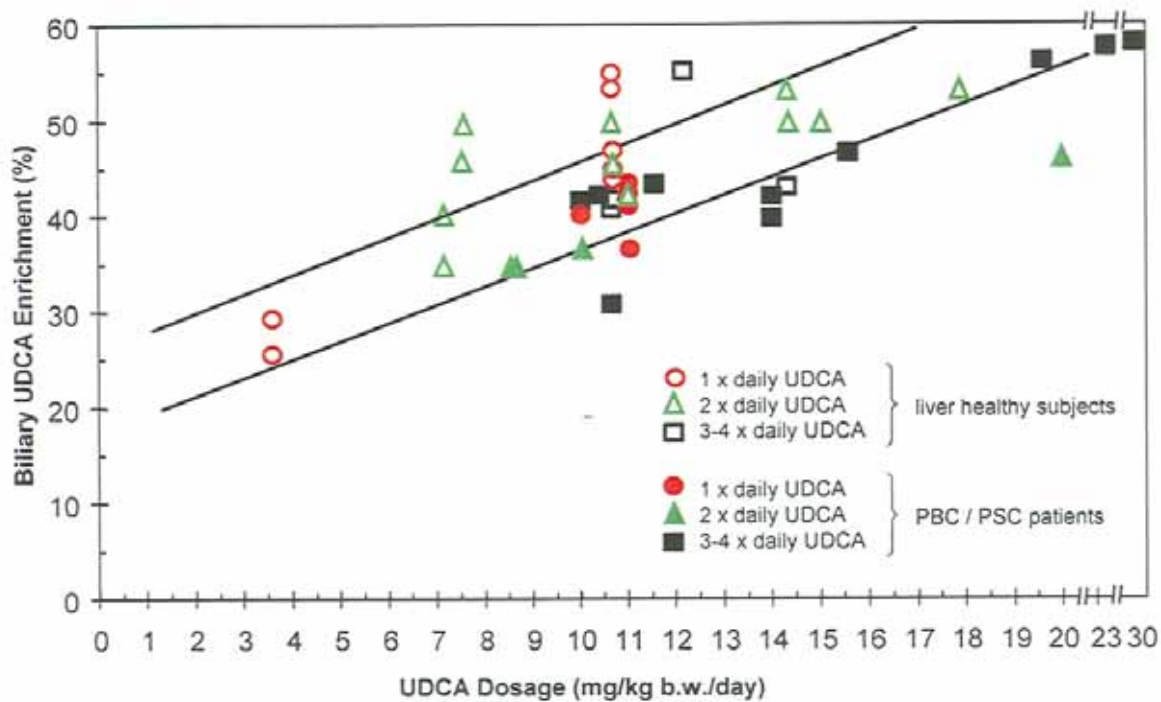
The degree of biliary enrichment of UDCA does not depend on the formulation or the number of doses administered per day, but rather the total daily dose. After absorption UDCA enters into the enterohepatic circulation which preserves bile acids to a high degree with only minor faecal and urinary loss. Biliary UDCA enrichment is dependent on the total daily dose and the function of the hepatocytes and cholangiocytes in the liver.

*Study URU-1/BIO* was a randomized, 3-way crossover bioequivalence study to compare the bioavailability of UrsOfalk suspension and 2 different capsules (250 mg and 150/300 mg capsules). Each subject received 750 mg UDCA in a once daily dose ( $\cong$  10 - 15 mg/kg /day) either as a suspension or as capsules for 14 days. After a 14-day washout period the alternate treatment was given. AUC, Cmax, Tmax and biliary enrichment were assessed (expressed as the relative %UDCA to total biliary bile acid concentration at the end of each 14-day treatment period). Bioequivalence of the 250 mg capsules and suspension was demonstrated. The PK of the 150/300 mg capsules were quite different from that of the suspension and the 250 mg capsules, however the degree of biliary bile acid enrichment was similar for all formulations.

The sponsor listed 41 published studies which included assessment of biliary UDCA concentration after administration of various doses of UDCA. These studies showed that the UDCA concentration in bile increased with UDCA dose. A figure from the sponsor's overview (Figure 1)

compared %UDCA in bile for 1, 2 and 3-4 daily dose groups in both subjects with healthy livers and those with PBC or PSC. There is a roughly linear relationship between total dose and %UDCA in bile. Dose frequency had no detectable effect on %UDCA in bile in either healthy subjects or those with PBC/PSC, at least at doses around 10–12 mg/ kg/day. There were limited data to permit comparisons at other total daily doses. Figure 1 also shows that subjects with healthy livers tend to have higher %UDCA in bile for the same total daily dose of UDCA compared with patients with PBC or PSC. A dose response study in patients with CF also showed a linear relationship between daily dose and %UDCA in bile for doses of up to 20 mg/kg/day.

