Bile Acid Salts Summary

December 2021

FDA-APPROVED INDICATIONS AND DOSAGES

Drug	Manufacturer	Indication(s)	Dosage	Availability
chenodiol (Chenodal®)[1]	Retrophin	▪ 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	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	250 mg tablets
cholic acid (Cholbam®)[2]	Manchester	▪ 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	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)	50 mg, 250 mg capsules

FDA-Approved Indications and Dosages (continued)

Drug	Manufacturer	Indication(s)	Dosage	Availability
maralixibat (Livmarli™)[3]	Mirum	▪ Treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 1 year of age and older	380 mcg/kg once daily taken 30 minutes prior to the first meal of the day Starting dose 190 mcg/kg orally once daily for 1 week, then increase to maintenance dose of 380 mcg/kg	9.5 mg/mL oral solution
obeticholic acid (Ocaliva®)[4]	Intercept	▪ Treatment of adults with primary biliary cholangitis (PBC) without cirrhosis, or with compensated cirrhosis without evidence of portal hypertension, either in combination with ursodeoxycholic acid (UDCA) in patients with an inadequate response to UDCA (defined as a trial of at least 1 year), or as a single therapy in patients 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	5 mg taken orally once daily with or without food; after 3 months, if an adequate 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 If concomitant bile acid binding resins are used, take Ocaliva at least 4 hours before or after the bile acid binding resin Hepatic impairment should be assessed using Child-Pugh classification, as detailed in the labeling, prior to initiation; 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	5 mg, 10 mg tablets
odevixibat (Bylvay™)[5]	Albireo	▪ Treatment of pruritis in patients 3 months of age and older with progressive familial intrahepatic cholestasis (PFIC)	40 mcg/kg once daily in the morning with a meal If no improvement after 3 months, may increase dose by 40 mcg/kg increments up to a max daily dose of 6 mg	200 mcg, 600 mcg oral pellets 400 mcg, 1,200 mcg capsules
ursodiol (URSO250)[6]	generic, Aptalis/Allergan	▪ Treatment of patients with primary biliary cirrhosis	13 to 15 mg/kg/day in 2 to 4 divided doses with food	250 mg tablets
ursodiol (URSO Forte®)[7]	generic, Aptalis/Allergan	▪ Treatment of patients with primary biliary cirrhosis	13 to 15 mg/kg/day in 2 to 4 divided doses with food Scored tablets can be broken in half to provide recommended dosage	500 mg tablets

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

FDA-Approved Indications and Dosages (continued)

Drug	Manufacturer	Indication(s)	Dosage	Availability
ursodiol[8,9]	generic, Allergan	▪ 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	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 (600 mg/day)	300 mg capsules Reltone*: 200 mg, 400 mg capsules

* Reltone is a branded generic ursodiol from Intra-Sana approved under an Abbreviated New Drug Application (ANDA).

OVERVIEW[10,11,12,13,14,15,16,17,18,19,20,21]

Gallstones

Gallstones form when bile crystalizes in the gallbladder. Gallstones are composed primarily of cholesterol, bilirubin, or calcium salts. In the United States (US), approximately 80% of patients with gallstones have cholesterol stones. Risk factors for cholesterol gallstones include ethnicity, increasing age, female gender, and family history. In addition, modifiable risks include obesity, rapid weight loss, and a sedentary lifestyle. 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 US population, and close to 1 million new cases are diagnosed each year. While the majority of individuals with gallstones remain asymptomatic, gallstone blockages of the cystic duct result in pain and inflammation, and possibly 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, the etiology of which is thought to be a result of environmental triggers along with genetic risk factors. 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 US. 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. Diagnosis is generally confirmed by the presence of antimitochondrial antibody (AMA); liver biopsy is not required for diagnosis according to the American Association for the Study of Liver Diseases (AASLD).[22]

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. Obeticholic acid is about 100 times stronger than chenodeoxycholic acid – the endogenous ligand. Due to new FDA warnings restricting its use in patients with advanced cirrhosis, it is contraindicated in those with advanced cirrhosis. Careful monitoring is recommended for anyone on this agent, even if the cirrhosis is not advanced.

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

Peroxisomes catalyze a variety of metabolic functions in cellular metabolism and peroxisomal disorders occur in over 1 in 20,000 individuals in the US. 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. Patients with these rare metabolic conditions lack the enzymes needed to synthesize cholic acid, a primary bile acid normally produced in the liver from cholesterol which leads to liver disease and complications from decreased fat-soluble vitamin absorption. 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.

Primary bile acid replacement therapy has been shown to improve liver function and weight gain. In 2015, the US Food and Drug Administration (FDA) approved cholic acid (Cholbam) for the treatment SED and PDs.

Pruritis Associated with Alagille syndrome (ALGS) or Progressive familial Intrahepatic Cholestasis (PFIC)

Two new agents have been approved for use in patients with pruritis resulting from either Alagille syndrome or progressive familial intrahepatic cholestasis: maralixibat (Livmarli) and odevixibat (Bylvay). Alagille syndrome is an inherited condition that causes a build-up of bile in the liver due to lack of adequate numbers of bile ducts to drain the bile. This leads to liver damage. Symptoms include severe itchy skin related to the presence of bilirubin.[23] Progressive familial intrahepatic cholestasis is characterized by an itch that is disabling and includes the eyes and ears.[24]

SPECIAL USAGE CONSIDERATIONS[25,26,27,28,29,30,31,32]

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 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.

