Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Literature Scan: Bile Therapy

Date of Review: December 2021

Date of Last Review: November 2019
Literature Search: 02/01/2017 – 09/16/2021

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:

- Since the last bile acid class review, 3 high-quality systematic reviews[1-3] and 2 high-quality clinical guidelines[4,5] were published.
- A 2020 Cochrane Review evaluated pharmacological interventions in patients with intrahepatic cholestasis of pregnancy (ICP).[1] Specific outcomes included maternal pruritus and adverse fetal impact.[1] The pruritus score is measured on a 100 mm visual analogue scale (VAS) where a score of zero indicates no itch and a score of 100 mm indicates severe itching.[1] In one RCT, a change of 30 mm on the VAS was considered clinically meaningful by the researchers and study participants.[6] There is no evidence this score has been validated to establish a minimal clinically important difference. Compared with placebo, ursodeoxycholic acid (ursodiol) probably results in a small, but clinically insignificant improvement in pruritus associated with ICP (mean difference [MD] −7.64 points, 95% CI −9.69 to −5.60 points; 2 trials, n=715, moderate-quality evidence).[1] The evidence for fetal distress and stillbirth were uncertain, due to serious limitations in study design and imprecision (risk ratio (RR) 0.70, 95% CI, 0.35 to 1.40 and RR 0.33, 95% CI, 0.08 to 1.37; 6 trials, n=955, low-quality evidence, respectively).[1] There is insufficient evidence to indicate if activated charcoal, dexamethasone, or cholestyramine are effective in treating patients with ICP.[1]
- A 2019 meta-analysis of 2 low-quality studies evaluated the clinical outcomes of the combination therapy of ursodeoxycholic acid and obeticholic acid compared with ursodeoxycholic acid monotherapy in patients with primary biliary cholangitis (PBC).[2] The co-primary endpoints for the 2 RCTs were 1) less than 1.67 times the upper limit of normal (ULN) of serum alkaline phosphatase with 15% reduction from baseline and 2) serum total bilirubin within normal limits at the completion of the trials (85 days and 12 months).[2] Fifty-two percent of patients in the combination therapy groups and 22% in the monotherapy groups met both of the endpoints, but there were no statistically significant differences between the groups (RR 2.75; 95% CI, 0.43 to 17.68, p=0.29).[2] Secondary outcomes of interest included liver biochemistry parameters including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGT), and conjugated bilirubin. The results of this meta-analysis indicate that combination therapy was significantly superior to monotherapy in reducing serum ALT (MD -15.63 IU/L; 95% CI, –21.59 to –9.68), AST (MD –6.63 IU/L; 95% CI, –11.03 to –2.24), and GGT (MD –131.30 IU/L; 95% CI, –177.52 to –85.08).[2] However, there was no significant difference between combination therapy groups and monotherapy groups for reducing conjugated bilirubin (MD –0.06 mg/dL; 95% CI, –0.28 to 0.15; p=0.56).[2] The results of this analysis indicated that combination therapy did not differ significantly from monotherapy in improving primary endpoints or reducing bilirubin, but was statistically significantly superior to monotherapy in reducing liver biochemical parameters.[2] The results of this meta-analysis are limited by the small number of low-quality trials that were available for inclusion and assessment. There is a need for high-quality RCTs that evaluate the safety and efficacy of combination ursodeoxycholic acid and obeticholic acid in patients with PBC who have an inadequate response to ursodeoxycholic acid monotherapy.[2]

