New Zealand Data Sheet

1 URSOSAN

URSOSAN 250 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One Ursosan capsule contains ursodeoxycholic acid (UDCA) 250 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Ursosan capsules are white hard gelatin capsules, containing a white or almost white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ursosan is indicated in the treatment of chronic cholestatic liver diseases, including primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC).

In primary biliary cirrhosis ursodeoxycholic acid improves liver enzymes and IgM and prevents worsening of liver histology in patients with less advanced forms of the disease, i.e. serum bilirubin less that 2 mg/dL and histologic changes in liver confined to the portal regions. Prevention of complications of chronic liver disease has not been established.

4.2 Dose and method of administration

This product may not be interchangeable with similar products on the New Zealand market.

Dose

Adults
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.

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

Body weight (kg)	***Daily dose (capsules)***	***Number of 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.

Elderly
In worldwide clinical studies of UDCA, approximately 14% of subjects were over 65 years of age (approximately 3% were over 75 years old). In a subgroup analysis of existing clinical trials, patients greater than 56 years of age did not exhibit statistically significantly different complete dissolution rates from the younger population. No age-related differences in safety and effectiveness were found. Other reported clinical experience has not identified difference in response in elderly and younger patients. However, small differences in efficacy and greater sensitivity of some elderly individuals taking UDCA cannot be ruled out. Therefore, it is recommended that dosing proceed with caution in this population.

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 one capsule of Ursosan daily, and the daily dose gradually increased until the recommended daily dose has been reached.

<u>Paediatric population</u>
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.

4.3 Contraindications

Ursosan 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).

UDCA will not dissolve calcified cholesterol stones, radio-opaque stones or radiolucent bile pigment stones. Hence patients with such stones are not candidates for UDCA therapy.

Patients with compelling reasons for cholecystectomy including unremitting acute cholecystitis, cholangitis, biliary obstruction, gallstone pancreatitis or biliary-gastrointestinal fistula are not candidates for UDCA therapy.

Allergy to bile acids.

4.4 Special warnings and precautions for use

UDCA has not been associated with liver damage.

Lithocholic acid, a naturally occurring bile acid, is known to be a liver-toxic metabolite. This bile acid is formed in the gut from UDCA less efficiently and in smaller amounts that that seen from chenodiol. Lithocholic acid is detoxified in the liver by sulfation and although man appears to be an efficient sulfater, it is possible that some patients may have a congenital or acquired deficiency in sulfation, thereby predisposing them to lithocholate induced liver damage.

Abnormalities in liver enzymes have not been associated with UDCA therapy and in fact UDCA has been shown to decrease liver enzyme levels in liver disease. However, 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 UDCA in patients with renal impairment has not been studied.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions
Some drugs, such as cholestyramine, charcoal, colestipol and certain antacids (e.g. aluminium hydroxide and/or smectite (aluminium oxide)) bind bile acids *in vitro*. They could therefore have a similar effect *in vivo* and may interfere with the absorption of UDCA. Should the use of a preparation containing one of these substances be necessary, it must be taken at least 2 hours before or after Ursosan.

UDCA may increase the absorption of cyclosporin in transplantation and non-transplant patients. Therefore, monitoring cyclosporin plasma concentrations is recommended.

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.

Oestrogens, oral contraceptives and clofibrate (and perhaps other lipid-lowering agents) increase hepatic cholesterol secretion, encourage cholesterol gallstone formation and hence may counteract the effectiveness of UDCA.

Pharmacodynamic interactions
Nil

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B3.
UDCA has been shown to cross the placenta in rats. There was no evidence of a teratogenic effect of UDCA following oral administration to rats, mice or rabbits at doses of up to 4,000, 1,500 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 2,000 mg/kg/day.

There are no adequate or well-controlled studies in pregnant women. Inadvertent exposure of 4 women to therapeutic doses in the first trimester of pregnancy during trials with UDCA led to no evidence of effects on the foetus or newborn baby. Although it seems unlikely, the possibility that ursodeoxycholic acid can cause foetal harm cannot be ruled out; hence, Ursosan is not recommended for use during pregnancy.

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

Breastfeeding

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 Ursosan is administered to a nursing mother. Alternatively, nursing can be discontinued.

Fertility

In a fertility study in Sprague-Dawley rats at oral doses up to 2,700 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 ≥ 1,000 mg/kg/day.

4.7 Effects on ability to drive and use machines

No information provided.

