For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

URSETOR

Ursodeoxycholic Acid Tablets B.P. (Ursodiol Tablets)

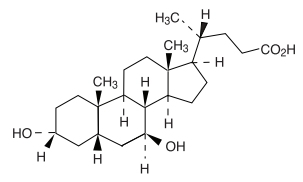
COMPOSITION

URSETOR 600

Each film coated tablet contains : Ursodeoxycholic acid B.P. 600 mg
(Ursodiol)
Colours: Yellow Oxide of Iron, Red Oxide of Iron & Titanium Dioxide I.P.

DESCRIPTION

Ursodeoxycholic acid, a naturally occurring bile acid found in small quantities in normal human bile and in the biles of certain other mammals. It is a bitter-tasting, white or almost white powder freely soluble in ethanol (96 per cent), slightly soluble in acetone,practically insoluble in methylene chloride and insoluble in water. The chemical name for ursodeoxycholic acid is 3α,7β-Dihydroxy-5β-cholan-24-oic acid ($C_{24}H_{40}O_4$). Ursodeoxycholic acid has a molecular weight of 392.6. Its structure is shown below:



CLINICAL PHARMACOLOGY

About 90% of a therapeutic dose of Ursodeoxycholic acid is absorbed in the small bowel after oral administration. After absorption, ursodeoxycholic acid enters the portal vein and undergoes efficient extraction from portal blood by the liver (i.e., there is a large “first-pass” effect) where it is conjugated with either glycine or taurine and is then secreted into the hepatic bile ducts. Ursodeoxycholic acid in bile is concentrated in the gallbladder and expelled into the duodenum in gallbladder bile via the cystic and common ducts by gallbladder contractions provoked by physiologic responses to eating. Only small quantities of ursodeoxycholic acid appear in the systemic circulation and very small amounts are excreted into urine. The sites of the drug’s therapeutic actions are in the liver, bile, and gut lumen.

Beyond conjugation, ursodeoxycholic acid is not altered or catabolized appreciably by the liver or intestinal mucosa. A small proportion of orally administered drug undergoes bacterial degradation with each cycle of enterohepatic circulation. Ursodeoxycholic acid can be both oxidized and reduced at the 7-carbon, yielding either 7-keto-lithocholic acid or lithocholic acid, respectively. Further, there is some bacterially catalyzed deconjugation of glyco- and tauro-ursodeoxycholic acid in the small bowel. Free ursodeoxycholic acid, 7-keto-lithocholic acid, and lithocholic acid are relatively insoluble in aqueous media and larger proportions of these compounds are lost from the distal gut into the feces. Reabsorbed free ursodeoxy cholic acid is reconjugated by the liver. Eighty percent of lithocholic acid formed in the small bowel is excreted in the feces, but the 20% that is absorbed is sulfated at the 3-hydroxyl group in the liver to relatively insoluble lithocholyl conjugates which are excreted into bile and lost in feces. Absorbed 7-keto-lithocholic acid is stereospecifically reduced in the liver to chenodiol. Lithocholic acid causes cholestatic liver injury and can cause death from liver failure in certain species unable to form sulfate conjugates. Lithocholic acid is formed by 7-dehydroxylation of the dihydroxy bile acids (ursodeoxycholic acid and chenodiol) in the gut lumen. The 7-dehydroxylation reaction appears to be alpha-specific, i.e., chenodiol is more efficiently 7-dehy droxylated than ursodeoxycholic acid and, for equimolar doses of ursodeoxycholic acid and chenodiol, levels of lithocholic acid appearing in bile are lower with the former. Man has the capacity to sulfate lithocholic acid. Although liver injury has not been associated with ursodeoxycholic acid therapy, a reduced capacity to sulfate may exist in some individuals, but such a deficiency has not yet been clearly demonstrated.

Pharmacodynamics

Ursodeoxycholic acid suppresses hepatic synthesis and secretion of cholesterol, and also inhibits intestinal absorption of cholesterol. It appears to have little inhibitory effect on synthesis and secretion into bile of endogenous bile acids, and does not appear to affect secretion of phospholipids into bile.