Author: Deanna Moretz, PharmD, BCPS

- A 2021 systematic review analyzed the safety and efficacy of obeticholic acid as treatment for non-alcoholic steatohepatitis (NASH), PBC, and primary sclerosing cholangitis (PSC).[3] Currently, there are no FDA-approved pharmacotherapy options to treat NASH or PSC. Ursodeoxycholic acid and obeticholic acid are FDA-approved as treatments for patients with PBC. Obeticholic acid 10 mg and 25 mg doses improved fibrosis in NASH patients, but neither dose was associated with steatosis improvement.[3] The use of 25 mg obeticholic acid resulted in higher treatment discontinuation rates and significant risk of pruritus.[3] Obeticholic acid treatment led to a significantly better response than the placebo in patients with PBC (OR 4.5, 95% CI, 2.74 to 7.4, $p<0.001$, $I^2 = 40.67$).[3] With the 10 mg obeticholic acid dose, the odds of improvement was 1.61 (95% CI, 1.03-2.51; p=0.03), while with the 25 mg dose, it was 2.23 (95% CI, 1.55-3.18; $p<0.001$).[3] The alkaline phosphatase response was better at lower doses (5 to 10 mg) than at higher doses of obeticholic acid (25 to 50 mg).[3] One RCT showed a significant reduction in alkaline phosphatase levels in PSC patients treated with obeticholic acid without the added risk of pruritus; however, further studies are required to validate the findings.[3]
- In April 2017, the National Institute for Health and Care Excellence (NICE) published guidance for the use of obeticholic acid for treating PBC.[4] Obeticholic acid is recommended as an option for treating PBC in combination with ursodeoxycholic acid for people whose disease has responded inadequately to ursodeoxycholic acid alone, or as monotherapy for people who cannot tolerate ursodeoxycholic acid.[4] Response to obeticholic acid should be assessed after 12 months with continuation only if there is evidence of clinical benefit.[4]
- The British Society of Gastroenterology (BSG) Liver Section and United Kingdom (UK)-PBC published guidance for PBC treatment and management in 2018.[5] Pharmacotherapy recommendations include:
    - Oral ursodeoxycholic acid is recommended at 13 to 15 mg/kg/day as the first-line pharmacotherapy in all patients with PBC. If tolerated, treatment should usually be life-long. (Strong Recommendation; High Quality of Evidence)[5]
    - In patients with inadequate response or intolerance to ursodeoxycholic acid as defined by alkaline phosphatase > 1.67 x ULN and/or elevated bilirubin 2 x ULN, the addition of obeticholic acid has been associated with improvements in biochemical surrogates of disease activity reasonably likely to predict improved outcomes.[6] Therefore, in keeping with the NICE evaluation of obeticholic acid, it is recommended the addition of obeticholic acid for patients with an inadequate response or intolerance to ursodeoxycholic acid, is considered.[6] (Strong Recommendation; Low Quality of Evidence).[5]
- The FDA issued a drug safety communication on September 21, 2017 regarding the increased risk of hepatic injury and death due to incorrect dosing of obeticholic acid.[7] As a result of this FDA alert, the manufacturer added a boxed warning in February 2018 regarding risk of hepatic decompensation and failure in incorrectly dosed PBC patients with Child-Pugh Class B or C or decompensated cirrhosis.[8] The recommended dosing for patients with impaired hepatic function at that point in time was 5 mg once a week.[8] The FDA issued a stronger safety advisory in May 2021 stating that due to the risk of serious hepatic injury, the use of obeticholic acid must be restricted in PBC patients with advanced cirrhosis.[9] The manufacturer strengthened the boxed warning regarding risk of fatal hepatic injury to obeticholic acid prescribing information in May 2021.[10] Obeticholic acid is contraindicated in PBC patients with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia).[10]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended at this time.
- Modify obeticholic acid prior authorization (PA) criteria (**Appendix 4**) to include recommended dosing parameters and safety precautions to avoid serious hepatic injury.
- After evaluation of costs in executive session, no PDL changes were recommended.

Summary of Prior Reviews and Current Policy:
Obeticholic acid, which is indicated for treatment of PBC, was reviewed by the Pharmacy and Therapeutics (P & T) Committee at the January 2017 meeting. After discussion, the P & T Committee made the following recommendations:

- Incorporate bile therapy drugs (obeticholic acid, ursodeoxycholic acid [ursodiol], and cholic acid) into one PDL class within the Oregon Practitioner-Managed Prescription Drug Plan (PMPDP).
- Designate ursodiol as a preferred medication and obeticholic acid as a non-preferred medication due to the lack of long-term efficacy and safety data.
- Approve PA criteria (**Appendix 4**) for all non-preferred drugs which encourages use of ursodiol as first-line therapy and restricts obeticholic acid use to populations that may benefit from this therapy without undue harm.

At the November 2019 P & T Committee meeting, the efficacy and safety of cholic acid for treatment of bile acid synthesis disorders and peroxisomal disorders (Zellweger spectrum disorders) were evaluated. After review, cholic acid was designated as a non-preferred agent on the PDL and PA criteria for cholic acid (**Appendix 4**) were implemented to ensure use according to FDA-approved indications.

Appendix 1 describes the PDL status of the different bile therapy drugs. Currently, ursodiol is preferred and all the other agents are non-preferred with PA required before utilization in Medicaid Fee-For-Service (FFS) patients. In the second quarter of 2021, most of the FFS utilization in the bile salt class resulted from claims for ursodiol (87%). There was minimal utilization of cholic acid (13%). No claims were submitted for obeticholic acid.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
Cochrane Review: Pharmacological Interventions For Treating Intrahepatic Cholestasis Of Pregnancy
A 2020 Cochrane Review focused on the evidence of pharmacological interventions to treat patients with ICP on maternal, fetal and neonatal outcomes.[1] The 2020 publication was an update of prior Cochrane reviews on this topic. Intrahepatic cholestasis of pregnancy is a liver disorder which appears most often in the third trimester.[1] It is a relatively benign though often very distressing condition for the patient, but it may adversely affect fetal outcome, as seen by associations with preterm labor, fetal distress and stillbirth, particularly in severe cases.[1] The diagnosis of ICP is based on a combination of pruritus and increased concentrations of serum bile acids (values usually at least 10 µmol/L). Pruritis classically affects palms and soles but may become generalized, though without a rash apart from excoriations.[1] Increased concentrations of serum transaminases (e.g. ALT greater than 50 U/L) are often seen.[1] The incidence may vary across ethnic groups. It has been reported in fewer than 1% of pregnancies in Central and Western Europe, North America and Australia, in 1% to 2% in Scandinavia and

