# Bile Acid Salts Summary

**December 2016**

## FDA-APPROVED INDICATIONS AND DOSAGES

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Indication(s)</th>
<th>Dosage</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>chenodiol (Chenodal®)</td>
<td>Manchester Pharm</td>
<td>Dissolve gallstones in patients with radiolucent stones in well-opacifying gallbladders, in whom selective surgery would be undertaken except for the presence of increased surgical risk due to systemic disease or age</td>
<td>13 to 16 mg/kg/day in 2 divided doses, morning, and night, starting with 250 mg twice daily for the first 2 weeks and increasing by 250 mg daily each week thereafter until the recommended or maximum tolerated dose is reached. Dosages less than 10 mg/kg/day are not recommended as they are usually ineffective and may increase the risk of cholecystectomy.</td>
<td>250 mg tablets</td>
</tr>
<tr>
<td>cholic acid (Cholbam®)</td>
<td>Asklepios</td>
<td>Treatment of bile acid synthesis disorders due to single enzyme defects (SEDs); Adjunctive treatment of peroxisomal disorders (PDs) including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat soluble vitamin absorption. Limitation of use: The safety and effectiveness of cholic acid on extrahepatic manifestations of bile acid synthesis disorders due to SEDs or PDs including Zellweger spectrum disorders have not been established.</td>
<td>10 to 15 mg/kg once daily or in 2 divided doses with food, in pediatric patients and adults (detailed weight-based dosing in number of capsules/day provided in prescribing information). A 10% increase in the recommended dosage may be needed in patients with newly diagnosed, or a family history of, familial hypertriglyceridemia due to poor absorption; the recommended dosage in patients with concomitant familial hypertriglyceridemia is 11 to 17 mg/kg once daily or in 2 divided doses with food and is adjusted based on clinical response. Should not be crushed or chewed; capsules may be opened with the contents mixed in infant formula, expressed breast milk, or soft food if patient is unable to swallow the capsule(s).</td>
<td>50 mg, 250 mg capsules</td>
</tr>
</tbody>
</table>
### FDA-Approved Indications and Dosages (continued)

<table>
<thead>
<tr>
<th>Drug</th>
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</thead>
<tbody>
<tr>
<td>obeticholic acid (Ocaliva®)</td>
<td>Intercept</td>
<td>Treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA (defined as a trial of at least 1 year), or as a single therapy in adults unable to tolerate UDCA. This indication is approved under accelerated approval based on a reduction in alkaline phosphatase (ALP); an improvement in survival or disease-related symptoms has not been established; continued approval for this indication may be contingent upon results of confirmatory trials.</td>
<td>5 mg taken orally once daily with or without food; after 3 months, if an inadequate reduction in ALP and/or total bilirubin has not been achieved, and therapy is tolerated, the dose can be increased to 10 mg once daily (maximum dose), if tolerated. Detailed dosing recommendations are provided in the prescribing information for management of select intolerable adverse effects and use in patients with moderate to severe hepatic impairment.</td>
<td>5 mg, 10 mg tablets</td>
</tr>
<tr>
<td>ursodiol (URSO 250®)</td>
<td>generic, Aptalis</td>
<td>Treatment of patients with primary biliary cirrhosis</td>
<td>13 to 15 mg/kg/day in 2 to 4 divided doses with food</td>
<td>250 mg tablets</td>
</tr>
<tr>
<td>ursodiol (URSO Forte®)</td>
<td>generic, Aptalis</td>
<td>Treatment of patients with primary biliary cirrhosis</td>
<td>13 to 15 mg/kg/day in 2 to 4 divided doses with food</td>
<td>500 mg tablets</td>
</tr>
<tr>
<td>ursodiol USP (Actigall®)</td>
<td>generic, Actavis</td>
<td>Dissolve gallstones in patients with radiolucent, noncalcified gallbladder stones &lt; 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.</td>
<td>Gallstone dissolution: 8 to 10 mg/kg/day in 2 to 3 divided doses Prevent gallstone formation in obese patients experiencing rapid weight loss: 300 mg twice daily</td>
<td>300 mg capsules</td>
</tr>
</tbody>
</table>

