URSOFALK

ORPHAN SA PHARMACEUTICALS (PTY) LTD

Ursodeoxycholic acid 250 mg per capsule

CTD MODULE 1: ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION

1.3 SOUTH AFRICAN LABELLING AND PACKAGING

1.3.1 SOUTH AFRICAN PACKAGE INSERT

1.3.1.1 PACKAGE INSERT

1.3.1.1 Amended Package Insert

Approved Package Insert (in line with amended Regulation 9)

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

URSOFALK (capsules)

COMPOSITION

Each capsule contains 250 mg ursodeoxycholic acid

Excipients

Colloidal anhydrous silica, magnesium stearate, maize starch, purified water and a gelatin capsule.

PHARMACOLOGICAL CLASSIFICATION

A 11.10 Medicines acting on the gastro-intestinal tract - Other

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

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.

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 functional impairment of the liver, renal excretion becomes a major route for elimination of bile acids.

INDICATIONS

Ursofalk has been used in the treatment of primary biliary cirrhosis (PBC), provided there is no decompensated hepatic cirrhosis.

CONTRA-INDICATIONS

Ursofalk is contra-indicated in cases of:

- Pre-existing hypersensitivity to the active ingredient or to any of the other components;
  Acute inflammation of the gall bladder or biliary tract;
- Occlusion of the biliary tract (occlusion of the common bile duct or cystic duct);
- Peptic ulcer disease;
- Frequent episodes of biliary colic;
- Non-functional gall bladder;
- Radio-opaque/ calcified gall stones.

WARNINGS AND SPECIAL PRECAUTIONS

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.

INTERACTIONS

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 reducing 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 increase 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.

Ursodeoxycholic acid reduces peak plasma concentrations and area under the curve of nitrendipine. On the basis of this, together with a single case report of an interaction with dapsone and in-vitro findings, it may be assumed that ursodeoxycholic acid induces the drug-metabolising enzyme cyto chromosome P450 3A4.

Although the clinical relevance of the induction effect of ursodeoxycholic acid on cytochrome P450 3A enzymes is unknown, caution should be exercised in cases of co-administration of agents metabolised via this enzyme and a dose adjustment may be necessary.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established. Women of childbearing age should be treated only if they use reliable contraception. Pregnancy must be excluded before the beginning of treatment. If treatment with Ursofalk capsules is necessary, the infant should be weaned.

DOSAGE AND DIRECTIONS FOR USE

The daily dosage depends on bodyweight and is approximately 2 to 6 capsules (approx 10-15 mg per kg body mass). The following regimen is recommended:

Body mass	Daily dose	Morning	Midday	Evening
34 – 50 kg	2 capsules	1	-	1
51 – 65 kg	3 capsules	1	1	1
66 – 85 kg	4 capsules	1	1	2
86 – 110 kg	5 capsules	1	2	2
Over 100 kg	6 capsules	2	2	2

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.

SIDE EFFECTS

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).