the Baltic states, but can be as high as 5% to 15% in Araucanian Indians in Chile and Bolivia.[11] Since the pathophysiology is poorly understood, therapies have been largely empiric.[1] As ICP is an uncommon condition (incidence less than 2% a year), many trials have included small numbers of participants.[1]

Literature for the 2020 update was searched through December 2019. Twenty-six trials involving 2,007 women met inclusion criteria.[1] Two placebo-controlled trials of ursodeoxycholic acid in 715 women were judged as having a low risk of bias.[1] The pruritus score is measured on a 100 mm VAS where a score of zero indicates no itch and a score of 100 mm indicates severe itching.[1] In one RCT, a change of 30 mm on the VAS was considered clinically meaningful by the researchers and study participants.[6] There is no evidence this score has been validated to establish a minimal clinically important difference. Compared with placebo, ursodeoxycholic acid probably results in a small, but clinically insignificant improvement in pruritus (MD −7.64 points; 95% CI, −9.69 to −5.60 points; moderate-quality evidence).[1] The evidence for fetal distress and stillbirth were uncertain, due to serious limitations in study design and imprecision (RR 0.70; 95% CI, 0.35 to 1.40 and RR 0.33; 95% CI, 0.08 to 1.37; respectively, 6 trials; 955 women; low quality evidence).[1]

There is insufficient evidence to indicate if activated charcoal, dexamethasone, or cholestyramine are effective in treating women with ICP.[1] When compared with placebo, ursodeoxycholic acid administered to women with ICP shows a slight reduction in pruritus.[1] For most pregnant patients and clinicians, the reduction may fall below the minimum clinically worthwhile effect.[1] The evidence was unclear for other adverse fetal outcomes, due to low-certainty evidence.[1]

Combination Obeticholic Acid And Ursodeoxycholic Acid In Patients With Primary Biliary Cholangitis Who Respond Incompletely To Ursodeoxycholic Acid

The aim of this 2019 meta-analysis was to evaluate the clinical outcomes of the combination therapy of ursodeoxycholic acid and obeticholic acid compared with ursodeoxycholic acid monotherapy in patients with PBC.[2] The literature search was conducted through September 2018. Primary biliary cholangitis is a rare, chronic, autoimmune cholestatic liver disease that predominantly occurs in middle-aged women.[2] Its peak incidence occurs in the fifth decade of life, and it is uncommon in persons under 25 years of age.[12] On the basis of data from case-finding studies, a latitudinal geoepidemiological pattern of occurrence of primary biliary cirrhosis has been proposed, with the disease being most frequent in northern Europe and North America.[13] The highest prevalence and incidence rates have been reported in Scandinavia, Great Britain, and the northern Midwest region of the United States.[13] Approximately 50 to 60 percent of patients with PBC are asymptomatic at diagnosis and are detected because of abnormalities in liver biochemical tests obtained for other reasons.[14] Among patients with symptoms, fatigue and pruritus are most commonly seen. In newly diagnosed patients, approximately one-half complain of fatigue and one-third pruritus.[12] The progressive destruction of small intrahepatic bile ducts, resulting in the development of fibrosis and potential cirrhosis is a unique feature of PBC.[2] Serum alkaline phosphatase and bilirubin are strongly associated with clinical outcomes (death or liver transplantation) in patients with PBC.[2]

Two studies (n=222) met inclusion criteria and were included in the meta-analysis.[2] The population included patients with PBC who incompletely responded to ursodeoxycholic acid (13–15 mg/kg/day).[2] These patients were randomly assigned to receive obeticholic acid at different doses (5 to 25 mg/day). The mean patient age was 54.9 years and the ratio of male to female was 1:13.[2] The duration of treatment of these two trials was 85 days and 12 months, respectively.[2] The two trials included in the meta-analysis were considered low quality as there are high or unclear risks for bias for at least one component of the Cochrane risk of bias assessment.[2]

The co-primary endpoints for the 2 RCTs were 1) less than 1.67 times the ULN of serum alkaline phosphatase with 15% reduction from baseline and 2) serum total bilirubin less than the ULN at the end of trials.[2] Fifty-eight of 111 patients (52%) in the combination therapy groups and 24 of 111 patients (22%) in the monotherapy groups had the primary endpoints, but there were no significant differences between the groups (RR 2.75; 95% CI, 0.43 to 17.68; p=0.29).[2] Secondary outcomes of interest included liver biochemistry parameters including serum ALT, AST, GGT, and conjugated bilirubin. The results of this meta-analysis indicate that combination therapy was significantly superior to monotherapy in reducing serum ALT (MD 15.63 IU/L; 95% CI, –21.59 to –9.68), AST (MD –

