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

Ursetor Plus

Ursodeoxycholic Acid and Silymarin Tablets

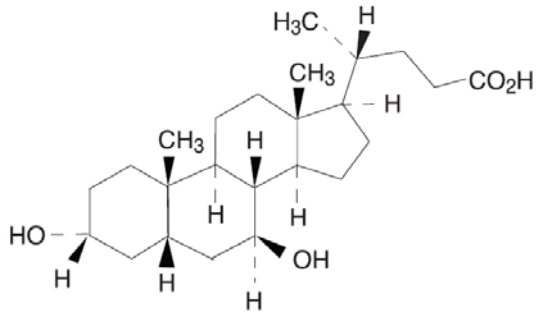
COMPOSITION

Each film coated tablets contains:
Ursodeoxycholic Acid I.P. 300 mg
Silymarin 140 mg
Colors: Red oxide of iron and Titanium Dioxide I.P.

DESCRIPTION

Ursodeoxycholic acid

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:



Silymarin

Silybum marianum contains silymarin, which is composed of the flavanolignans silybin, silydianin, and silychristine, with silybin being the most biologically active. Silymarin is found in highest concentrations in the fruit portion of the plant but is also found in the leaves and seeds. The seeds also contain betaine, trimethylglycine and essential fatty acids, which may contribute to silymarin's hepatoprotective and anti-inflammatory effects.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Ursodeoxycholic acid

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.

Silymarin

Mechanisms of Action

Silymarin's hepatoprotective effects are accomplished via several mechanisms including antioxidation, inhibition of lipid peroxidation, enhanced liver detoxification via inhibition of Phase I detoxification and enhanced glucuronidation, and protection of glutathione depletion. Studies have also shown silymarin exhibits several anti-inflammatory effects, including inhibition of leukotriene and prostaglandin synthesis, Kupffer cell inhibition, mast cell stabilization, and inhibition of neutrophil migration. In addition, silymarin has been shown to increase hepatocyte protein synthesis, thereby promoting hepatic tissue regeneration. Animal studies have also demonstrated silybin reduces the conversion of hepatic stellate cells into myofibroblasts, slowing or even reversing fibrosis.

Pharmacokinetics

Ursodeoxycholic acid

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-ketolithocholic 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.

Silymarin

Bioavailability

Silybin is the primary and most active component of the silymarin complex. All pharmacokinetic parameters of silymarin are referred to, and standardized as, silybin. Orally administered silymarin (silybin) is rapidly absorbed with a t_{max} (2-4 hours) and $t_{1/2}$ (6 hours). Only 20-50 percent of oral silymarin is absorbed from the gastrointestinal tract where it undergoes extensive enterohepatic circulation. Therefore, absorption of silymarin from the gastrointestinal tract is low, making bioavailability poor.

Tissue Distribution

Zhao and Agarwal performed a tissue distribution experiment in mice and concluded that silybin (50 mg/kg), both in free and conjugated form (e.g. glucuronide and sulfate conjugated forms), is quickly absorbed after oral administration and has a good tissue distribution profile in various tissues examined.

Metabolism

Silymarin (standardized as silybin) undergoes phase I and phase II biotransformation in the liver. It is metabolized by CYP450-2C8 in vitro into o-demethylated silybin (major) and mono- and dihydroxy- silybin (minor) metabolites. During phase II, multiple conjugation reactions have been observed that include the formation of silybin monoglucuronide, silybin diglucuronide, silybin monosulfate, and silybin diglucuronide sulfate.

Excretion

Silybin in humans and rats demonstrates rapid elimination of both free and conjugate forms. Wen et al, through pharmacokinetic analysis, discovered that silymarin flavonolignans were rapidly eliminated with short half-lives (1-3 and 3-8 hours for free and conjugated forms, respectively). Studies in humans and rodents suggest that biliary excretion of glucuronide and sulfate conjugates is the major route for silymarin's elimination.

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.

Silymarin specially indicated in Amanita Mushroom Poisoning, Hepatitis, Alcoholic Liver Disease and Cirrhosis, Hypercholesterolemia and Psoriasis.

Combination especially indicated in patients of gall bladder stone having predisposition or co-existing hepatic damage.

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 (300 mg b.i.d.).

All clinical trials of milk thistle conducted in the past have demonstrated safety up to 1,500 mg/day. The typical oral adult dose of silymarin is 240-800 mg/day in two or three divided doses.

Combination can be given as one tablet 2-3 times a day as per physician advice

CONTRAINDICATIONS

Hypersensitivity to Ursodeoxycholic acid and Silymarin or any ingredient of the Ursetor Plus.

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.

WARNINGS AND PRECAUTIONS

Ursodeoxycholic acid

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.

Silymarin
In theory, Silymarin may lower blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs that affect blood sugar. Serum glucose levels may need to be monitored.

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.

SPECIFIC POPULATIONS:
Ursodeoxycholic acid
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.

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.

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.

Silymarin
Pregnancy & Lactation
There are currently no adequate and well-controlled trials with Silymarin in pregnant and lactating women. Silymarin should be used only when clearly needed.

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.

DRUG INTERACTIONS
Ursodeoxycholic acid
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.

Silymarin
While no drug interactions could be found with Silymarin. The influence that Silymarin has on liver function should be taken into account when pharmaceutical drugs are given concomitantly.

ADVERSE REACTIONS:

Ursodeoxycholic acid

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 diarrhea 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 is 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.

Silymarin

Silymarin is reported to have a very good safety profile. Both animal and human studies showed that silymarin is non-toxic even when given at high doses (>1500 mg/day). However, a laxative effect is noted at these doses, which may be due to increased bile secretion and bile flow.

Other commonly noted adverse effects are: bloating, dyspepsia, nausea and irregular stools. Silymarin may also cause an allergic reaction in some individuals, particularly those with known allergies to plants in the *Asteraceae* family (thistles, daisies, artichokes). No other widely reported side effects are known when Silymarin is taken in proper therapeutic dosages.

OVERDOSAGE

Ursodeoxycholic acid

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
Do not use later than the date of expiry.

STORAGE
Store protected from light & moisture, at a temperature not exceeding 30°C.

Keep out of reach of children

PRESENTATION
Ursetor Plus available in Alu-Alu Blister pack of 10' s Tablets.

MARKETED BY

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