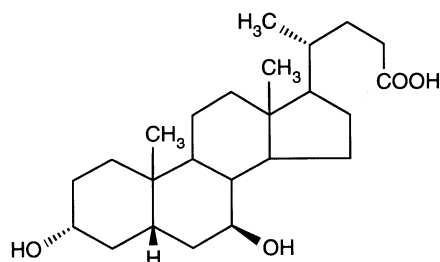


## PRODUCT INFORMATION

### URSOFALK® (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) URISOFALK 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 URISOFALK.

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, URISOFALK 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, URISOFALK 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.  
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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

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