

Bile Acid Salts Review

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Bile Acid Salts Review

FDA-Approved Indications

Drug	Manufacturer	Indications
ursodiol (URSO 250 [®]) ¹	generic, Axcan	Treatment of patients with primary biliary cirrhosis
ursodiol (URSO Forte [®]) ²	generic, Axcan	Treatment of patients with primary biliary cirrhosis
ursodiol USP (Actigall [®]) ³	generic, Watson	Dissolve gallstones in patients with radiolucent, noncalcified gallbladder stones < 20 mm in greatest diameter in whom elective cholecystectomy would be undertaken except for the presence of increased surgical risk Prevent gallstone formation in obese patients experiencing rapid weight loss

*A new formulation of chenodiol (Chenodal[™]) has been approved but is not yet available nor is its product information available.

Overview

Gallstones are crystallized pieces of bile found in the gall bladder. In general, either cholesterol or bilirubin precipitates out of solution to form stones, but not both. In the United States, almost 80 percent of patients with gallstones have cholesterol stones.⁴ The size of a gallstone ranges from microscopic to approximately one inch, and the gallbladder may contain anywhere from one stone to hundreds.⁵ Gallstone diseases affect 10 to 15 percent of the U.S. population, and close to 1 million new cases are diagnosed each year.⁶ Gallstone blockage of the bile duct results in pain and inflammation, and these may lead to fever, jaundice, and infections. If a gallstone passes down the bile duct, it could reach the pancreas and cause inflammation and blockage of the bile duct drainage.⁷

Treatment is usually unnecessary if gallstones are not causing symptoms; it is estimated that one-quarter of the affected population requires treatment.⁸ If treatment is warranted, cholecystectomy, the surgical removal of the gallbladder, is the most widely used therapy when symptoms arise.⁹ An alternative to cholecystectomy is dissolution of the stones by chemicals – ursodiol or chenodiol. Ursodiol is the 7-beta epimer of chenodeoxycholic acid (chenodiol). Large amounts of ursodiol have been recovered in the bile of patients treated with chenodiol, indicating litholytic activity.¹⁰ These oral medications thin the bile and allow stones to dissolve. However, use of drugs is limited to small stones predominantly composed of cholesterol for rapid and complete dissolution.¹¹

According to the 2009 American Association for the Study of Liver Diseases (AASLD) Guidelines, ursodiol plays a key role in the treatment of primary biliary cirrhosis (PBC) since it is the only FDA-approved treatment for this condition.¹² Dosing plays a significant role in that the dose of 13 to 15 mg/kg/day demonstrated superiority in one study over other lower and higher dosages in terms of biochemical response as well as cost.

Pharmacology

Ursodiol achieves bile desaturation by decreasing secretion of cholesterol into the bile. Ursodiol reduces cholesterol absorption and suppresses liver cholesterol synthesis, but does not inhibit bile acid synthesis.¹³ This alters bile composition from supersaturated to unsaturated. Ursodiol also promotes the formation of liquid cholesterol crystal complexes which enhance removal of the cholesterol from the gallbladder into the intestine to be expelled.¹⁴

Pharmacokinetics¹⁵

Drug	Bioavailability (%)	T _{max} (hr)	Metabolism	Excretion
ursodiol (URSO 250)	90	100	Enterohepatic recycling: two inactive metabolites	Primarily feces
ursodiol (URSO Forte)	90	100	Enterohepatic recycling: two inactive metabolites	Primarily feces
ursodiol USP (Actigall)	90	100	Enterohepatic recycling: two inactive metabolites	Primarily feces

Contraindications/Warnings^{16,17,18}

All three ursodiol products are contraindicated in patients with a known hypersensitivity to a bile acid. Actigall[®] shall not be used in patients with calcified cholesterol stones, radio-opaque stones, or radiolucent bile pigment stones. In addition, patients with compelling reasons for cholecystectomy including unremitting acute cholecystitis, cholangitis, biliary obstruction, gallstone pancreatitis, or biliary-gastrointestinal fistula are not candidates for Actigall[®] therapy.