With repeated dosing, bile ursodeoxycholic acid concentrations reach a steady state in about 3 weeks. Although insoluble in aqueous media, cholesterol can be solubilized in at least two different ways in the presence of dihydroxy bile acids. In addition to solubilizing cholesterol in micelles, ursodeoxycholic acid acts by an apparently unique mechanism to cause dispersion of cholesterol as liquid crystals in aqueous media. Thus, even though administration of high doses (e.g., 15-18 mg/kg/day) does not result in a concentration of ursodeoxycholic acid higher than 60% of the total bile acid pool, ursodeoxycholic acid-rich bile effectively solubilizes cholesterol. The overall effect of ursodeoxycholic acid is to increase the concentration level at which saturation of cholesterol occurs.

The various actions of ursodeoxycholic acid combine to change the bile of patients with gallstones from cholesterol-precipitating to cholesterol solubilizing, thus resulting in bile conducive to cholesterol stone dissolution. After ursodeoxycholic acid dosing is stopped, the concentration of the bile acid in bile falls exponentially, declining to about 5%-10% of its steadystate level in about 1 week.

Specific populations:

Nursing Mothers

It is not known whether ursodeoxycholic acid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Ursodeoxycholic acid is administered to a nursing mother.

Pediatric Use

The safety and effectiveness of Ursodeoxycholic acid in pediatric patients have not been established.

Geriatric Use

In worldwide clinical studies of Ursodeoxycholic acid, 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 differences in response in elderly and younger patients. However, small differences in efficacy and greater sensitivity of some elderly individuals taking Ursodeoxycholic acid cannot be ruled out. Therefore, it is recommended that dosing proceed with caution in this population.

INDICATIONS AND USAGE

- Ursodeoxycholic acid is indicated for patients for dissolution of small to medium sized radiolucent, noncalcified gallbladder stones < 20 mm in greatest diameter in whom elective cholecystectomy would be undertaken except for the presence of increased surgical risk due to systemic disease, advanced age, idiosyncratic reaction to general anesthesia, or for those patients who refuse surgery. Safety of use of Ursodeoxycholic acid beyond 24 months is not established.
- Ursodeoxycholic acid is indicated for the prevention of gallstone formation in obese patients experiencing rapid weight loss.

CONTRAINDICATIONS

- Ursodeoxycholic acid will not dissolve calcified cholesterol stones, radiopaque stones, or radiolucent bile pigment stones. Hence, patients with such stones are not candidates for Ursodeoxycholic acid therapy.
- Patients with compelling reasons for cholecystectomy including unremitting acute cholecystitis, cholangitis, biliary obstruction, gallstone pancreatitis, or biliary-gastrointestinal fistula are not candidates for Ursodeoxycholic acid therapy.
- Allergy to bile acids.

WARNINGS AND PRECAUTIONS

Liver Tests

Ursodeoxycholic acid therapy 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 ursodeoxycholic acid less efficiently and in smaller amounts than 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 Ursodeoxycholic acid therapy and, in fact, Ursodeoxycholic acid has been shown to decrease liver enzyme levels in liver disease. However, patients given Ursodeoxycholic acid should have SGOT (AST) and SGPT (ALT) measured at the initiation of therapy and thereafter as indicated by the particular clinical circumstances.

SPECIAL NOTE

Gallbladder stone dissolution with ursodeoxycholic acid treatment requires months of therapy. Complete dissolution does not occur in all patients and recurrence of stones within 5 years has been observed in up to 50% of patients who do dissolve their stones on bile acid therapy. Patients should be carefully selected for therapy with ursodeoxycholic acid, and alternative therapies should be considered.

Pregnancy & Lactation:

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits with ursodeoxycholic acid doses up to 200-fold the therapeutic dose and have revealed no evidence of impaired fertility or harm to the fetus at doses of 20- to 100-fold the human dose in rats and at 5-fold the human dose (highest dose tested) in rabbits. Studies employing 100- to 200- fold the human dose in rats have shown some reduction in fertility rate and litter size. There have been no adequate and well-controlled studies of the use of ursodeoxycholic acid in pregnant women, but inadvertent exposure of 4 women to therapeutic doses of the drug in the first trimester of pregnancy during the Ursodeoxycholic acid trials led to no evidence of effects on the fetus or newborn baby. Although it seems unlikely, the possibility that ursodeoxycholic acid can cause fetal harm cannot be ruled out; hence, the drug is not recommended for use during pregnancy.