6.63 IU/L; 95% CI, –11.03 to –2.24), and GGT (MD –131.30 IU/L; 95% CI, –177.52 to –85.08).[2] However, there was no significant difference between combination therapy groups and monotherapy groups for reducing conjugated bilirubin (MD –0.06 mg/dL; 95% CI, –0.28 to 0.15; p=0.56).[2] No significant association with increased risks of adverse events was found between patients with combination therapy versus monotherapy.[2] The results of this study indicate that combination therapy did not differ significantly from monotherapy in improving primary endpoints, conjugated bilirubin, or adverse events, but was superior to monotherapy in reducing liver biochemical indices including ALT, AST, and GGT.[2] The results of this meta-analysis are limited by the small number of low-quality trials that were available for inclusion and assessment. There is a need for high-quality RCTs that evaluate the safety and efficacy of combination ursodeoxycholic acid and obeticholic acid in patients with PBC who have an inadequate response to ursodeoxycholic acid monotherapy.[2]

Efficacy And Safety Of Obeticholic Acid In Liver Disease

A 2021 systematic review and meta-analysis analyzed the safety and efficacy of obeticholic acid as treatment for non-alcoholic steatohepatitis (NASH), PBC, and PSC.[3] Literature was searched from January 2000 through March 2020. Currently, there are no FDA-approved pharmacotherapy options to treat NASH or PSC. Ursodeoxycholic acid and obeticholic acid are FDA-approved as treatments for patients with PBC. Outcomes of interest included histological improvement in NASH (fibrosis and steatosis), reduction in alkaline phosphatase (less than 1.67 the ULN) in patients with PBC, mean reduction in alkaline phosphatase levels in patients with PSC, and the adverse effects of obeticholic acid (pruritus and drug discontinuation). Seven RCTs (n=2834) conducted in adults met inclusion critiera.[3] Three RCTs (n=2317) were in patients with NASH, 3 RCTs (N=441) were in PBC patients, and 1 RCT (N=76) in patients with PSC.[3] The methodological quality of the included studies was of moderate to high quality.[3] All the included trials were placebo-controlled RCTs, reported complete data, and had low heterogeneity.[3] The main limitation of this meta-analysis is the small number of studies for each hepatic disease.[3]

Three RCTs evaluated fibrosis improvement in NASH. Three hundred twelve patients received 10 mg obeticholic acid, 410 patients received 25 mg obeticholic acid, and 720 patients received placebo.[3] The studies were conducted over 52 to 72 weeks. The meta-analysis showed fibrosis improvement was significantly better in NASH patients who received either dose of obeticholic acid compared to patients in the placebo group (OR 1.95; 95% CI, 1.47 to 2.59; p<0.001; $I^2 = 0$).[3] With the 10 mg obeticholic acid dose, the odds of improvement was 1.61 (95% CI, 1.03-2.51; p=0.03), while with the 25 mg dose, it was 2.23 (95% CI, 1.55-3.18; p<0.001).[3] There was no significant effect on steatosis with either 10 mg or 25 mg dose of obeticholic acid (OR 1.19; 95% CI, 0.88 to 1.6; p=0.24).[3] However, 25 mg obeticholic acid led to significant adverse events and discontinuation of the drug (OR 2.8; 95% CI 1.42 to 3.02; p<0.001) compared with 10 mg obeticholic acid (OR 0.95; 95% CI 0.6 to 1.5; p=0.84).[3]

Three studies on patients with PBC reported a response to obeticholic acid (alkaline phosphatase 1.67 ULN or less).[3] One hundred thirty-one patients were treated with obeticholic acid 10 mg, 70 patients received 5 mg, 48 patients received 25 mg, and 57 patients received 50 mg, compared to 134 patients who received placebo.[3] Obeticholic acid treatment led to a significantly better response than the placebo in patients with PBC (OR 4.5; 95% CI, 2.74 to 7.4; p<0.001, $I^2 = 40.67$).[3] The alkaline phosphatase response was better at lower doses (5 to 10 mg) than at higher doses of obeticholic acid (25 to 50 mg).[3] The response to 5 mg obeticholic acid was an OR of 7.66 (95% CI, 3.12 to 18.81; p<0.001), 10 mg was 5.18 (95% CI, 2 to 13.41; p=0.001), 25 mg was 2.36 (95% CI, 0.94 to 5.93; p=0.06) and 50 mg was 4.08 (95% CI 1.05 to 15.78; p=0.04).[3]

Only one phase 2, dose-finding study reported on the safety of obeticholic acid in PSC.[3] The dose of obeticholic acid was increased from 1.5 to 3 mg or 5 mg increased to 10 mg after 3 months of therapy.[3] The median dose of obeticholic acid was 5 mg. At 6 months, the mean reduction in alkaline phosphatase compared to placebo was −80.97 IU/L (95% CI, −137.84 to −24.05; p=0.005).[3] Nearly 50% of patients received concomitant ursodeoxycholic acid therapy. However, the magnitude of alkaline phosphatase reduction was greater in patients who did not receive ursodeoxycholic acid (25−30% reduction) than in those

who did receive ursodeoxycholic acid (15% reduction), and the reason for this is unknown.[3] Further studies are required to validate the findings from this single phase 2 trial.