Figure 1: Biliary UDCA enrichment in dependence of total daily UDCA dosage



**Biliary UDCA enrichment in dependence of total daily oral UDCA dosage and on dosing frequency in liver-healthy subjects and in PBC/PSC patients. The upper straight represents the relationship of total daily dose in liver-healthy subjects; the lower straight the relationship of total daily dose in patients with cholestatic liver diseases. Data included from liver-healthy subjects: URU-1/BIO, Parts I, II, Angelin et al. 1986, Bateson et al. 1980, von Bergmann et al. 1984, Fischer et al. 1993, Frenkiel et al. 1986, Nilsell et al. 1983, Roda et al. 1979, Rudolph et al. 2002, Sauer et al. 1999, Stiehl et al. 1984; patients with liver diseases: Batta et al. 1997, Combes et al. 1995, Combes et al. 1999, Crosignani et al. 1991a, van Hoogstraten et al. 1998b, Lindor et al. 1994, Lindor et al. 1998, Mazzella et al. 1993, van de Meeberg et al. 1996, Podda et al. 1989, Roda et al. 1989, Rost et al. 2004, Stiehl et al. 1995**

## Efficacy

### Primary Biliary Cirrhosis

The primary evidence to support the proposed dose interval amendment was an open, randomised, crossover study to compare the efficacy of simplified (1 or 2 doses daily) vs. multiple (3 or 4 doses

daily) dose regimens of UDCA in patients with PBC.<sup>1</sup> 60 patients received UDCA 13-15 mg/kg/d for 14–133 months (median 71.5 months). 50 patients initially received UDCA in 4 divided doses, 10 in 3 divided doses. Patients were randomised to receive the same total dose of UDCA they had been receiving but in 2 fewer dosages daily (1 or 2) vs. containing the 3 or 4 divided dosages for 6 months. Patients then received the alternate regimen for another 6 months. Efficacy was assessed by changes in liver test results, Mayo risk score and serum enrichment with UDCA.

Patient compliance and preference after 1 year of treatment were also assessed. There were no clinically or statistically significant differences in outcome measures for the 2 dose regimens. Patients generally preferred the 1-2 daily dose regimen.

In another study 150 patients with PBC were randomised to receive 5-7, 13-15 or 23-25 mg/kg/day UDCA over 12 months.<sup>2</sup> Only an abstract was submitted. This reported that there was no difference in liver biochemistry or Mayo risk scores between the 13-15 mg and 23-25 mg/kg/day dose groups but that those given 5-7 mg/kg/d had worse outcomes.

A meta-analysis of 7 randomised, controlled (placebo or untreated) studies in patients with PBC given from UDCA for from 24- 88 months was described. In one study patients were given 10-12 mg/kg/day UDCA, in the other 6 studies the minimum dose was 12 mg/kg/day and the maximum was 16 mg/kg/d. A total of 1038 patients were included in the analysis with 522 given UDCA. The primary efficacy variable was the combined evaluation of liver transplantation and death. Liver transplantation is the only effective treatment for end stage PBC and can be considered as a surrogate for death. There were 42/522 deaths in the UDCA group vs. 42/516 in the control group. Liver transplant was reported for 33 (6.3%) given UDCA vs. 37 (7.2%) for controls. Meta-analysis of clinical events in the original trials showed UDCA had no effect on the incidence of death, liver-related death or liver transplantation.

A further meta-analysis including extended follow-ups found no difference in mortality (OR 1.01, 95%CI 0.72-1.41) and a significant difference for incidence of liver transplantation (OR 0.65, 95%CI 0.46 – 0.91, p=0.01). 5 of the studies in that meta-analysis report on histological change. One of these studies used the 10-12 mg/kg/day UDCA, the other 4 used the proposed dose and these 4 were pooled to analyse the effect of 2 years of UDCA treatment on histological progression of PBC. A total of 367 patients (200 treated with UDCA, 167 with placebo) were selected. Overall there was no significant difference in the progression of the histological stage between the UDCA and placebo groups. However, in the subgroup of patients with initial stages (UDCA n=96; placebo n=81) there was a significant decrease in histological stage progression in the UDCA group (p< 0.03).

A further 5 studies had information on longer term survival of patients with PBC given 12-16 mg/kg/day UDCA. These studies showed survival/ survival without liver transplant was more likely for patients given UDCA than placebo or historic controls and in one study was comparable to the normal population over 72 months of observation. Outcomes up to 96 months were examined.

### *Primary Sclerosing Cholangitis*

The sponsor has noted that UDCA is stated to be the mainstay of therapy in PSC in the Australian Therapeutic Guidelines, Gastrointestinal. While the current dose improved LFTs it had no effect on time to treatment failure and survival without liver transplantation. The sponsor has proposed to

---

<sup>1</sup> Angulo et al. Comparison of ursodeoxycholic acid dosage schedules in primary biliary cirrhosis: a randomised, cross-over study. *J of Hepatology* 1999;30:830-5.

