PROFESSIONAL INFORMATION FOR

URSOFALK

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

URSOFALK 250 mg ursodeoxycholic acid, capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg ursodeoxycholic acid.

Sugar free.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Hard gelatine capsules

URSOFALK is a white, opaque, hard gelatine capsules, size 0, containing a white, compressed powder or granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

URSOFALK has been used in the treatment of primary biliary cholangitis (PBC), provided there is no decompensated hepatic cirrhosis, and for the dissolution of radiolucent gallstones in patients with a functioning gall bladder.

4.2 Posology and method of administration

Posology

The following regimen is recommended

For primary biliary cholangitis (PBC)

The daily dose depends on body weight, and ranges from 3 to 7 capsules (14 ± 2 mg ursodeoxycholic acid per kg of body weight).

For the first 3 months of treatment, URSOFALK capsules should be taken divided over the day. With improvement of the liver values the daily dose may be taken once daily in the evening.

Body weight (BW) in kg	**Daily dose (mg/kg BW)**	**URSOFALK 250 mg hard capsules**			
		First 3 months			**Subsequently**
		Morning	**Midday**	**Evening**	**Evening (1 x daily)**
47 to 62	12 to 16	1	1	1	3
63 to 78	13 to 16	1	1	2	4
79 to 93	13 to 16	1	2	2	5
94 to 109	14 to 16	2	2	2	6
Over 110		2	2	3	7

The capsules should be swallowed whole with some liquid. Care should be taken to ensure that they are taken regularly.

In patients with PBC, the clinical symptoms may worsen at the beginning of treatment, e.g. pruritus may increase. Should this occur, therapy should be continued with a dose of one URSOFALK

capsule daily, and the dosage should then be gradually increased (by one capsule daily each week) until the dose indicated in the regimen is reached.

Dissolution of Gallstones

Adults: The usual dose is 8 to 12 mg/kg/day to be taken in the evening, e.g. 750 mg, daily in the evening. The time required for dissolution of gallstones is likely to range from 6 to 24 months depending on stone size and composition.

Follow-up cholecystograms or ultrasound investigation may be useful at 6-month intervals until the gallstones have disappeared.

Treatment should be continued until 2 successive cholecystograms and/or ultrasound investigations 4 to 12 weeks apart have failed to demonstrate gallstones. This is because these techniques do not permit reliable visualisation of stones less than 2 mm in diameter.

Method of administration

URSOFALK is for oral administration.

4.3 Contraindications

URSOFALK is contraindicated in:

- Patients with known hypersensitivity to ursodeoxycholic acid (UDCA) or to any of the excipient in URSOFALK (see **section 6.1**).
- Patients with acute inflammation of the gall bladder or biliary tract.
- Patients with occlusion of the biliary tract (occlusion of the common bile duct or cystic duct).
- Patients with frequent episodes of biliary colic.
- Patients with non-functional or impaired contractility of the gall bladder.

- Patients with radio-opaque/ calcified gall stones.
- Pregnant women and women of childbearing age (see s**ection 4.4.** and **4.6**).

4.4 Special warnings and precautions for use

In the first 3 months of treatment, liver function tests (AST, ALT and γ-GT) should be monitored by the doctor every 4 weeks, thereafter every 3 months. Apart from allowing for identification of responders and non-responders in patients being treated for primary biliary cholangitis (PBC), this monitoring would also enable early detection of potential hepatic deterioration, particularly in patients with advanced stage PBC.

When used for treatment of advanced stage of PBC

In very rare cases decompensation of hepatic cirrhosis has been observed, which partially regressed after the treatment was discontinued.

In patients with PBC, in rare cases the clinical symptoms may worsen at the beginning of treatment, e.g. the itching may increase. In this case the dose of URSOFALK should be reduced to one URSOFALK 250 mg capsule daily and then gradually increased again to the prescribed dose (see **section 4.2**).

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

When used for dissolution of cholesterol gallstones

To assess therapeutic progress and for timely detection of any calcification of the gallstones, depending on stone size, the gall bladder should be visualised (oral cholecystography) with

overview and occlusion views in standing and supine positions (ultrasound control) 6 to 10 months after the beginning of treatment.

If the gall bladder cannot be visualised on X-ray images, or in cases of calcified gallstones, impaired contractility of the gall bladder or frequent episodes of biliary colic, URSOFALK should not be used.

Female patients taking URSOFALK for dissolution of gallstones should use an effective non-hormonal method of contraception, since hormonal contraceptives may increase biliary lithiasis (see **section 4.5** and **4.6**)

4.5 Interaction with other medicines and other forms of interaction

URSOFALK capsules should not be administered concomitantly with cholestyramine, colestipol or antacids containing aluminium hydroxide and or aluminium oxide, because these preparations bind ursodeoxycholic acid in the intestine thereby inhibiting its absorption. 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 capsules.