Nursing Mothers

It is not known whether ursodeoxycholic acid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Ursodeoxycholic acid is administered to a nursing mother.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Ursodeoxycholic acid was tested in 2-year oral carcinogenicity studies in CD-1 mice and Sprague - Dawley rats at daily doses of 50, 250, and 1000 mg/kg/day. It was not tumorigenic in mice. In the rat study, it produced statistically significant dose-related increased incidences of pheochromo - cytomas of adrenal medulla in males (p=0.014, Peto trend test) and females (p=0.004, Peto trend test).

A 78-week rat study employing intrarectal instillation of lithocholic acid and tauro-deoxycholic acid, metabolites of ursodeoxycholic acid and chenodiol, has been conducted. These bile acids alone did not produce any tumors. A tumor-promoting effect of both metabolites was observed when they were co-administered with a carcinogenic agent. Results of epidemiologic studies suggest that bile acids might be involved in the pathogenesis of human colon cancer in patients who had undergone a cholecystectomy, but direct evidence is lacking. Ursodeoxycholic acid is not mutagenic in the Ames test. Dietary administration of lithocholic acid to chickens is reported to cause hepatic adenomatous hyperplasia.

ADVERSE REACTIONS:

The evaluation of undesirable effects is based on the following frequency data:
Very common (1/10)
Common (1/100 to < 1/10)
Uncommon (1/1,000 to < 1/100)
Rare (1/10,000 to < 1/1,000)
Very rare / Not known (< 1/10,000 / cannot be estimated from available data)

Gastrointestinal disorders :

In clinical trials, reports of pasty stools or diarrhoea during ursodeoxycholic acid therapy were common.

Very rarely, severe right upper abdominal pain has occurred during the treatment of primary biliary cirrhosis. Ursodeoxycholic acid may give rise to nausea and vomiting. The frequency of these effects are not known.

Hepatobiliary disorders :

During treatment with ursodeoxycholic acid, calcification of gallstones can occur in very rare cases making them unable to be dissolved by bile acid therapy and resulting in surgery for some patients. During therapy of the advanced stages of primary biliary cirrhosis, in very rare cases decompensation of hepatic cirrhosis has been observed, which partially regressed after the treatment was discontinued.

Skin and subcutaneaous disorders :

Very rarely, urticaria can occur.

Ursodeoxycholic acid may give rise to pruritus. The frequency of this effect is not known.

DRUG INTERACTIONS

Bile acid sequestering agents such as cholestyramine and colestipol may interfere with the action of Ursodeoxycholic acid by reducing its absorption. Aluminum-based antacids have been shown to adsorb bile acids in vitro and may be expected to interfere with Ursodeoxycholic acid 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 Ursodeoxycholic acid.

DOSAGE AND ADMINISTRATION

Gallstone Dissolution

The recommended dose for Ursodeoxycholic acid treatment of radiolucent gallbladder stones is 8-10 mg/kg/day given in 2 or 3 divided doses.

Ultrasound images of the gallbladder should be obtained at 6-month intervals for the first year of Ursodeoxycholic acid therapy to monitor gallstone response. If gallstones appear to have dissolved, Ursodeoxycholic acid therapy should be continued and dissolution confirmed on a repeat ultrasound examination within 1-3 months. Most patients who eventually achieve complete stone dissolution will show partial or complete dissolution at the first on-treatment reevaluation. If partial stone dissolution is not seen by 12 months of Ursodeoxycholic acid therapy, the likelihood of success is greatly reduced.

Gallstone Prevention

The recommended dosage of Ursodeoxycholic acid for gallstone prevention in patients undergoing rapid weight loss is 600 mg/day.

OVERDOSAGE

Neither accidental nor intentional overdosing with Ursodeoxycholic acid has been reported. Doses of Ursodeoxycholic acid in the range of 16-20 mg/kg/day have been tolerated for 6-37 months without symptoms by 7 patients. The LD50 for ursodeoxycholic acid in rats is over 5000 mg/kg given over 7-10 days and over 7500 mg/kg for mice. The most likely manifestation of severe overdose with Ursodeoxycholic acid would probably be diarrhea, which should be treated symptomatically.

EXPIRY DATE

Do not use later than the date of expiry. **STORAGE**

Store at a temperature not exceeding 30^{O}C, Protected from moisture.
Keep out of reach of children

PRESENTATION

URSETOR 600 is available in blister strips of 10 tablets

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Vill. Bhud & Makhnu Majra, Baddi-173 205,
Teh. Nalagarh, Dist. Solan (H.P.), INDIA.