<sup>2</sup> Lindor et al. Comparison of three different doses of ursodeoxycholic acid in the treatment of primary biliary cirrhosis – A randomized trial [abstract]. *Hepatology* 1997; 26: 438.



double the current daily dose to 20-30 mg/ kg/ day and has presented 2 clinical studies to support this proposal.

The first study was a pilot randomised, dose-ranging study to determine whether further enrichment of the bile acid pool with UDCA would lead to an improvement in outcome for PSC patients.<sup>3</sup>

31 patients with PSC were randomised to treatment with either 10, 20 or 30 mg/kg/day UDCA for 2 years. Patients were assessed every 12 weeks and underwent liver biopsy at the beginning and end of the 2 years treatment. Eight patients were excluded from the final analysis: five declined a second biopsy, two had additional azathioprine or 6-mercaptopurine and one was non-compliant. Serum LFTs significantly improved during treatment for all doses and greater reductions were seen with high dose compared to low dose UDCA. Histology was measured using a Ludwig score which tended to improve or was stable after 2 years in the 20 and 30 mg/kg/day treatment groups with only one of 16 patients progressing a stage. Two of ten patients in the 10 mg/kg/day group progressed a stage. None of the individual criteria or the total Knodell score showed significant changes between the 3 dosage groups.

The Mayo risk score, an established surrogate marker of prognosis in PSC, was used to calculate the effect of treatment on survival probability after 1, 2, 3 and 4 years. Survival probability significantly improved ( $p < 0.02$ ) in the high dose group by the end of the study and tended to improve in the other dose groups.

The second study was of similar size, examining 30 patients given either 25 or 30 mg/kg/ day UDCA for 12 months.<sup>4</sup> There was a reduction in LFTs compared with baseline and an improvement in the Mayo score which would translate into a significant improvement in survival probability compared with baseline. There was no comparison with patients given the current dose regimen.

#### *Cystic Fibrosis-related Cholestasis*

Clinical cholestatic liver disease is rare in patients with CF. The main goals of therapy are to decrease bile acid viscosity, to replace hepatotoxic bile acids and to prevent progression to cirrhosis. The current PI notes that doses of 20 mg/kg/day for 12 months to patients with CF-related cholestasis resulted in a more pronounced improvement in GGT and ALT compared to UDCA 10 mg/kg/day and that improvements in AST and ALP were comparable. It also states that “whether UDCA improves quality of life, histology or survival is unknown”.

The sponsor cited 4 published studies of UDCA treatment of CF-related cholestasis which it claims have demonstrated that UDCA is able to prevent progression and may be able to revert hepatobiliary changes in a great number of patients if therapy is started early enough. Other studies claim a positive effect on nutrition and absorption of fat-soluble vitamins as well as on growth development and muscle mass of children if given at an adequate dosage.

Three studies were identified to support the use of a UDCA dose of up to 30 mg/kg/day. Only one of these was a published paper, the other 2 references were an abstract and a conference poster. The published paper described a randomised, double-blind, placebo-controlled, crossover study to examine changes in the lipid profile and in the status of fat-soluble vitamins in response to UDCA in children with CF.<sup>5</sup> Nineteen subjects aged 7 to 17 years with CF and hepatic abnormalities,

---

<sup>3</sup> Cullen et al. High dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis is safe and effective. *J Hepatol* 2008; 48:792-800.

<sup>4</sup> Harnois et al. High-dose ursodeoxycholic acid as a therapy for patients with primary sclerosing cholangitis. *Am J Gastroenterol*. 2001 May; 96:155-62.

<sup>5</sup> Lepage et al. Ursodeoxycholic acid improves the hepatic metabolism of essential fatty acids and retinol in children with cystic fibrosis. *J Pediatr* 1997; 130:52-8.

confirmed by repeated LFT abnormalities, hepatic ultrasound or biopsy, were enrolled and received either UDCA 15 mg/kg/day (which was increased to 30 mg/kg/day in the absence of a 50% reduction in ALT or AST) or placebo for 6 months. In the second 6 month treatment period those previously given UDCA received placebo and those given placebo received UDCA. Through the 12 months study patients continued their usual medications. After 12 months all patients continued to receive UDCA. Liver enzyme profile, fat soluble vitamins and lipid profile were measured at baseline and at 6 and 12 months.

Six patients discontinued study, one due to death, none due to adverse events. Cirrhosis was suspected in 12 patients due to the presence of a nodular or hard liver, splenomegaly, the presence of indicators of portal hypertension on ultrasound or a combination of these elements. There was a significant improvement in LFTs after either 6 or 25 months of treatment with UDCA. ALT and GGT which had reduced in children given UDCA increased when they were given placebo. Benefits were also seen in plasma lipid levels however the number of children given 30 mg/kg/day UDCA was not stated.

