Ursofalk® 250 mg Capsules

Active ingredient :
Each capsule contains:
Ursodeoxycholic acid ------250 mg

Description
Ursofalk® 250 mg is available in capsules for oral administration.
Ursodeoxycholic acid (UDCA) is a naturally occurring bile acid found in small quantities in normal human bile and in larger quantities in the biles of certain species of bears. It is a bitter-tasting white powder consisting of crystalline particles freely soluble in ethanol and glacial acetic acid, slightly soluble in chloroform, sparingly soluble in ether, and practically insoluble in water.
Inactive ingredients:
Gelatin, Colloidal silicon oxide, Magnesium stearate, Maize starch,Sodium dodecyl sulphate, Titanium dioxide (E 171).

Clinical Pharmacology:
UDCA is normally present as a minor fraction of the total bile acids in humans (about 5 %).
Following oral administration, the majority of UDCA is absorbed by passive diffusion and its absorption is incomplete. Once absorbed, UDCA undergoes hepatic extraction to the extent of about 50 % in the absence of liver disease. As the severity of liver disease increases, the extent of extraction decreases. In the liver, UDCA is conjugated with glycine or taurine , then secreted into bile. These conjugates of UDCA are absorbed in the small intestine by passive and active mechanisms. The conjugates can also be deconjugated in the ileum by intestinal enzymes, leading to the formation of free UDCA that can be reabsorbed and reconjugated in the liver. Non absorbed UDCA passes into the colon where it is mostly 7-dehydroxylated to lithocholic acid. Some UDCA is epimerized to chenodeoxycholic acid (CDCA) via 7-oxo intermediate. CDCA also undergoes 7-dehydroxylation to form lithocholic acid. These metabolites are poorly soluble and excreted in the feces. A small portion of lithocholic is reabsorbed conjugated in the liver with glycine, or taurine and sulfated at the 3 position. The resulting sulfated lithocholic acid conjugates are excreted in bile and then lost in the feces. Lithocholic acid, when administered chronically to animals, causes cholestatic liver injury that may lead to death from liver failure in certain species unable to form sulfate conjugates. UDCA is 7-dehydroxylated more slowly than CDCA. For equimolar doses of UDCA and CDCA, steady state levels of lithocholic acid in biliary bile acids are lower during UDCA administration than with CDCA administration. Humans and chimpanzees can sulfate lithocholic acid. Although liver injury has not been associated with UDCA therapy, a reduced capacity to sulfate may exist in some individuals. However, such as a deficiency has not yet been clearly demonstrated and must be extremely rare, given the several thousand patient-years of clinical experience with UDCA.
In healthy subjects, at least 70 % of UDCA (unconjugated) is bound to plasma protein. No information is available on the binding of conjugated UDCA to plasma protein in healthy subjects or primary biliary cirrhosis (PBC) patients. Its volume of distribution has not been determined, but is expected to be small since the drug is mostly distributed in the bile and small intestine. UDCA is excreted primarily in the feces. With treatment, urinary excretion increases, but remains less than 1 % except in severe cholestatic liver disease.
During chronic administration of UDCA, it becomes a major biliary and plasma bile acids. At a chronic dose of 13 to 15 mg/kg/day, UDCA constitutes 30-50 % of biliary and plasma bile acids.

Indications and usage:
Ursofalk® 250 mg (UDCA) capsules are indicated for the treatment of patients of primary biliary cirrhosis.

Contraindications:
Hypersensitivity or intolerance to UDCA or any of the components of the formulation.

Warring & Precautions:
-Patients with variceal bleeding, hepatic encephalopathy, ascites or in need of an urgent liver transplant should receive appropriate specific treatment.
-Improved serum liver tests do not always correlate with improved liver disease status.
Continue monitoring of GGT, alkaline phosphatase, AST, ALT and bilirubin every month for three months after start therapy, and every six months thereafter.
-Treatment should be discontinued if the levels of these parameters increase.
-Long-term use of doses exceeding the recommended doses of Ursofalk® (i.e. 13-15 mg/kg/day) was associated with improvement in serum liver tests but did not improve survival, and was associated with higher rates of serious adverse events (including death or liver transplantation) compared to placebo.