Compared with placebo, obeticholic acid increased the odds of pruritus in all 3 cholestatic liver diseases by 2.3 times (95% CI, 1.56 to 3.4; p<0.001).[3] In NASH patients, the 25 mg obeticholic acid dose increased the odds of pruritus by 3.93 times (95% CI, 2.0 to 7.38, p<0.001), while the 10 mg obeticholic acid dose increased the odds of pruritus 1.65 times (95% CI, 1.27 to 2.14; p<0.001) compared to placebo.[3] In NASH, the odds of discontinuation seemed to be similar in those with 10 mg obeticholic acid and placebo (OR 0.95; 95% CI, 0.6 to 1.5; p=0.84).[3] However, with 25 mg obeticholic acid, the odds of discontinuation of the drug were higher than those with the placebo (OR 2.8; 95% CI, 1.42 to 3.02; p<0.001).[3 3]

After review, 3 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[15-17]

New Guidelines:

High Quality Guidelines:

National Institute for Health and Care Excellence

NICE guidance published in April 2017 provided evidence-based recommendations for the use of obeticholic acid in treatment of adults with PBC.[4] The committee considered the clinical evidence for obeticholic acid plus ursodeoxycholic acid compared with ursodeoxycholic acid plus placebo from the POISE trial, and obeticholic acid monotherapy compared with placebo for adults who cannot tolerate ursodeoxycholic acid.[4] People who took part in POISE were mainly women (91%) and younger than 65 years (81%).[4] Inclusion criteria included a serum alkaline phosphatase level of at least 1.67 times the upper limit of normal, and/or elevated total bilirubin level above the upper limit of normal.[4] A small number of patients (n=11) in the trial could not tolerate ursodeoxycholic acid.[4] A higher number of people were classified as responders according to the primary outcome in POISE for obeticholic acid plus ursodeoxycholic acid compared with placebo plus ursodeoxycholic acid (47% in the obeticholic acid 10 mg group and 46% in the obeticholic acid titration group compared with 10% in the placebo group, p<0.0001 for both comparisons).[4] Obeticholic acid plus ursodeoxycholic acid was also more effective at lowering alkaline phosphatase levels by at least 40% from the baseline (34% in the obeticholic acid 10 mg group and 30% in the obeticholic acid titration group, compared with 1% in the placebo group).[4] Obeticholic acid plus ursodeoxycholic acid was more effective at lowering the total bilirubin level, which at 12 months was 9.7 mg/dL for the obeticholic acid 10 mg group, 9.9 mg/dL for the obeticholic acid titration group, and 13.2 mg/dL for the placebo group.[4] The committee concluded that obeticholic acid plus ursodeoxycholic acid is clinically effective in improving the surrogate outcomes associated with the progression of PBC.[4] Pruritus was the most common adverse event with obeticholic acid, occurring in 66% of patients taking 10 mg, and 50% of patients taking 5 mg, compared with 37% in the placebo arm.[4]

NICE pharmacotherapy recommendations are as follows:

- Obeticholic acid is recommended as an option for treating PBC in combination with ursodeoxycholic acid for people whose disease has responded inadequately to ursodeoxycholic acid or as monotherapy for people who cannot tolerate ursodeoxycholic acid.[4]
- The starting dose of obeticholic acid is 5 mg once daily. Based on assessment of tolerability after 3 months, the dose should be increased to 10 mg once daily for optimal response.[4]
- Assess the response to obeticholic acid after 12 months. Only continue therapy if there is evidence of clinical benefit.[4]

The British Society of Gastroenterology and United Kingdom Primary Biliary Cholangitis Council