The conference poster described an examination of the case histories of 570 children with CF given UDCA 20 to 30 mg/kg/day prior to treatment and after 12 and 24 months.<sup>6</sup> The number of children assessed, the extent of cirrhosis in these children and the extent of change in LFTs and the actual dose of UDCA given could not be determined from the poster.

The abstract described results in 20 CF patients with mildly elevated LFTs randomised to receive 20 (n=4), 30 (n=8) or 40 (n=8) mg/kg/day UDCA for 2 months.<sup>7</sup> Bile acids were determined in duodenal bile, serum and urine at baseline and at 2 months. There was no additional bile acid enrichment from increasing the dose beyond 20 mg/kg/day.

#### Intrahepatic cholestasis of pregnancy

The sponsor submitted two study reports, two literature reviews, published reports of five placebo-controlled studies, 8 comparative studies with cholestyramine, dexamethasone or S-adenosylmethionine (SAMe), six studies with an untreated control group and five papers describing case reports of use of UDCA in women with ICP.

*Study URC-105/PCH* was an open, randomised, active-controlled study of 84 patients with ICP who were in the third trimester of pregnancy. Patients received UDCA 8-10 mg/kg/day or cholestyramine 8 g/day for 14 days. The evaluator has made considerable comment on the limitations of this study, including its open design, lack of justification for dose or duration of treatment, dose not consistent with the proposed dose, and use of an unvalidated primary efficacy parameter. The sample size was too small to comment on differences in fetal outcomes.

*Study URU-3/NEO* was a randomised, double-blind, placebo-controlled, parallel group study to evaluate whether UDCA shortens the duration of total/ supplementary parenteral nutrition and increases fat absorption in preterm infants during the first weeks of life. Thirty two pre-term infants aged  $\leq 34$  weeks were enrolled and received either UDCA at an initial dose of 5 mg/kg/day increasing to 20 mg/kg/day or placebo from the third day of life until 4-6 weeks of life. Efficacy was measured by time to achieve full enteral feeding, % fat absorption, lipase activity in the duodenum, nutritional status and occurrence of cholestasis. There were no significant differences in any of the efficacy parameters. This study is of value in permitting an examination of the safety of UDCA in infants of  $\leq 34$  weeks gestation.

---

<sup>6</sup> Kapustina et al. Cystic fibrosis related liver disease: frequency, risk factors and treatment with ursodeoxycholic acid. *J Cystic Fibrosis* 2003; 2: s77.

<sup>7</sup> Setchell et al. Markedly decreased biliary ursodeoxycholic acid (UDCA) enrichment with high dose UDCA in cystic fibrosis (CF) associated liver disease – Optimization of the therapeutic dose. *Hepatology* 1994; 20: 262A.

Further published studies showed that reduction in pruritus and improvement in LFTs were generally reported in patients given UDCA.

### Safety

UDCA is known to be well tolerated with diarrhoea the major side effect, reported in up to 3% of patients in previously evaluated studies. Nausea, vomiting and rarely urticaria have also been reported. Decompensation of hepatic cirrhosis and calcification of gallstones has also been reported in  $\leq 1/10,000$  patients.

In this submission tolerability of the 20 and 30 mg/kg/day doses was assessed in the dose finding study for PSC. In that study patients considered UDCA to be satisfactory, good or very good in 100%, 81% and 90% at 10, 20 and 30 mg/kg/day respectively. Only two patients and one investigator considered tolerability to be poor. Similarly in the studies in children with CF given up to 40 mg/kg/day problems with tolerability were not reported.

Adverse events tended not to be reported in the published studies and there was no indication of increases in adverse events with increasing doses of UDCA.

In study URC-105/PCH no adverse reactions were reported in pregnant women. In the published papers for ICP only two UDCA-treated patients reported adverse events, which were both diarrhoea. Patients received up to 25 mg/kg/day UDCA.

ICP is associated with adverse fetal outcomes. The sponsor identified 15 of the published studies which included assessment of pregnancy outcomes such as birth weights, number of newborns with low birth weight, premature labour/delivery and pregnancies with meconium passage. These data are of limited value because the studies were small and either not randomised or with no evidence of control for other pregnancy risk factors or interventions. However, mean gestational age at delivery was similar in the UDCA, cholestyramine, dexamethasone, SAME and placebo treated groups. UDCA-treated mothers tended to have less meconium passage compared to SAME-treated and non-treated mothers as shown in Table 1:

Table 1: Passage of meconium

Reference	UDCA	SAMe	Placebo	Dex	Non-treatment	UDCA + SAMe
Roncaglia et al. 2004	2/24 (8%)	5/22 (23%)				
Binder et al. 2006	3/26 (12%)	5/25 (20%)				4/24 (7%)
Glanz et al 2005	18/47 (38.3%)		17/47 (34%)	13/36 (36.1%)		
Liu et al 2006	4/34 (11.8%)*				12/34 (35.3%)	

\*  $p < 0.05$  compared to control

### Risk-Benefit Analysis

The bioequivalence study, URU-1/BIO supports the contention that the total dose rather than the formulation affects biliary UDCA concentration and that once daily dosing leads to increases in biliary UDCA concentration. This has previously been accepted by the TGA. Data from published papers also demonstrated that the degree of UDCA enrichment of bile is dependent on the total daily dose and that the number of times a day the total daily dose is given does not influence the

%UDCA in bile. The extent to which efficacy is reflected in %UDCA in bile is unclear and likely to vary with the extent and cause of the cholestasis.

The relationship between efficacy, tolerability and dose regimen was examined in the efficacy studies. The strongest evidence that outcomes are similar for a given total daily dose was in patients with PBC where there was a direct comparison of the current and proposed dose intervals but only 60 patients were examined.<sup>1</sup>

For PBC the sponsor proposes a small increase in total daily dose (from 10-15 mg/kg/day to 12-16 mg/kg/day. There was evidence that patients given 5-7 mg/kg/day do worse than those given 13 mg/kg/day or higher doses but limited information on the outcome of patients given 10 or 11 mg/kg/day. Most of the data examined efficacy in patients given the proposed 12-16 mg/kg/day UDCA dose. On balance the Delegate considered that the requested increase in total daily dose for treatment of PBC is adequately supported.

For patients with PSC the data strongly suggest slower progression with the proposed 20-30 mg/kg/day dose compared with the current 10- 15 mg/kg/day dose and the dose increase was supported by the Delegate.

For patients with CF-related cholestasis the proposed dose increase from 20 mg/kg/day to 20-30 mg/kg/day was not supported by the efficacy data submitted. The only published study demonstrated the beneficial effects of UDCA in children with CF and hepatic abnormalities but the initial UDCA dose was below the currently approved total daily dose, the number of children receiving 30 mg/kg/day was not stated and it was not clear if those who did receive an increase in dose to 30 mg/kg/day received any benefit from that dose increase. The submitted abstract claimed there was no additional benefit from increasing the dose beyond 20 mg/kg/day and the conference poster had insufficient information to be interpreted.

Patients with ICP are not a subgroup of patients with chronic cholestatic liver disease and if this indication were accepted it would be presented as an additional indication. The current *Use in Pregnancy* section of the PI for Ursosalk notes that there is evidence of fetal toxicity in rats (reduction in live fetuses and tail malformations) in rats given UDCA 2,000 mg/kg. No teratogenic effects were found following oral administration to mice or rabbits at doses of up to 1,500 and 300 mg/kg/day, respectively. It is currently recommended that UDCA should not be used during the first three months of pregnancy and that women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with UDCA.

ICP causes maternal distress and is associated with an increased risk of fetal death, prematurity, and postpartum haemorrhage. The current recommended treatment is cholestyramine, though no medication is specifically indicated to treat this condition. In the data submitted there was no systematic assessment of outcomes, particularly neonatal outcomes following exposure to UDCA and no assessment of the optimum dose for either maternal or fetal outcomes. Large scale studies would be required to support this extension of indication. However it is clear that maternal LFTs improve with UDCA. There is a case for summarising the limited available information concerning use of UDCA during pregnancy in the *Use in Pregnancy* section of the PI.

The Delegate proposed to approve the following variations to the conditions of registration for Urso/Ursosalk:

- For Primary Biliary Cirrhosis (PBC) the dose regimen to be amended from 10-15 mg/kg/day given in 2 - 4 divided doses to 12-16 mg/kg/day given either as a single daily dose or in 2- 3 divided doses.
- For Primary Sclerosing Cholangitis (PSC) the dose regimen to be amended from 10-15 mg/kg/day given in 2-4 divided doses to 20-30 mg/kg/day given in 2- 3 divided doses.

- For Cystic Fibrosis (CF)-related cholestasis the dose regimen to be amended from 20 mg/kg/day in 2-4 divided doses to 20 mg/kg/day in 2-3 divided doses.