Drug interactions:
Bile acids sequestering agents such as cholestyramine and colestipol may interfere with the action of Ursofalk® 250 mg capsules by reducing its absorption. Aluminium-based antacids have been shown to adsorb bile acids in vitro and may be expected to interfere with Ursofalk® 250 mg in the same manner as the bile acid sequestering agents. Estrogens, oral contraceptives, and clofibrate (and perhaps other lipid lowering drugs) increase hepatic cholesterol secretion, and encourage cholesterol gallstone formation and hence may counteract the effectiveness of Ursofalk® 250 mg.

Pregnancy
Pregnancy category B
There are no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing mothers:
It is not known whether UDCA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Ursofalk® 250 mg is administered to a nursing mother.

Pediatric use :
The safety and effectiveness of Ursofalk® 250 mg in pediatric patients have not been established.

Adverse events (AEs):
The following table summarizes the AEs observed in the two placebo-controlled clinical trials.

Adverse events	Visit at 12 months		Visit at 24 months	
	UDCA n (%)	Placebo n (%)	UDCA n (%)	Placebo n (%)
Diarrhea	---	---	1 (1.32)	---
Elevated creatinine	---	---	1 (1.32)	---
Elevated blood glucose	1 (1.18)	---	1 (1.32)	---
Leukopenia	---	---	2 (2.63)	---
Peptic lucer	---	---	1 (1.32)	---
Skin rash	---	---	2 (2.63)	---

Note: Those AEs occurring at the same or the higher incidence in the placebo as in the UDCA group have been deleted from this table (this includes diarrhea and thrompocytopenia at 12 months, nausea/ vomiting, fever and other toxicity).

In a randomized, cross-over study in sixty PBC patients, four patients (6.7 %) experienced one serious adverse event each (diabetes mellitus, cyst and breast neoplasm (experienced by two patients). No deaths occurred in the study. Forty-three patients (71.7 %) experienced at least one treatment-emergent adverse event (TEAEs) during the study. The most common (>5%) TEAEs were asthenia (11.7%), dyspepsia
(10 %), peripheral edema (8.3 %), hypertension (8.3 %), nausea (8.3%) GI disorders (5 %), chest pain (5%), and pruritus (5 %). Seven patients (11.6 %) reported nine events that were judged as possibly or probably related
to study medication. These nine TEAEs included abdominal pain and asthenia (1 patient each), nausea (3 patients), dyspepsia (2 patients), and anorexia and esophagitis (1 patient each). One patient on the b.i.d. regimen (total dose 1000 mg) withdrew due to nausea. All of these nine TEAEs except esophagitis were observed with the b.i.d. regimen at a total daily dose of 1000 mg or greater.

Overdose :
Accidental or intentional overdosage with UDCA has not been reported. The most severe manifestation of overdosage would likely consist of diarrhea which should be treated symptomatically.
Single oral doses of UDCA at 10.5 and 10 g/kg in mice, rats and dogs respectively were not lethal. A single oral dose of UDCA at 1.5g/kg was lethal in hamsters. Symptoms of acute toxicity were salivation and vomiting in dogs, and ataxia, dyspnea, ptosis, agonal convulsions and coma in hamsters.

Dosage and administration:
The recommended dose of Ursofalk® 250 mg for adults with cholestatic disease (PBC) is 13-15 mg/kg/day administered in two to four divided doses with food. Dosing regimen should be adjusted according to each patient's need at the discretion of the physician.
Call your doctor for medical advice about side effects.

How supplied:
Each Ursofalk® 250 mg capsule contains 250 mg of UDCA. Available in two Al/PVC strips each of 10 capsules in a carton box with insert.

Package:
A box containing 2 strips each of 10 capsules with insert.

Storage:
Store in a dry place at temperature not exceeding 30 °C.

Produced by:
Manufactured by Minapharm Company for pharmaceuticals
& chemical industries – Egypt under license Dr. Falk Pharma – Germany.

Keep medicines out of the reach of children

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