Labeling for ursodiol capsules advise that the product should not be used in patients with calcified cholesterol stones, radio-opaque stones, or radiolucent bile pigment stones since it is not effective in this setting. 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 ursodiol capsules therapy.

Ursodiol (Urso 250, Urso Forte) is contraindicated with complete biliary obstruction and known hypersensitivity or intolerance to ursodiol or any component. Patients with variceal bleeding, hepatic encephalopathy, ascites, or in need of an urgent liver transplant should receive specific treatment. Liver function tests (LFTs) and bilirubin levels should be monitored every month for 3 months then every 6 months thereafter, and treatment discontinuation should be considered if parameters increase to a level clinically significant when previous LFTs have shown stable levels. Caution should be exercised to maintain bile flow in patients using ursodiol.

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 indictors of worsening liver function persist. Cases of severe hepatotoxicity have been seen in the post-marketing setting when used in patients with cirrhosis; the potential exists that cholic acid exacerbated liver dysfunction in these individuals.

Obeticholic acid (Ocaliva) is contraindicated in patients with complete biliary obstruction, decompensated cirrhosis, and compensated cirrhosis with evidence of portal hypertension. 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. Discontinuation should be considered in those who continue to experience intolerable pruritis despite management. 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. In 2017,

the US Food and Drug Administration (FDA) issued a Drug Safety Communication regarding obeticholic acid after identifying a trend that it was being incorrectly dosed in some patients with liver impairment, resulting in liver injury and death in some cases. As a result, the FDA required several labeling changes for obeticholic acid regarding this risk, including a boxed warning, updated and clarified dosing information, additional warning language, and a Medication Guide. The FDA warned that obeticholic acid is being incorrectly dosed (higher dose and frequency) in some patients with moderate to severe hepatic impairment, resulting in an increased risk of serious liver injury and death. Healthcare providers should assess liver function prior to initiation of obeticholic acid, and patients with moderate to severe liver impairment should be started on the approved lower dosing schedule as outlined in the prescribing information. Patients should be monitored frequently for disease progression, and the dose should be reduced for patients who progress to moderate or severe liver impairment.[33] The FDA issued a subsequent Drug Safety Communication in 2021 for obeticholic acid in patients with PBC with advanced cirrhosis due to the risk of serious liver harm, sometimes requiring liver transplant. This contraindication has been added to the product labeling. Permanently discontinue obeticholic acid use in those who develop laboratory or clinical evidence of hepatic decompensation, or who develop portal hypertension with compensated cirrhosis or who develop significant adverse reactions.[34]

There are no known contraindications with either maralixibat or odevixibat.

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 possibly other drugs that lower serum lipids may counteract the effectiveness of both 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 or obeticholic 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. Avoid use of inhibitors of bile salt efflux pump with obeticholic acid, if possible. If this is not possible, monitor serum transaminases and bilirubin levels.

Both maralixibat and odevixibat may be bound by bile acid binding resins in the gut. Administer these agents either 4 hours before or after the bile acid binding resin.

Adverse Effects

Chenodiol is associated with more adverse events, particularly diarrhea, compared to 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 (Urso 250, Urso Forte) 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%). Oropharyngeal pain, dizziness, constipation, eczema, and thyroid function changes have also been reported at rates ≥ 5%.

The most commonly reported adverse reactions with ursodiol capsules (≥ 10% and more often than placebo) include diarrhea, alopecia, dyspepsia, upper respiratory tract infection, constipation, nausea, back pain, pruritis, rash, and dizziness.

Maralixibat and odevixibat both are associated with liver function test abnormalities. A dose reduction or treatment interruption should be considered if abnormalities occur. The most common adverse reactions include diarrhea, abdominal pain, vomiting, and fat-soluble vitamin deficiency. Additional adverse reactions reported with maralixibat use are gastrointestinal bleeding and bone fractures.

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 3 weeks of age and older for its approved indications.

Maralixibat and odevixibat are indicated for use in pediatrics as young as 1 year of age and 3 months of age, respectively. Use of these products in geriatrics or in the presence of hepatic impairment have not been established.

PLACE IN THERAPY[35,36,37,38,39,40,41,42,43]

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 the 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 (capsule) are the drug of choice for dissolving cholesterol gallstones. Chenodiol is the oral formulation of chenodeoxycholic acid and was 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 (Urso 250, Urso Forte) is the drug of choice for treating primary biliary cirrhosis. According to the American Association for the Study of Liver Diseases (AASLD) guidelines 2021 update, ursodiol plays a key role in the treatment of primary biliary cirrhosis/cholangitis (PBC) and is still considered first-line therapy. Dosing of ursodiol plays a significant role and a 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 after 1 year of therapy; however, AASLD discourages its use in patients with decompensated liver disease (Child-Pugh B and C). 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. Response was 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%) met the criteria for being a responder. 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 and who do not have decompensated hepatic impairment. Ursodiol remains the drug of choice for dissolving cholesterol gallstones and the primary pharmacologic treatment of PBC.

Pruritis Associated with Alagille syndrome (ALGS) or Progressive familial Intrahepatic Cholestasis (PFIC)

Maralixibat (Livmarli) and odevixibat (Bylvay) are not yet addressed in treatment guidelines for their respective indications for the treatment of pruritis associated with select errors of bile acid transport.

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