The BSG Liver Section and UK-PBC Council published guidance for PBC treatment and management in 2018.[5] UK-PBC is a Medical Research Council-funded rare disease medical initiative which provides support to providers, patients, and researchers for managing PBC.[5] Members of the guideline writing committee

included gastroenterologists, hepatologists, transplant physicians, liver pathologists and patient representatives.[5] The guidelines were produced using a systematic review of publications identified searches in line with the Appraisal of Guidelines Research & Evaluation II (AGREE II) instrument.[5]
In PBC, a dose of ursodeoxycholic acid 13 to 15 mg/kg/day has been shown to be superior to 5 to 7 mg/kg/day or 23 to 25 mg/kg/day.[5] Three large double-blind randomized trials used the same dose of ursodeoxycholic acid (13–15 mg/kg/day), and the results have been analyzed according to an intention-to-treat principle.[5] Ultimately, this combined analysis of the three trials (548 patients) showed a one-third reduction in the risk of death or transplant for patients with moderate to severe PBC.[5] Ursodeoxycholic acid at the recommended dose is very safe with minimal side effects (weight gain of 3 kg in the first 12 months, hair loss and, rarely, diarrhea and flatulence are reported).[5] There are no data to suggest that ursodeoxycholic acid is teratogenic.[5]

Relevant trial data to support safety and efficacy of obeticholic acid are from studies spanning phase 2 and 3 drug development.[5] In a phase 2 randomized, double-blind, controlled trial of obeticholic acid in PBC, the therapeutic efficacy of three doses (10, 25 and 50 mg/day) as add-on therapy to ursodeoxycholic acid in patients having persistent elevations in serum alkaline phosphatase (>1.5 × ULN) was evaluated.[5] The primary endpoint was a significant reduction in serum alkaline phosphatase from baseline, and was met across all three doses of obeticholic acid versus placebo.[5] In a phase 3 clinical trial, patients with high-risk PBC (alkaline phosphatase >1.67 x ULN and/or elevated total bilirubin >2 x ULN) were evaluated in a placebo controlled RCT.[5] The primary endpoint during the 12-month double-blind period was attainment of both an alkaline phosphatase value <1.67 × ULN (with a ≥15% reduction from baseline) and a normal serum bilirubin.[5] In an intention-to-treat analysis, biochemical response was met in 10% of the placebo group and in 47% and 46% in the 10 mg and 5–10 mg dose-titrated obeticholic acid groups, respectively (P<0.0001 for both).[5] The mean decrease in serum alkaline phosphatase from baseline was 39% and 33% in the 10 mg and titrated OCA groups, respectively, versus 5% for patients in the placebo group (P<0.0001 for both).[5]

Treatment with obeticholic acid is associated with a dose-dependent exacerbation in pruritus leading to treatment discontinuation in 1–10% of patients.[5] These observations emphasize the importance of dose titration for symptom control.[5] Obeticholic acid-treated patients may also exhibit (reversible) alterations in serum lipid levels, most notably a small decrease in HDL.[5] It is not yet known whether these changes impact the long-term cardiovascular risk.[5]

Specific pharmacotherapy recommendations for PBC include:

- Oral ursodeoxycholic acid is recommended at 13–15 mg/kg/day as the first-line pharmacotherapy in all patients with PBC. If tolerated, treatment should usually be life-long (Strong Recommendation; High Quality of Evidence).[5]
- In patients with inadequate response or intolerance to ursodeoxycholic acid as defined by alkaline phosphatase >1.67 x ULN and/or elevated bilirubin 2 x ULN, the addition of obeticholic acid has been associated with improvements in biochemical surrogates of disease activity reasonably likely to predict improved outcomes.[5] Therefore, in keeping with the NICE evaluation of obeticholic acid, it is recommended the addition of obeticholic acid for patients with an inadequate response to ursodeoxycholic acid or intolerant of ursodeoxycholic acid, be considered.[5] Dose adjustment in patients with advanced liver disease as per the drug label is recommended. (Strong Recommendation; Low Quality of Evidence)[5]

After review, 1 guideline was excluded due to poor quality.[18]

New FDA Safety Alerts:
The FDA issued a drug safety communication on September 21, 2017 regarding the increased risk of hepatic injury and death due to incorrect dosing of obeticholic acid.[7] Some patients received excessive dosing, particularly a higher frequency of dosing than is recommended in the drug label.[7] Nineteen cases of death were identified, of which 8 provided information about the patient's cause of death.[7] The cause of death was reported to be worsening of PBC disease in seven cases, with cardiovascular disease cited in the other cases.[7] Seven of these 8 cases described patients with moderate to severe decreased liver function