Drug Interactions^{19,20,21}

Bile acid-sequestering agents such as cholestyramine and colestipol may interfere with the action of ursodiol by reducing its absorption. For patients requiring bile acid sequestrants, ursodiol should be given two to four hours before or after their ingestion.

Aluminum-based antacids have been shown to adsorb bile acids *in vitro* and may be expected to interfere with ursodiol in the same manner as the bile acid-sequestering agents.

Estrogens, oral contraceptives, and clofibrate (and potentially other lipid-lowering drugs) increase hepatic cholesterol secretion and encourage cholesterol gallstone formation. Hence, they may counteract the effectiveness of ursodiol.

Adverse Effects for Gallstone Dissolution

Drug	Arthritis	Dyspepsia	Pharyngitis	Diarrhea	Vomiting
ursodiol USP (Actigall) ²² 8-10mg/kg/day n=314	5.8 (2.5)	16.8 (11.3)	8.4 (3.1)	27.1 (21.4)	9.7 (6.9)

Adverse Effects for Gallstone Prevention

Drug	Back Pain	Nausea	Constipation	Diarrhea	Dizziness
ursodiol USP (Actigall) ²³ 600mg/day n=647	11.8 (6.5)	17.4 (13.2)	26.4 (22.2)	25.2 (20.9)	16.5 (12.9)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses.

From the adverse effects observed in two placebo-controlled clinical trials using URSO 250® 13-15 mg/kg/day and a combined population of 402 patients, the treatment groups had one reported case of each of the following: diarrhea, elevated creatinine, elevated blood glucose, and peptic ulcer.²⁴ In addition, there were two reported cases of leukopenia and skin rash.²⁵ These adverse events were not observed in the placebo groups.

Special Populations^{26,27,28}Pediatrics

Safety and efficacy of these products have not been established in pediatric patients. Their use is not recommended in children.

Pregnancy

All agents in this category are Pregnancy Category B.

Geriatrics

There are no specific clinical studies that have been performed in patients ages 65 and older. Therapy should be initiated with the lowest recommended dose and include routine monitoring.

Hepatic Impairment

Caution should be used with all agents in patients with chronic liver disease. All patients should have liver function testing (e.g. SGOT (AST) and SGPT (ALT)) at the initiation of therapy and routinely thereafter.

Dosages

Drug	Indication	Dosage	Availability
ursodiol (URSO 250) ²⁹	Treatment of primary biliary cirrhosis	13-15 mg/kg/day in two to four divided doses with food	250 mg tablets
ursodiol (URSO Forte) ³⁰	Treatment of primary biliary cirrhosis	13-15 mg/kg/day in two to four divided doses with food. Scored tablets can be broken in halves to provide recommended dosage	500 mg scored tablets
ursodiol USP (Actigall) ³¹	Gallstone dissolution	8-10 mg/kg/day in two to three divided doses	300 mg capsules
	Prevention of gallstone formation in patients undergoing rapid weight loss	600 mg/day	

Clinical TrialsSearch Strategy

Articles were identified through searches performed on PubMed, ClinicalTrials.gov, and review of information sent by manufacturers. Search strategy included the use of ursodiol, ursodeoxycholic acid (UDCA), and bile acid salts. Randomized controlled comparative trials for specific liver diseases are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Due to the paucity of data in the literature and the unavailability of comparative clinical trials related to ursodiol, no further information is available at this time.

Summary

Ursodiol, a bile acid, is naturally produced by the body and stored in the gall bladder. It works by decreasing the production of cholesterol and by dissolving the cholesterol in bile so that it cannot form stones. Ursodiol is the drug of choice for treating primary biliary cirrhosis and dissolving cholesterol gallstones. Currently, there are three ursodiol formulations approved in the United States. There are no significant clinical differences among these products.

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