Ursodiol Tablets, USP Initial U.S. Approval: 1997

1 INDICATIONS AND USAGE

Ursodiol tablets, USP are bile acids indicated for the treatment of patients with primary biliary cirrhosis (PBC).

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

The recommended adult dosage for ursodiol is 13 to 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.

2.2 Scoring the 500 mg Tablet

The ursodiol 500 mg scored tablet can be broken in halves to provide recommended dosage.

2.2.1 Instructions for Breaking the Tablet

To break ursodiol 500 mg scored tablet easily, place the tablet on a flat surface with the scored section up. Press gently on the scored section to separate the halves. To break the halves easily, place each half on a flat surface and press gently to separate.

3 DOSAGE FORMS AND STRENGTHS

• Ursodiol 250 mg tablet (3)
• Ursodiol 500 mg scored tablet (3)

4 CONTRAINDICATIONS

Known hypersensitivity or intolerance to ursodiol or any of the components of the formulation.

5 WARNINGS AND PRECAUTIONS

Patients with variceal bleeding, hepatic encephalopathy, ascites or in need of an urgent liver transplant, should receive appropriate specific treatment.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Elevated creatinine (0.8%)
Diarrhea (0.6%)
Thrombocytopenia (1.3%)
Elevated bilirubin (1.3%)
Leukopenia (2.5%)
Peptic ulcer (1.3%)
Dyspepsia (1.3%)
Elevated alkaline phosphatase (1.3%)}

6.2 Postmarketing Experience

There have been no reports of accidental or intentional overdose with ursodiol. Single oral doses of ursodiol at 10 g/kg in mice and dogs, and 55 g/kg in rats were not lethal. A single oral dose of ursodiol at 1.5 g/kg was lethal in hamsters. Symptoms of acute toxicity were salivation and vomiting in dogs, and ataxia, dyspnea, loss of coordination and diarrhea in hamsters.

11 DESCRIPTION

Ursodiol tablets, USP 250 mg are available as a film-coated tablet for oral administration. Ursodiol tablets, USP 500 mg are a scored film-coated tablet for oral administration.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

13.2 Pregnancy

Nursing Mothers

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

14.2 Efficacy of ursodiol administered at 14 mg/kg/day as a once daily dose to PBC patients

90% of ursodiol tablets, USP 500 mg administered in twice a day versus four times a day divided dosing schedules to PBC patients

15.1 Appropriate Treatments

In a randomized, cross-over study in sixty PBC patients, seven patients (11.6%) reported nine adverse reactions monitored with the use of ursodiol during worldwide postmarketing and clinical experience (21% are) in an alphabetical order: abdominal discomfort, abdominal pain, dyspepsia, diarrhea, nausea, pruritus, and rash.

15.2 Drug Interactions

• Bile Acid Sequestering Agents: May interfere with the action of ursodiol by reducing its absorption
• Aluminum-based Antacids: May interfere with the action of ursodiol by reducing its absorption
• Drugs that alter the metabolism of lipids or induce cholestasis may interfere with the action of ursodiol

17.2 Drug Interactions

• Sections or subsections omitted from the full prescribing information are not listed.

17.3 Drugs Affecting Lipid Metabolism

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 ursodiol.

17.4 Use in Specific Populations

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Pregnancy

8.1 Pregnancy

8.2 Lactation

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8.4 Pediatric Use

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

10 OVERDOSAGE

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12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Ursodiol, a naturally occurring hydrophilic bile acid, derived from cholesterol, is present as a minor fraction of the total biliary acids in humans (about 5%). Following oral administration, the majority of unabsorbed ursodiol is excreted by passive diffusion and its absorption is incomplete. Once absorbed, ursodiol 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, ursodiol is conjugated with glycine or taurine, then secreted into bile. These conjugates of ursodiol 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 ursodiol that can be reabsorbed and reexcreted in the liver. Nonabsorbed ursodiol passes into the colon where it is mostly 7-dehydroxylated to lithocholic acid. Some ursodiol is epimerized to chenodiol (CDCA) via a 7-oxo intermediate. Chenodiol also undergoes 7-dehydroxylation to form lithocholic acid. These metabolites are poorly soluble and excreted in the feces. A small portion of lithocholic acid is reabsorbed, conjugated in the liver with glycine, or sulfated and excreted in the urine. The resulting sulfated lithocholic acid conjugates are excreted in bile and then lost in feces. In healthy subjects, at least 70% of unabsorbed (unconjugated) ursodiol is bound to plasma proteins. Some ursodiol is secreted into the urine by healthy subjects or 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. Ursodiol is excreted primarily in the feces. Treatment, urinary excretion increases, but remains less than 1% except in severe cholestatic liver disease.

During chronic administration of ursodiol, it becomes a major biliary and plasma bile acid. At a chronic dose of 130 to 150 mg/kg/day, ursodiol constitutes 30 to 50% of biliary and plasma bile acids. 13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenicity, Mutagenicity and Impairment of Fertility
In two 24-month oral carcinogenicity studies in mice, ursodiol at doses up to 1,000 mg/kg/day (3,000 mg/m²/day) was not tumorigenic. Based on body surface area, for a 50 kg person of average height (1.44 m²), an average adult male of average build represents 5.4 times the recommended maximum adult dose of 5 mg/kg/day (555 mg/m²/day).

In a two-year oral carcinogenicity study in Fischer 344 rats, ursodiol at doses up to 300 mg/kg/day (1,800 mg/m²/day, 3.2 times the recommended maximum human dose based on body surface area) was not tumorigenic.