URSOFALK capsules can affect the absorption of ciclosporin from the intestine. In patients receiving ciclosporin treatment, blood concentrations of this substance should therefore be checked by the doctor and the ciclosporin dose adjusted if necessary.

URSOFALK can reduce the absorption of ciprofloxacin.

In a clinical study in healthy volunteers, concomitant use of ursodeoxycholic acid (500 mg / day) and rosuvastatin (20 mg / day) resulted in slightly elevated plasma levels of rosuvastatin. The clinical relevance of this interaction also with regard to other statins is unknown.

Ursodeoxycholic acid reduces peak plasma concentrations (C_{max}) and area under the curve (AUC) of nitrendipine in healthy volunteers. Close monitoring of the outcome of concurrent use of nitrendipine and ursodeoxycholic acid is recommended. An increase of the dose of nitrendipine may be necessary.
An interaction with a reduction of the therapeutic effect of dapsone was also reported.

These observations, together with in-vitro findings, could indicate a potential for UDCA to induce cytochrome P450 3A enzymes. Induction by UDCA has, however, not been observed in a well-designed interaction study with budesonide, which is a known cytochrome P450 3A substrate.

Oestrogenic hormones and blood cholesterol lowering agents such as clofibrate increase hepatic cholesterol secretion and may therefore encourage biliary lithiasis, which is a counter-effect to ursodeoxycholic acid used for dissolution of gallstones.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established. There are no or limited amounts of data from the use of URSOFALK in pregnant women. Studies in animals have shown reproductive toxicity during the early phase of gestation. Women of childbearing age should be treated only if they use reliable contraception: non-hormonal or low-oestrogen oral contraceptive measures are recommended. However, in patients taking URSOFALK capsules for dissolution of gallstones, effective non-hormonal contraception should be used, since hormonal oral contraceptives may increase biliary lithiasis. Pregnancy must be excluded before the beginning of treatment.
According to few documented cases of breastfeeding women, milk levels of UDCA are very low and probably no adverse reactions are to be expected in breastfed infants.

4.7 Effects on ability to drive and use machines

URSOFALK has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions reported as more than an isolated case is listed below, by system organ class and by frequency.

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10000, < 1/1000), very rare (< 1/10000).

Tabulated list of adverse reactions

MedDRA system organ class	Frequency	Side effects
Gastrointestinal disorders	*Common:*	Reports of pasty stools or diarrhoea.
	Very rare	Severe right-side upper abdominal pain during treatment of PBC.
	Unknown frequency:	Nausea, vomiting, dyspepsia, constipation.
Hepato-biliary disorders	*Very rare*	Calcification of gallstones. During therapy of the advanced stages of PBC, decompensation of the hepatic cirrhosis has been observed, which partially regressed after treatment was discontinued.
Skin and subcutaneous tissue disorders:	*Very rare*	Urticaria.
	Unknown frequency:	Pruritus.

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website, or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

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

No specific treatment measures are necessary, and the consequences of diarrhoea should be treated symptomatically with restoration of fluid and electrolyte balance.

Additional information on special populations

Long-term, high-dose UDCA therapy (28 to 30 mg/kg/day) in patients with primary sclerosing cholangitis (off-label use) was associated with higher rates of serious adverse events.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 11.10 Medicines acting on the gastro-intestinal tract – Other.

Pharmacotherapeutic group: Bile and liver therapy, bile acids and derivatives.

ATC code: A05AA02 and A05B

Mechanism of action

The mechanism of action of ursodeoxycholic acid (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 of immunological effects, including a reduction of abnormal expression of HLA Class I antigens on hepatocytes and a suppression of immunoglobulin and cytokine production.

5.2 Pharmacokinetic properties

UDCA occurs naturally in the body. After oral administration of a single 500 mg dose of UDCA to healthy volunteers, peak plasma concentrations were 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 to 98 %.

First pass extraction of UDCA from the portal vein by the liver ranges from 50 to 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 to 44 % of the dose was excreted in faeces in the first three days as UDCA (2 to 4 %), lithocholic acid (37 %) and 7-ketolithocholic acid (5 %).

The biological half-life, obtained by radioactive labelling, of orally administered UDCA is 3,5 to 5,8 days due to the effective enterohepatic circulation of UDCA in the body.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Gelatine

Magnesium stearate

Maize starch

Purified water

Sodium lauryl sulphate

Titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

6.5 Nature and contents of container

URSOFALK is packed in transparent PVC/Aluminium blisters. 50, 100 or 200 capsules are packed in a cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville,

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

43/11.10/0442

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 25 March 2011.

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

26 March 2026