*Cholic acid and obeticholic acid are available through select specialty pharmacies.*
**OVERVIEW**

**Gallstones**

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 U.S., almost 80% of patients with gallstones have cholesterol stones. The size of a gallstone ranges from microscopic to approximately 1 inch, and the gallbladder may contain anywhere from 1 stone to hundreds. Gallstone diseases affect 10% to 15% of the U.S. population, and close to 1 million new cases are diagnosed each year. Gallstone blockages of the cystic duct result in pain and inflammation, and these may lead to fever, jaundice, and infections. If a gallstone passes down the main bile duct, it could reach the pancreas and cause inflammation and blockage of the bile duct drainage.

**Primary Biliary Cholangitis**

Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is a rare, chronic autoimmune disease characterized by chronic cholestasis and progressive impaired bile acid secretion from the liver. PBC is typically diagnosed between the ages of 40 and 60. It affects more women than men and is the second leading cause of liver transplant in women in the U.S. A worse prognosis is generally seen in men and in those with younger age at onset (diagnosed before 50 years of age). Over 60% of the newly diagnosed cases are asymptomatic and most patients become symptomatic within 10 years. If left untreated, PBC typically progresses to hepatic fibrosis, cirrhosis, hepatic decompensation, and death unless a liver transplant is performed. Like other chronic liver diseases, without treatment, the average natural disease course is approximately 20 years from onset to death. Hepatocytes damaged by accumulation of bile acid release alkaline phosphatase (ALP) resulting in elevated serum levels. Increased bilirubin levels are seen with advanced disease. Liver biopsy is not required for diagnosis according to the American Association for the Study of Liver Diseases (AASLD).

Ursodeoxycholic acid (UDCA), also known as ursodiol, replaces and displaces toxic endogenous bile acids that accumulate with PBC, is cytoprotective of liver and bile duct epithelial cells, has immunomodulatory effects, and stimulates bile secretion. Activation of farnesoid X receptor (FXR), found in the nucleus of cells primarily in the liver and intestine, regulates bile acid homeostasis enterohepatically, as well as inflammation and fibrosis in response to liver injury. Obeticholic acid (Ocaliva) acts by binding to FXR and activates the signaling cascade, resulting in increased bile flow from the liver and suppression of bile acid production in the liver, thus reducing the exposure of the liver to toxic levels of bile acids.

**Peroxisomal disorders (PDs) and Bile Acid Synthesis Disorders Due to Single Enzyme Defects (SEDs)**

Peroxisomes catalyze a variety of metabolic functions in cellular metabolism. Various PDs are inborn errors resulting in impaired metabolism and often manifesting as neurologic dysfunction. These disorders can result from deficiency in a SED or be generalized biogenesis disorders, such as Zellweger syndrome. Zellweger syndrome (cerebrohepatorenal syndrome) is an autosomal recessive disorder that affects bile acid synthesis by disrupting peroxisomal biogenesis along with other peroxisomal activities. As the final steps in bile acid synthesis occur in the peroxisomes, Zellweger syndrome is the most severe peroxisome biogenesis disorder. Patients with Zellweger syndrome may present with craniofacial abnormalities, neurologic complications, polycystic kidney development, ophthalmic abnormalities,
bone abnormalities, and chronic liver disease. Zellweger syndrome is usually fatal in the first 2 years of life with treatment being largely supportive and palliative.

**SPECIAL USAGE CONSIDERATIONS**

**Contraindications/Warnings**

Caution should be used with all agents in patients with chronic liver disease.