In a life-span (126 to 138 weeks) oral carcinogenicity study, Sprague-Dawley rats were treated with doses of 10 to 300 mg/kg/day. 0.4 to 3.2 times the recommended maximum human dose based on body surface area. Ursodiol produced a significantly (p<0.5, Fisher’s exact test) increased incidence of pheochromocytomas of the adrenal medulla in females of the highest dose group.

In 103-week oral carcinogenicity studies of lithocholic acid, a metabolite of ursodiol, doses up to 250 mg/kg/day in mice and 500 mg/kg/day in rats did not produce any tumors. In a 78-week rat study, intratracheal instillation of lithocholic acid (1 mg/kg) for 13 months did not produce colorectal tumors.

A tumor-promoting effect was observed when it was administered after a single intrarectal instillation of lithocholic acid (1 mg/kg/day) for 13 months did not produce colorectal tumors. A tumor-promoting effect was observed when it was administered after a single intrarectal instillation of lithocholic acid (1 mg/kg/day) for 13 months did not produce colorectal tumors.

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Ursodiol was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y TK+/-) forward mutation test, the human lymphocyte sister chromatid exchange test, the mouse spermatogonia chromosome aberration test, the Chinese hamster micronucleus test and the Chinese hamster bone marrow cell chromosome aberration test. Ursodiol at oral doses of up to 2.790 mg/kg/day (16,200 mg/m²/day, 29 times the recommended maximum human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES
14.1 Efficacy of ursodeoxycholic acid administered at 13 to 15 mg/kg/day in 3 or 4 divided doses to PBC patients
A U.S.- multicenter, randomized, double-blind, placebo-controlled study was conducted to evaluate the efficacy of ursodeoxycholic acid at a dose of 13 to 15 mg/kg/day, administered in 3 or 4 divided doses in 180 patients with PBC (78% received four times a day dosing). Upon completion of the double-blind portion, all patients entered an open-label active treatment extension phase. Treatment failure, the main efficacy and point measured during this study, was defined as death, need for liver transplantation, histologic progression by two stages or to cirrhosis, development of various, ascites or encephalopathy, marked worsening of fatigue or pruritus, inability to tolerate the drug, doubling of serum bilirubin and voluntary withdrawal. After two years of double-blind treatment, the incidence of treatment failure was significantly (p<0.01) reduced in the ursodiol 250 mg group (20 of 86 (23%) as compared to the placebo group (40 of 86 (47%) Of the patients in the ursodiol 250 mg group and n=106 for the placebo group), transaminases (-50.3% for the ursodiol 250 mg group vs. -40.5% for the placebo group); alkaline phosphatase (-47.61% for the ursodiol 250 mg group vs. -13.1% for the placebo group), in favor of ursodiol, was demonstrated in the following: reduction in the proportion of patients exhibiting a more than 50% increase in serum bilirubin; median percent decrease in bilirubin (-17.1% for the ursodiol 250 mg group vs. +20.0% for the placebo group), transaminases (-30.5% for the ursodiol 250 mg group vs. -5.11% for the placebo group); alkaline phosphatase (-47.61% for the ursodiol 250 mg group vs. -6.65% for the placebo group); incidence of treatment failure; and time to treatment failure. The definition of treatment failure included discontinuing the study for any reason; a total serum bilirubin level greater than or equal to 1.5 mg/dl or increasing to a level equal to or greater than two times the baseline level; and the development of ascites or encephalopathy. Evaluation of patients at 4 years or longer was inadequate due to the high drop out rate (n=10 for placebo group) vs. n=15 from the placebo group) and small number of patients. Therefore, death, need for liver transplantation, histological progression by two stages or to cirrhosis, development of various, ascites or encephalopathy, marked worsening of fatigue or pruritus, inability to tolerate the drug, doubling of serum bilirubin and voluntary withdrawal were not assessed.

14.2 Efficacy of ursodiol administered at 14 mg/kg/day as a once daily dose to PBC patients
A second study conducted in Canada randomized 222 PBC patients to ursodiol, 14 mg/kg/day or placebo, administered as a once daily dose in a double-blind manner during a two-year period. All patients were reassessed every six months. As compared to the placebo group, treatment with ursodiol 250 mg resulted in a significant improvement in the following serum hepatic biochemistries when compared to baseline: total bilirubin, SGOT, alkaline phosphatase and GGT.

14.3 Efficacy of ursodiol 250 mg administered in twice a day versus four times a day divided dosing schedules to PBC patients
A randomized, two-year crossover study in fifty PBC patients compared the efficacy of ursodiol 250 mg in twice a day versus four times a day divided dosing schedules in 50 patients for 6 months in each crossover period. Mean percent changes from baseline in liver test results and Mayo risk score (mRS) and serum enrichment with UDCA (n=34) were not statistically significant with any dosage at any time interval. This study demonstrated that UDCA (13 to 15 mg/kg/day) given twice a day is equally effective to UDCA given four times a day. In addition, ursodiol 250 mg was given as a single versus three times a day dosing schedules in 10 patients. Due to the small number of patients in this arm of the study, it was not possible to conduct statistical comparisons between these regimens.

16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 Ursodiol Tablet, USP 250 mg
The 250 mg dosage form is a white to off-white, modified capsule shaped, film-coated tablet, imprinted with “P” and “413” on one side and plain on the other side.

16.2 Ursodiol Tablet, USP 500 mg
The 500 mg dosage form is a white to off-white, modified capsule shaped, film-coated tablet, imprinted with “P” and “413” on one side and plain on the other side.

17.2 Drug Interactions
Patients should be informed that adsorption of ursodiol may be reduced if they are taking bile acid sequestrating agents, such as cholestyramine and colestipol, aluminum-based antacids, or drugs known to alter the metabolism of cholesterol. [see Drug Interactions (7)].

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