*The sponsor informed the TGA of its decision to withdraw the application to amend the dose regimen of UDCA for PSC from 10-20 mg/kg/day to 20-30 mg/kg/day. The sponsor made it clear that it was not withdrawing the entire submission, just the variation to increase the dose of UDCA for PSC. A multicentre, long-term, double-blind controlled study enrolling 150 North American patients with PSC who were treated using high doses (28-30 mg/kg/day) of UDCA was recently published.<sup>8</sup> This study was terminated after 6 years because of enhanced risk in the UDCA treatment group. This outcome was completely unanticipated because of the previous body of evidence and usage experience of UDCA in PSC. The sponsor has therefore decided to withdraw this variation until there is greater clarity regarding the higher 30 mg/kg/day dose.*

The Delegate proposed to reject the sponsor's proposal to include ICP as a subgroup of patients to receive Urso/Ursofalk within the current indication because:

- ICP is not a chronic cholestatic liver disease;
- the efficacy measures in the studies of ICP for either maternal or fetal outcomes were not justified or systematically assessed; and
- there were insufficient data to determine differences in fetal outcomes of most concern, particularly intrauterine fetal death and premature delivery.

The advice of the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded the Australian Drug Evaluation Committee [ADEC]), was requested, particularly concerning the extent of information describing use of UDCA in ICP that should be included in the PI.

The ACPM having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

The ACPM recommended approval of the submission from Orphan Australia Pty Ltd to change the dosage regimen for ursodeoxycholic acid (Ursofalk / Urso) capsule and oral liquid 250 mg & 250 mg /5 mL.

For Primary Biliary Cirrhosis (PBC) the dose regimen to be amended from 10-15 mg/ kg/day given in 2-4 divided doses to 12-16 mg/kg/day given either as a single daily dose or in 2-3 divided doses.

For Cystic Fibrosis (CF)-related cholestasis the dose regimen to be amended from 20-30 mg/kg/day in 2-4 divided doses to 20 mg/kg/day in 2-3 divided doses with improvement in liver function the dose may be taken as a single daily dose in the evening

The ACPM recommended rejection of the submission from Orphan Australia Pty Ltd to extend the indication to include use in patients with intrahepatic cholestasis of pregnancy (ICP) on the grounds that the proposed indication did not adequately demonstrate safety or efficacy, in particular, improvements in neonatal outcomes were not adequately demonstrated. However the Committee notes the strong evidence of efficacy in the symptomatic control of pruritus in patients with ICP. The ACPM agreed with the Delegate that this information should be included in the Use in Pregnancy section of the Product Information.

## **Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration for Urso and Ursofalk containing ursodeoxycholic acid 250mg capsules in blister packs and 250mg/5ml oral liquid bottles for the new changes in dose regimen as follows:

---

<sup>8</sup> Lindor KD et al. High dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. *Hepatology* 2009; 50: 808-814; editorial: Chapman RW. *Hepatology* 2009; 50: 671-673.

For Primary Biliary Cirrhosis (PBC), the dose regimen to be amended to

*12-16mg/kg/day given either as a single dose or in 2-3 divided doses*

For Cystic Fibrosis (CF)-related cholestasis, the dose regimen to be amended to

*20mg/kg/day in 2-3 divided doses*

For PSC, the dose regimen to be amended to

*2-3 divided doses per day*

The sponsor's proposal to withdraw the application to amend the dose regimen for Primary Sclerosing Cholangitis (PSC) from 10-20 mg/kg/day to 20-30 mg/kg/day was noted and accepted.

The application to extend the indications to include patients with intrahepatic cholestasis of pregnancy (ICP) was rejected on the grounds that safety and efficacy, in particular, improvements in neonatal outcomes were not adequately demonstrated.

## ***Attachment 1. Product Information***

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at [www.tga.gov.au](http://www.tga.gov.au).

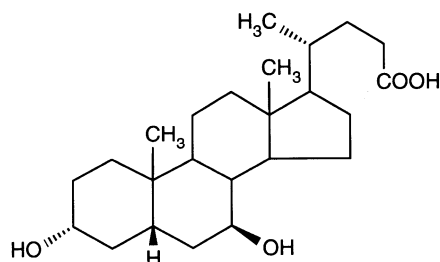
## PRODUCT INFORMATION

**URSO<sup>®</sup>**

(Ursodeoxycholic Acid)

### NAME OF THE MEDICINE

The chemical structure of ursodeoxycholic acid is as follows:



CAS number: 128-13-2

### DESCRIPTION

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 - 204°C. The IUPAC chemical name of UDCA is 3 $\alpha$ , 7 $\beta$ -dihydroxy-5-cholan-24-oic acid.

URSO Capsule contains UDCA 250 mg, maize starch, colloidal silicon dioxide, magnesium stearate, gelatine, titanium dioxide, sodium lauryl sulfate and purified water.

### PHARMACOLOGY

#### 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 choleric 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.

### **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 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 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  $^{14}C$  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, obtained by radioactive labelling, of orally administered UDCA is 3.5 - 5.8 days due to the effective enterohepatic circulation of UDCA in the body.

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

## **CLINICAL TRIALS**

### **Primary Biliary Cirrhosis**

Primary biliary cirrhosis (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 UDCA in the treatment of primary biliary cirrhosis (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 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 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 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.