who received obeticholic acid 5 mg daily, instead of a dose no greater than 10 mg twice weekly as recommended in the label prescribing information for patients with this extent of decreased liver function.[7] FDA also identified 11 cases of serious liver injury with obeticholic acid use.[7] Six of the patients who had moderate or severe decreases in liver function at baseline and developed serious liver injury were receiving obeticholic acid 5 mg daily, instead of a dose no greater than 10 mg twice weekly as recommended by FDA in the drug label at that time.[7] Three of these 6 patients died, which were included in the 19 death cases mentioned previously.[7] Obeticholic acid was discontinued in 4 of 6 cases, which resulted in one patient experiencing symptom resolution and an improvement in a liver blood test.[7] The remaining three cases did not report the response after discontinuation.[7] The other five cases of serious liver injury were reported in patients with no or mild decreases in liver function prior to initiating obeticholic acid.[7] Four of these five patients received obeticholic acid 5 mg daily, and one did not report the dose.[7] Obeticholic acid was discontinued in all 5 cases, which resulted in one patient experiencing symptom resolution and one patient experiencing improved liver blood tests and symptom resolution.[7] As a result of this FDA alert, the manufacturer added a boxed warning in February 2018 regarding risk of hepatic decompensation and failure in incorrectly dosed PBC patients with Child-Pugh Class B or C or decompensated cirrhosis.[8] The recommended dosing for patients with impaired hepatic function at that point in time was 5 mg once a week.[8]

The FDA issued a stronger safety advisory in May 2021 stating that due to the risk of serious hepatic injury, the use of obeticholic acid must be restricted in PBC patient with advanced cirrhosis.[9] In the 5 years since obeticholic acid's accelerated approval, FDA identified 25 cases of serious liver injury leading to liver decompensation or liver failure associated with obeticholic acid in PBC patients with cirrhosis, both in those without clinical signs of cirrhosis (compensated) or in those with clinical signs of cirrhosis (decompensated).[9] Many of these PBC patients had advanced cirrhosis before starting obeticholic acid.[9] The 25 cases include only those submitted to FDA and those found in the medical literature, so there may be additional cases about which the FDA is unaware.[9] All of these patients were taking obeticholic acid at recommended dosages.[9] After starting obeticholic acid, the pace of the liver decompensation or failure reported suggested these adverse events, which resulted in liver transplant in a small number of cases, were related to the drug rather than progression of the underlying PBC.[9] The manufacturer strengthened the boxed warning regarding risk of fatal hepatic injury to obeticholic acid prescribing information in May 2021.[10] Obeticholic acid is contraindicated in PBC patients with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia).[10]

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Obeticholic Acid	OCALIVA	2/2018	Boxed Warning	WARNING: HEPATIC DECOMPENSATION AND FAILURE IN INCORRECTLY DOSED PBC PATIENTS WITH CHILD-PUGH CLASS B OR C OR DECOMPENSATED CIRRHOSIS[8] • In Postmarketing reports, hepatic decompensation and failure, in some cases fatal, have been reported in patients with PBC with decompensated cirrhosis or Child-Pugh Class B or C hepatic impairment when OCALIVA was dosed more frequently than recommended.[8] • The recommended starting dosage of OCALIVA is 5 mg once weekly for patients with Child-Pugh Class B or C hepatic impairment or a prior decompensation event.[8]

Obeticholic Acid	OCALIVA	5/2021	Boxed Warning	WARNING: HEPATIC DECOMPENSATION AND FAILURE IN PRIMARY BILIARY CHOLANGITIS PATIENTS WITH CIRRHOSIS[10] • Hepatic decompensation and failure, sometimes fatal or resulting in liver transplant, have been reported with OCALIVA treatment in PBC patients with either compensated or decompensated cirrhosis.[10] • OCALIVA is contraindicated in PBC patients with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension(e.g., ascites, gastroesophageal varices, persistent thrombocytopenia).[10] • Permanently discontinue OCALIVA in patients who develop laboratory or clinical evidence of hepatic decompensation, have compensated cirrhosis and develop evidence of portal hypertension, or experience clinically significant hepatic adverse reactions while on treatment.[10]

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
ursodiol	ACTIGALL	ORAL	CAPSULE	Y
ursodiol	URSODIOL	ORAL	CAPSULE	Y
ursodiol	URSO	ORAL	TABLET	Y
ursodiol	URSO FORTE	ORAL	TABLET	Y
ursodiol	URSODIOL	ORAL	TABLET	Y
cholic acid	CHOLBAM	ORAL	CAPSULE	N
obeticholic acid	OCALIVA	ORAL	TABLET	N
ursodiol	RELTONE	ORAL	CAPSULE	N
chenodiol	CHENODAL	ORAL	TABLET	Not reviewed
dehydrocholic acid	DECHOLIN	ORAL	TABLET	Not reviewed

Appendix 2: New Comparative Clinical Trials

A total of 29 citations were manually reviewed from the initial literature search. After further review, 29 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to September Week 2 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to September 16, 2021

1.	Cholangitis/ or Non-alcoholic Fatty Liver Disease or Liver Cirrhosis, Biliary	23317
2.	Chenodeoxycholic Acid/ or "Bile Acids and Salts"/ or Ursodeoxycholic Acid/	12975
3.	Ursodeoxycholic Acid/	2952
4.	Cholic Acid	784
5.	obeticholic acid.mp.	457
6.	Dehydrocholic Acid/	37
7.	odexvixibat.mp	2
8.	Cholestasis, Intrahepatic/ or Biliary Atresia/	5344
9.	1 and 8	292
10.	2 or 3 or 4 or 5 or 6 or 7	13548
11.	9 and 10	29

Appendix 4: Prior Authorization Criteria

Cholic Acid (Cholbam™)

Goal(s):

- To ensure appropriate use of cholic acid in patients with bile acid synthesis disorders (BASDs) due to a single enzyme defects (SEDs) or as an adjunct to patients with peroxisomal disorders (PD), including Zellweger spectrum disorders, who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat-soluble vitamin absorption.

