

Clinical Results

Gallstone Dissolution

On the basis of clinical trial results in a total of 868 patients with radiolucent gallstones treated in 8 studies (three in the U.S. involving 282 patients, one in the U.K. involving 130 patients, and four in Italy involving 456 patients) for periods ranging from 6 to 78 months with ursodiol doses ranging from about 5-20 mg/kg/day, an ursodiol dose of about 8-10 mg/kg/day appeared to be the best dose. With an ursodiol dose of about 10 mg/kg/day, complete stone dissolution can be anticipated in about 30% of unselected patients with uncalcified gallstones < 20 mm in maximal diameter treated for up to 2 years. Patients with calcified gallstones prior to treatment, or patients who develop stone calcification or gallbladder non-visualization on treatment, and patients with stones > 20 mm in maximal diameter rarely dissolve their stones. The chance of gallstone dissolution is increased up to 50% in patients with floating or floatable stones (i.e., those with high cholesterol content), and is inversely related to stone size for those < 20 mm in maximal diameter. Complete dissolution was observed in 81% of patients with stones up to 5 mm in diameter. Age, sex, weight, degree of obesity, and serum cholesterol level are not related to the chance of stone dissolution with ursodiol.

A non-visualizing gallbladder by oral cholecystogram prior to the initiation of therapy is not a contraindication to ursodiol therapy (the group of patients with non-visualizing gallbladders in the ursodiol studies had complete stone dissolution rates similar to the group of patients with visualizing gallbladders). However, gallbladder non-visualization developing during ursodiol treatment predicts failure of complete stone dissolution, and in such cases, therapy should be discontinued.

Partial stone dissolution occurring within 6 months of beginning therapy with ursodiol appears to be associated with a > 70% chance of eventual complete stone dissolution with further treatment; partial dissolution observed within 1 year of starting therapy indicates a 40% probability of complete dissolution.

Stone recurrence after dissolution with ursodiol therapy was seen within 2 years in 8/27 (30%) of patients in the U.K. studies. Of 16 patients in the U.K. study whose stones had previously dissolved on Chenodiol but later recurred, 11 had complete dissolution on ursodiol. Stone recurrence has been observed in up to 50% of patients within 5 years of complete stone dissolution on ursodiol therapy. Serial ultrasonographic examinations should be obtained to monitor for recurrence of stones, bearing in mind that radiolucency of the stones should be established before another course of ursodiol is instituted. A prophylactic dose of ursodiol has not been established.

Gallstone Prevention

Two placebo-controlled, multicenter, double-blind, randomized, parallel group trials in a total of 1,316 obese patients were undertaken to evaluate ursodiol in the prevention of gallstone formation in obese patients undergoing rapid weight loss. The first trial consisted of 1,004 obese patients with a body mass index (BMI) ≥ 38 who underwent weight loss induced by means of a very low calorie diet for a period of 16 weeks. An intent-to-treat analysis of this trial showed that gallstone formation occurred in 23% of the placebo group, while those patients on 300, 600, or 1200 mg/day of ursodiol experienced a 6%, 3%, and 2% incidence of gallstone formation, respectively. The mean weight loss for this 16-week trial was 47 lbs. for the placebo group, and 47, 48, and 50 lbs. for the 300, 600, and 1200 mg/day ursodiol groups, respectively.

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 pheochromocytomas 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 ursodiol 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. Ursodiol is not mutagenic in the Ames test. Dietary administration of lithocholic acid to chickens is reported to cause hepatic adenomatous hyperplasia.

Pregnancy

Reproduction studies have been performed in rats and rabbits with ursodiol 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 ursodiol in pregnant women, but inadvertent exposure of 4 women to therapeutic doses of the drug in the first trimester of pregnancy during the ursodiol trials led to no evidence of effects on the fetus or newborn baby. Although it seems unlikely, the possibility that ursodiol 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 ursodiol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ursodiol is administered to a nursing mother.