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

## **INDICATIONS**

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

## CONTRAINDICATIONS

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

## PRECAUTIONS

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.

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

URSO is not recommended in patients with dominant stenoses of the bile ducts unless the obstructed bile ducts are dilated (see DOSAGE AND ADMINISTRATION).

### Effects on fertility

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 body surface area/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  $\geq 250$  mg/kg/day (2.5 times the maximum recommended human dose based on BSA) and of embryoletality (resulting in a reduction in number of live foetuses) at doses  $\geq 1000$  mg/kg/day.

### Use in pregnancy (Category B3)

UDCA has been shown to cross the placenta in rats. Animal studies have provided evidence of a teratogenic effect of UDCA during the early phase of gestation. In studies in rats, tail malformations occurred after a dose of 2000 mg per kg of body weight. In one of two studies in rats, there was evidence of embryoletality, with a reduction in number of live foetuses and live births at oral doses of 2000 mg/kg/day. In studies in rabbits, embryotoxic effects from a dose of 100 mg per kg of body weight were found. No teratogenic effects were found in the study of UDCA following oral administration to mice or rabbits at doses of up to 1500 and 300 mg/kg/day, respectively.

There are no adequate or well-controlled studies in pregnant women during the first trimester. Therefore, UDCA 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 UDCA.

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

### Use in lactation

It is not known whether UDCA 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 UDCA is administered to a nursing mother. Alternatively, breastfeeding can be discontinued.

### **Carcinogenicity**

In two 24-month oral carcinogenicity studies in mice, UDCA 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, UDCA 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 UDCA, doses up to 250 mg/kg/day in mice and 500 mg/kg/day in rats did not produce any tumours.

### **Mutagenicity**

UDCA 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.

### **Interactions with other drugs**

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

UDCA may increase the absorption of cyclosporin in transplantation and non-transplant patients. Therefore, monitoring cyclosporin plasma concentrations are recommended and cyclosporin dose adjusted if necessary.

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

UDCA 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 UDCA 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.

## **ADVERSE 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.

Severe right upper abdominal pain has occurred during the treatment of PBC ( $\leq 1$  in 10,000 patients). During advanced stages of PBC, in very rare cases ( $\leq 1$  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  $\leq 1$  in 10,000 patients.

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

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

## **DOSAGE AND 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 UDCA is recommended.

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

For PSC, the dosage of 10-15 mg/kg body weight/day of UDCA 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, URSO capsules 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, URSO capsules should be taken in 2 to 3 doses over the day.

The capsules should be swallowed whole with some liquid.

Care should be taken to ensure that URSO 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 of URSO 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 URSO.

## **OVERDOSAGE**

Diarrhoea may occur in cases of overdose. 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 overdose are unlikely because the absorption of UDCA decreases with increasing dose and therefore more is excreted with the faeces.

Serious adverse effects are also unlikely to occur in overdose. 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 Poisons Information Centre (telephone 13 11 26).

## **PRESENTATION**

URSO Capsules 250 mg are presented as white, opaque, hard gelatin capsules. It is supplied in clear PVC blister strips of aluminium foil backing packed in cardboard cartons. Each carton contains 100 capsules.

## **STORAGE CONDITIONS**

Store below 25°C.

## **NAME AND ADDRESS OF THE SPONSOR**

Orphan Australia Pty. Ltd.  
300 Frankston-Dandenong Road  
Dandenong  
Victoria 3175  
Australia

**DISTRIBUTOR**

Sigma Pharmaceuticals (Australia) Pty. Ltd.  
96 Merrindale Drive  
Croydon  
Victoria 3136  
Australia

**POISON SCHEDULE OF THE MEDICINE**

S4

**DATE OF APPROVAL**

Date of TGA approval: 16 February 2010

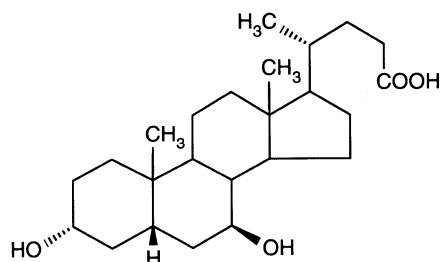
URSO® is a registered trademark of Dr Falk Pharma GmbH, Germany, used under licence by Orphan Australia Pty. Ltd.

## PRODUCT INFORMATION

### URSOFALK<sup>®</sup> (Ursodeoxycholic Acid)

#### NAME OF THE MEDICINE

The chemical structure of ursodeoxycholic acid is as follows:



CAS number: 128-13-2

#### DESCRIPTION

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 - 204°C. The IUPAC chemical name of UDCA is 3 $\alpha$ , 7 $\beta$ -dihydroxy-5-cholan-24-oic acid.