Chenodiol (Chenodal) contraindications include biliary tract disease including bile ductal abnormalities such as intrahepatic cholestasis, primary biliary cirrhosis, or sclerosing cholangitis, in patients whose gallbladder is confirmed as non-visualizing after 2 consecutive single doses of dye, and in patients with calcified radiopaque stones. Patients with gallstone complications or gallbladder disease necessitating surgery due to unremitting acute cholecystitis, cholangitis, biliary obstruction, gallstone pancreatitis, or biliary-gastrointestinal (GI) fistula are not candidates for chenodiol therapy. During chenodiol therapy, oral cholecystograms or ultrasonograms are recommended at 6 to 9 month intervals to monitor response. Complete dissolution of stones should be confirmed by a repeat test after 1 to 3 months of continued therapy. If at the first test stones show partial dissolution, then it is likely that complete dissolution will occur with continued therapy. Treatment success is greatly reduced if at least partial dissolution is not evident within 12 months of continuous therapy. Therapy should be discontinued if no response is evident by 18 months.

Ursodiol (Actigall) should 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.

Cholic acid (Cholbam) treatment should be initiated and monitored by an experienced hepatologist or pediatric gastroenterologist. Patients using cholic acid should have liver function monitored and discontinue its use if any signs of worsening liver function begin to emerge. Laboratory tests that should be monitored include serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), serum gamma glutamyltransferase (GGT), ALP, bilirubin, and international normalized ratio (INR) every month for the first 3 months of therapy. Continue monitoring every 3 months for the next 9 months, then every 6 months for the next 3 years and annually thereafter. Monitoring should be more frequent during periods of rapid growth, concomitant disease, and pregnancy, and the lowest dose of cholic acid should be used to maintain liver function. Simultaneous elevations of serum GGT and ALT may indicate a cholic acid overdose. Should this occur, immediately discontinue treatment of cholic acid. Additionally, if at any time clinical or laboratory indicators of worsening liver function or cholestasis occur, therapy should be stopped. With continued liver function monitoring, treatment may be resumed at reduced doses if levels return to baseline. Treatment with cholic acid should be terminated if liver function does not improve within 3 months after the initiation of therapy or if complete biliary obstruction develops. Likewise, treatment should be stopped if clinical and laboratory indicators of worsening liver function persist.

Obeticholic acid (Ocaliva) is contraindicated in patients with complete biliary obstruction. Liver-related adverse reactions including jaundice, worsening ascites and primary biliary cholangitis flare were reported in clinical trials with daily doses of obeticholic acid of at least 10 mg. Liver function tests should be monitored during treatment with obeticholic acid; discontinue if complete biliary obstruction occurs. Severe widespread pruritus, typically requiring medical attention, has been reported in clinical trials.
Recommended management includes the addition of bile acid binding resins or antihistamines, dose reduction of obeticholic acid, and/or temporary disruption of obeticholic acid therapy. Pruritus is also a common symptom of the PBC condition itself. Dose-dependent reductions in high-density lipoprotein cholesterol (HDL-C) were reported in clinical trials; serum lipid levels should be monitored during treatment. Likewise, hyperlipidemia, with increases in both HDL-C and low-density lipoprotein cholesterol (LDL-C), is a common feature of PBC. Plasma exposure of obeticholic acid and its active metabolites may increase significantly in patients with moderate to severe hepatic impairment (Child-Pugh B and C). A reduced dose is advised in patients with moderate to severe impairment.

Drug Interactions

Bile acid-sequestering agents (e.g., cholestyramine, colestipol) may interfere with the action of chenodiol, cholic acid, obeticholic acid, and ursodiol by reducing their absorption. Aluminum-based antacids also may interfere with the action of chenodiol, cholic acid, and ursodiol by reducing their absorption; therefore, administration time must be separated. 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 and chenodiol. Patients using medications that are bile salt efflux pump (BSEP) inhibitors, such as cyclosporine, may experience an exacerbated accumulation of conjugated bile salts in the liver and display clinical symptoms. If concomitant use with cholic acid is deemed necessary, bilirubin and liver transaminase levels should be monitored. Coadministration of warfarin and obeticholic acid may result in decreased INR. Monitor INR and adjust warfarin dose as needed. Obeticholic acid may also increase the exposure of CYP1A2 substrates when taken concomitantly; therefore, therapeutic monitoring of a CYP1A2 substrate with a narrow therapeutic index should be performed.