Pediatric Use

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

Geriatric Use

In worldwide clinical studies of ursodiol, 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 ursodiol cannot be ruled out. Therefore, it is recommended that dosing proceed with caution in this population.

ADVERSE REACTIONS

To report SUSPECTED ADVERSE REACTIONS, contact Intra-Sana Laboratories at 1-702-980-8963 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

The nature and frequency of adverse experiences were similar across all groups.

The following tables provide comprehensive listings of the adverse experiences reported that occurred with a 5% incidence level:

GALLSTONE DISSOLUTION				
	<u>Ursodiol</u> 8-10 mg/kg/day (N=155)		<u>Placebo</u> (N=159)	
	N	(%)	N	(%)
<u>Body as a Whole</u>				
Allergy	8	(5.2)	7	(4.4)
Chest Pain	5	(3.2)	10	(6.3)
Fatigue	7	(4.5)	8	(5.0)
Infection Viral	30	(19.4)	41	(25.8)
<u>Digestive System</u>				
Abdominal Pain	67	(43.2)	70	(44.0)
Cholecystitis	8	(5.2)	7	(4.4)
Constipation	15	(9.7)	14	(8.8)
Diarrhea	42	(27.1)	34	(21.4)
Dyspepsia	26	(16.8)	18	(11.3)
Flatulence	12	(7.7)	12	(7.5)
Gastrointestinal Disorder	6	(3.9)	8	(5.0)
Nausea	22	(14.2)	27	(17.0)
Vomiting	15	(9.7)	11	(6.9)
<u>Musculoskeletal System</u>				
Arthralgia	12	(7.7)	24	(15.1)
Arthritis	9	(5.8)	4	(2.5)
Back Pain	11	(7.1)	18	(11.3)
Myalgia	9	(5.8)	9	(5.7)
<u>Nervous System</u>				
Headache	28	(18.1)	34	(21.4)
Insomnia	3	(1.9)	8	(5.0)
<u>Respiratory System</u>				
Bronchitis	10	(6.5)	6	(3.8)
Coughing	11	(7.1)	7	(4.4)
Pharyngitis	13	(8.4)	5	(3.1)
Rhinitis	8	(5.2)	11	(6.9)
Sinusitis	17	(11.0)	18	(11.3)
Upper Respiratory Tract Infection	24	(15.5)	21	(13.2)

Urogenital System

Urinary Tract Infection	10	(6.5)	7	(4.4)
-------------------------	----	-------	---	-------

GALLSTONE PREVENTION

	<u>Ursodiol</u> 600 mg (N=322)		<u>Placebo</u> (N=325)	
	N	(%)	N	(%)
<u>Body as a Whole</u>				
Fatigue	25	(7.8)	33	(10.2)
Infection Viral	29	(9.0)	29	(8.9)
Influenza-like Symptoms	21	(6.5)	19	(5.8)
<u>Digestive System</u>				
Abdominal Pain	20	(6.2)	39	(12.0)
Constipation	85	(26.4)	72	(22.2)
Diarrhea	81	(25.2)	68	(20.9)
Flatulence	15	(4.7)	24	(7.4)
Nausea	56	(17.4)	43	(13.2)
Vomiting	44	(13.7)	44	(13.5)
<u>Musculoskeletal System</u>				
Back Pain	38	(11.8)	21	(6.5)
Musculoskeletal Pain	19	(5.9)	15	(4.6)
<u>Nervous System</u>				
Dizziness	53	(16.5)	42	(12.9)
Headache	80	(24.8)	78	(24.0)
<u>Respiratory System</u>				
Pharyngitis	10	(3.1)	19	(5.8)
Sinusitis	17	(5.3)	18	(5.5)
Upper Respiratory Tract Infection	40	(12.4)	35	(10.8)
<u>Skin and Appendages</u>				
Alopecia	17	(5.3)	8	(2.5)
<u>Urogenital System</u>				
Dysmenorrhea	18	(5.6)	19	(5.8)

OVERDOSAGE

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