4.8 Undesirable effects

a. Summary of the safety profile

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

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

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

b. Tabulated summary of adverse reactions

The following tables provide comprehensive listings of the adverse experiences reported that occurred with a 5% incidence level:

GALLSTONE DISSOLUTION

	UDCA 8 - 10 mg/kg/day (N = 155)		Placebo (N = 159)	
	N	(%)	N	(%)
Body as a Whole				
Allergy	8	(5.2)	7	(4.4)
Chest pain	5	(3.2)	10	(6.3)
Fatigue	7	(4.5)	8	(5.0)
Infection viral	30	19.4	41	(25.8)
Digestive System				
Abdominal pain	67	(43.2)	70	(44.0)
Cholecystitis	8	(5.2)	7	(4.4)
Constipation	15	(9.7)	14	(8.8)
Diarrhoea	42	(27.1)	34	(21.4)
Dyspepsia	26	(16.8)	18	(11.3)
Flatulence	12	(7.7)	12	(7.5)
Gastrointestinal disorder	6	(3.9)	8	(5.0)
Nausea	22	(14.2)	27	(17.0)
Vomiting	15	(9.7)	11	(6.9)
Musculoskeletal System				
Arthralgia	12	(7.7)	24	(15.1)
Arthritis	9	(5.8)	4	(2.5)
Back pain	11	(7.1)	18	(11.3)
Myalgia	9	(5.8)	9	(5.7)
Nervous System				
Headache	28	(18.1)	34	(21.4)
Insomnia	3	(1.9)	8	(5.0)
Respiratory System				
Bronchitis	10	(6.5)	6	(3.8)
Coughing	11	(7.1)	7	(4.4)
Pharyngitis	13	(8.4)	5	(3.1)
Rhinitis	8	(5.2)	11	(6.9)
Sinusitis	17	(11.0)	18	(11.3)
Upper respiratory tract infection	24	(15.5)	21	(13.2)
Urogenital System				
Urinary tract infection	10	(6.5)	7	(4.4)

GALLSTONE PREVENTION

	UDCA 600 mg (N = 322)		Placebo (N = 325)	
	N	(%)	N	(%)
Body as a Whole				
Fatigue	25	(7.8)	33	(10.2)
Infection viral	29	(9.0)	29	(8.9)
Influenza-like symptoms	21	(6.5)	19	(5.8)
Digestive System				
Abdominal pain	20	(6.2)	39	(12.0)
Constipation	85	(26.4)	72	(22.2)
Diarrhoea	81	(25.2)	68	(20.9)
Flatulence	15	(4.7)	24	(7.4)
Nausea	56	(17.4)	43	(13.2)
Vomiting	44	(13.7)	44	(13.5)
Musculoskeletal System				
Back pain	38	(11.8)	21	(6.5)
Musculoskeletal pain	19	(5.9)	15	(4.6)
Nervous System				
Dizziness	53	(16.5)	42	(12.9)
Headache	80	(24.8)	78	(24.0)
Respiratory System				
Pharyngitis	10	(3.1)	19	(5.8)
Sinusitis	17	(5.3)	18	(5.5)
Upper respiratory tract infection	40	(12.4)	35	(10.8)
Skin and Appendages				
Alopecia	17	(5.3)	8	(2.5)
Urogenital System				
Dysmenorrhoea	18	(5.6)	19	(5.8)

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
https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Serious adverse effects are unlikely to occur in overdosage. Doses of UDCA in the range of 16 - 20 mg/kg/day have been tolerated for 6 - 37 months without symptoms by 7 patients. The LD_{50} for UDCA in rats is over 5,000 mg/kg given over 7 - 10 days and over 7,500 mg/kg for mice.

The most likely manifestation of severe overdose with UDCA would probably be diarrhoea, which should be treated symptomatically.

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).

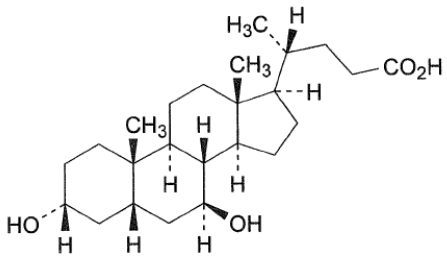
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alimentary tract and metabolism bile acids and derivatives
ATC code: A05AA02

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.

Chemical structure



The IUPAC chemical name of UDCA is 3a, 7β-dihydroxy-5-cholan-24-oic acid.

MW: 392.6
CAS number: 128-13-2

Mechanism of action

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

Absorption

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. 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.

Distribution

In plasma, protein binding is 96 - 98%.

Biotransformation

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%).

Elimination

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

Carcinogenicity
In two 24-month oral carcinogenicity studies in mice, ursodeoxycholic acid at doses up to 1,000 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.

Genotoxicity
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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Starch – maize
Starch – pregelatinised maize
Magnesium stearate
Silica – colloidal anhydrous
Gelatin
Titanium dioxide

6.2 Incompatibilities

Nil

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Blister packs of 100 capsules.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

BNM Group
39 Anzac Road
Browns Bay
Auckland 0753

Phone 0800 565 633

9 DATE OF FIRST APPROVAL

6 June 2013

10 DATE OF REVISION OF TEXT

30 December 2020

Summary table of changes

Section changed	Summary of new information
6.3	Change in shelf life from 2 years to 4 years