Adverse Effects

Chenodiol is associated with more adverse events, particularly more diarrhea than ursodiol. Some other adverse effects reported with chenodiol include hepatobiliary adverse effects, an increased cholecystectomy rate, an increase in low-density lipoprotein (LDL), and decreases in the white blood cell (WBC) count. Other common adverse effects reported with ursodiol formulations include abdominal discomfort, abdominal pain, alopecia, nausea, pruritus, cough, back pain, dizziness, and rash.

The most common adverse effect seen in clinical trials with cholic acid was diarrhea, which was seen in approximately 2% of patients reporting adverse events. Other less commonly reported adverse effects (< 1%) included reflux esophagitis, malaise, jaundice, skin lesion, nausea, abdominal pain, intestinal polyp, urinary tract infection, and peripheral neuropathy.

The most common adverse events reported in clinical trials with obeticholic acid (≥ 10%) were pruritus (56% to 70%), fatigue (19% to 25%), abdominal pain (10% to 19%), rash (7% to 10%), and arthralgia (6% to 10%).

Special Populations

All ursodiol products in this category are Pregnancy Category B. Chenodiol is Pregnancy Category X. There are no adequate and well-controlled studies of cholic acid or obeticholic acid in pregnant women to inform users or drug-associated risks.
The safety and effectiveness of ursodiol products, chenodiol, and obeticholic acid in pediatric patients have not been established. Safety and effectiveness of cholic acid (Cholbam) in pediatric patients have been established for patients beginning at 3 weeks of age and up for its approved indications.

**PLACE IN THERAPY**

**Gallstones**

Gallstone treatment is usually unnecessary if they are not causing symptoms; it is estimated that one-quarter of the affected population requires treatment. If treatment is warranted, laparoscopic cholecystectomy is treatment of choice. An alternative to cholecystectomy is dissolution of the stones by the bile salts – ursodiol or chenodiol. Ursodiol is the 7-beta epimer of chenodeoxycholic acid (chenodiol). 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. Not every patient experiences complete dissolution of stones, and recurrence has been observed in up to 50% of patients within 5 years following bile acid therapy.

Ursodiol is the drug of choice for dissolving cholesterol gallstones. There are currently 3 FDA approved ursodiol formulations. Chenodiol is the oral formulation of chenodeoxycholic acid and is FDA-approved as Chenodal after demonstrating therapeutic equivalence to the previously available reference drug. Chenodiol should be reserved for select patients who are able to adhere to the recommended monitoring including systematic liver function tests, periodic oral cholecystograms or ultrasonograms, and cholesterol tests. There is a paucity of comparative trials among chenodiol and ursodiol formulations.

**Primary Biliary Cholangitis**

Ursodiol/UDCA is the drug of choice for treating primary biliary cirrhosis. 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/cholangitis (PBC); however, the role of obeticholic acid was not addressed as it was not available during guideline development. Dosing of ursodiol plays a significant role in that the dose of 13 to 15 mg/kg/day demonstrated superiority in 1 study over other lower and higher dosages in terms of biochemical response. Therapy with ursodiol improves serum ALP and bilirubin levels and delays histological progression of the disease, thereby increasing liver transplant-free survival. Up to 50% of PBC patients fail to adequately respond to ursodiol. Patients left untreated, or who have not responded to ursodiol, are at risk for liver failure and death. Liver transplant has significantly improved mortality in this patient population; however, due to the nature of this autoimmune disease, PBC often recurs post transplant.