URSOFALK Capsule contains UDCA 250 mg, maize starch, colloidal silicon dioxide, magnesium stearate, gelatine, titanium dioxide, sodium lauryl sulfate and purified water.

URSOFALK Suspension contains UDCA 50 mg/mL, benzoic acid, purified water, xylitol, glycerol, microcrystalline cellulose and carmellose sodium, propylene glycol, sodium citrate, sodium cyclamate, anhydrous citric acid, sodium chloride and lemon flavouring (Giovaudan 87017).

#### PHARMACOLOGY

##### 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 choleric 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.

### **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 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 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  $^{14}C$  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, obtained by radioactive labelling, of orally administered UDCA is 3.5 - 5.8 days due to the effective enterohepatic circulation of UDCA in the body.

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

## **CLINICAL TRIALS**

### **Primary Biliary Cirrhosis**

Primary biliary cirrhosis (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 UDCA in the treatment of primary biliary cirrhosis (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 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 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 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.

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

## **INDICATIONS**

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

## CONTRAINDICATIONS

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

## PRECAUTIONS

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.

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

URSOFALK is not recommended in patients with dominant stenoses of the bile ducts unless the obstructed bile ducts are dilated (see DOSAGE AND ADMINISTRATION).

One measuring spoonful (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.

### Effects on fertility

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 body surface area/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  $\geq$  250 mg/kg/day (2.5 times the maximum recommended human dose based on BSA) and of embryoletality (resulting in a reduction in number of live foetuses) at doses  $\geq$  1000 mg/kg/day.

### Use in pregnancy (Category B3)

UDCA has been shown to cross the placenta in rats. Animal studies have provided evidence of a teratogenic effect of UDCA during the early phase of gestation. In studies in rats, tail malformations occurred after a dose of 2000 mg per kg of body weight. In one of two studies in rats, there was evidence of embryoletality, with a reduction in number of live foetuses and live births at oral doses of 2000 mg/kg/day. In studies in rabbits, embryotoxic effects from a dose of 100 mg per kg of body weight were found. No teratogenic effects were found in the study of UDCA following oral administration to mice or rabbits at doses of up to 1500 and 300 mg/kg/day, respectively.

There are no adequate or well-controlled studies in pregnant women during the first trimester. Therefore, UDCA 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 UDCA.

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

### **Use in lactation**

It is not known whether UDCA 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 UDCA is administered to a nursing mother. Alternatively, breastfeeding can be discontinued.

### **Carcinogenicity**

In two 24-month oral carcinogenicity studies in mice, UDCA 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, UDCA 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 UDCA, doses up to 250 mg/kg/day in mice and 500 mg/kg/day in rats did not produce any tumours.

### **Mutagenicity**

UDCA 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.

### **Interactions with other drugs**

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

UDCA may increase the absorption of cyclosporin in transplantation and non-transplant patients. Therefore, monitoring cyclosporin plasma concentrations are recommended and cyclosporin dose adjusted if necessary.

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

UDCA 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 UDCA 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.

## **ADVERSE 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.

Severe right upper abdominal pain has occurred during the treatment of PBC ( $\leq 1$  in 10,000 patients). During advanced stages of PBC, in very rare cases ( $\leq 1$  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  $\leq 1$  in 10,000 patients.

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

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

## **DOSAGE AND 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 UDCA is recommended.

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

For PSC, the dosage of 10-15 mg/kg body weight/day of UDCA 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 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 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, URSOFALK suspension should be used.

The capsules 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 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.

## **OVERDOSAGE**

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 UDCA 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 advice on the management of overdosage, please contact the Poisons Information Centre (telephone 13 11 26).

## **PRESENTATION**

URSOFALK Capsules 250 mg are presented as white, opaque, hard gelatin capsules. It is supplied in clear PVC blister strips of aluminium foil backing packed in cardboard cartons. Each carton contains 100 capsules.

URSOFALK Suspension 50 mg/mL is presented as a white homogenous suspension containing small air bubbles and with a lemon flavour (Giovaudan 87017). It is available in bottles of 250 mL.

## **STORAGE CONDITIONS**

Store below 25°C.

Do not use URSOFALK Suspension after 4 months of opening the bottle.

## **NAME AND ADDRESS OF THE SPONSOR**

Orphan Australia Pty. Ltd.  
300 Frankston-Dandenong Road  
Dandenong  
Victoria 3175  
Australia

Website: [www.orphan.com.au](http://www.orphan.com.au)

## **POISON SCHEDULE OF THE MEDICINE**

S4

## **DATE OF APPROVAL**

Date of TGA approval: 16 February 2010

URSOFALK® is a registered trademark of Dr Falk Pharma GmbH, Germany, used under licence by Orphan Australia Pty. Ltd.