Obeticholic acid offers an option for treatment of PBC in patients who cannot tolerate or had an inadequate response to ursodiol. Obeticholic acid can be used either as monotherapy or in combination with ursodiol. A 12-month, double-blind, parallel-group, phase 3 study evaluated the efficacy of obeticholic acid in 216 adults with PBC who were taking ursodiol or unable to tolerate ursodiol. Patients were randomized (1:1:1) to receive once daily obeticholic acid 10 mg, obeticholic acid titration (5 to 10 mg based on tolerability and efficacy), or placebo. The primary composite endpoint was the proportion of patients achieving ALP < 1.67 times the upper limit of normal (ULN) (with a ≥ 15% reduction) and bilirubin ≤ ULN. After 12 months, 47%, 46% and 10% of patients in the obeticholic acid 10 mg, obeticholic acid titration, and placebo arms achieved the primary endpoint, respectively (both obeticholic acid
groups p<0.0001 compared to placebo). The mean bilirubin levels did not change from baseline in the obeticholic acid groups, while it increased in the placebo group; suggestive of a slowing of disease progression with obeticholic acid. Three open-label long-term extension studies reported that ALP and bilirubin response was maintained after 2 years on therapy.

**PDs and Bile Acid Synthesis Disorders Due to SEDs**

Cholic acid (Cholbam) is the only product FDA approved for SED and PD disorders of bile acid synthesis. As the drug is not indicated for the more typical bile salt uses, it should only be used in cases where a definitive diagnosis has been made or is indicated by laboratory and clinical findings.

The efficacy of cholic acid in the treatment of bile acid synthesis disorders resulting from SEDs was studied in 2 trials with doses set at 10 to 15 mg/kg per day, an open-label, single-arm, randomized trial (n = 50) and an extension of the first trial including both rolled-over and new patients (n = 33). The majority of the patients were treated for an average of 310 weeks (6 years). Treatment response in these trials was measured by reductions in ALT or AST, bilirubin, lack of cholestasis, and weight gain. Responders were defined as the presence of 2 of the former criteria as well as the patient being alive at the last follow-up. In total, 28 of 44 patients (64%) fell into the responder category. Overall, 67% of the patients with SEDs survived greater than 3 years following entry in 1 of the trials. The efficacy of cholic acid in the treatment of PDs, including Zellweger syndrome, was evaluated in the same trials as listed for SED, again at a dosage of 10 to 15 mg/kg per day. The first was an open-label, single-arm, randomized trial (n = 29), and the second was an extension of the first trial including both rolled-over and new patients (n = 12). The majority of patients received concomitant docosahexaenoic acid (DHA) and vitamins A, D, E, and K therapy. Most of the patients were treated for an average duration of 254 weeks (4.8 years). Treatment response for cholic acid in the PD trials was assessed using the same laboratory criteria that were used in the SED trials. Overall, 11 of 24 patients (46%) in the PD trials were considered to be responders. Forty-two percent of patients in the PD trials survived greater than 3 years from their time of enrollment in the trials. Cholic acid treatment did not have an effect on any of the extrahepatic manifestations of PDs, including Zellweger disorders, such as neurologic symptoms.

The long-term clinical survival outcomes remain to be seen with cholic acid; however, it represents the only FDA approved treatment for SEDs and PDs. Long-term clinical outcomes are also unknown with obeticholic acid; it should be reserved for PBC patients who cannot tolerate or had an inadequate response to ursodiol. Ursodiol remains the drug of choice for dissolving cholesterol gallstones and the primary pharmacologic treatment of PBC.
REFERENCES

1 Chenodal [package insert]. San Diego, CA; Retrophin; June 2015.
2 Cholbam [package insert]. San Diego, CA; Retrophin; March 2015.
15 Chenodal [package insert]. San Diego, CA; Retrophin; June 2015.
19 Cholbam [package insert]. San Diego, CA; Retrophin; March 2015.
27 Cholbam [package insert]. San Diego, CA; Retrophin; March 2015.