Length of Authorization:

- Up to 12 months

Requires PA:

Cholic acid

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 5
5. Is cholic acid prescribed by a hepatologist or pediatric gastroenterologist?	**Yes:** Go to # 6	**No:** Pass to RPh. Deny; not funded by the OHP.
6. Has baseline hepatic function been assessed? *The manufacturer recommends providers to monitor aspartate transaminase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), bilirubin, and international normalized ratio (INR) every month for the first 3 months of therapy, every 3 months for the next 9 months, every 6 months during the next 3 years and annually thereafter.[1]	**Yes:** Approve for 3 months. Document baseline hepatic function values (AST,ALT, Alk Phos, bilirubin) and date obtained:_____	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there evidence of improvement of primary biliary cholangitis, defined as: a. ALP <1.67-times the ULN; AND b. Decrease of ALP >15% from baseline: AND c. Normal total bilirubin level?	**Yes:** Document ALP and total bilirubin level. Go to # 2 ALP:_____ units/L Total Bilirubin _____ mg/dL	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
2. Has the patient's condition stabilized or improved as assessed by the prescribing provider?	**Yes:** Approve for 12 months.	**No**: Pass to RPh. Deny; medical appropriateness

1. Cholbam (cholic acid) capsules [Full Prescribing Information]. San Diego, CA: Retrophin, Inc. March 2015.

P&T/DUR Review: 12/21 (DM); 11/19 (DM)
Implementation: 1/1/2020

Obeticholic Acid (Ocaliva®)

Goal(s):
- Encourage use of ursodiol or ursodeoxycholic acid which has demonstrated decrease disease progression and increase time to transplantation.
- Restrict use to populations for which obeticholic acid has demonstrated efficacy.

Length of Authorization:
- Up to 12 months

Requires PA:
- Obeticholic acid

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this request for continuation of therapy previously approved by the FFS program (patient has already been on obeticholic acid)?	**Yes:** Go to Renewal Criteria	**No:** Go to #3

Approval Criteria		
3. Is the treatment for an adult with primary biliary cholangitis either: • without cirrhosis OR • with compensated cirrhosis who do not have evidence of portal hypertension (e.g. ascites, gastroesophageal varices, persistent thrombocytopenia)?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does patient have a documented intolerance or contraindication to ursodiol?	**Yes:** Document symptoms of intolerance or contraindication and go to #6.	**No:** Go to #5
5. Has patient had a 12-month trial of ursodiol with inadequate response to therapy (Alkaline phosphatase [ALP] ≥1.67-times the ULN or total bilirubin greater than the ULN)?	**Yes**: Document baseline ALP and total bilirubin level and go to # 6 ALP:_____ units/L Total Bilirubin _____ mg/dL	**No**: Pass to RPh. Deny; medical appropriateness
6. Is obeticholic acid dosed according to the guidelines outlined in Table 1?	**Yes:** Approve for 12 months	**No**: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there evidence of improvement of primary biliary cholangitis, defined as: a. ALP <1.67-times the ULN; AND b. Decrease of ALP >15% from baseline: AND c. Normal total bilirubin level?	**Yes**: Document ALP and total bilirubin level go to # 2 ALP:_____ units/L Total Bilirubin _____ mg/dL	**No**: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
2. Does dosing meet parameters outlined in Table 1?	**Yes**: Approve for up to 12 months	**No**: Pass to RPh. Deny; medical appropriateness

Table 1. Obeticholic Acid Dosing Regimen by Patient Population[1]

Staging/Classification	Non-Cirrhotic or Compensated Child-Pugh Class A	Patients with Intolerable Pruritus*	Decompensated cirrhosis (Child-Pugh Class B or C OR Patients with a Prior Decompensation Event (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia).
Initial dose for first 3 months	5 mg once daily	5 mg every other day for patients intolerant to 5 mg once daily 5 mg once daily for patients intolerant to 10 mg once daily Temporarily interrupt administration for 2 weeks. Restart at reduced dosage.	**Obeticholic acid therapy is contraindicated in these patients.**
Dose titration after first 3 months for patients who have not achieved adequate reduction in ALP and/or total bilirubin and who are tolerating obeticholic acid	10 mg once daily		
Maximum dose	10 mg once daily	5 mg once daily	

*Add an antihistamine or bile acid binding resin

1. OCALIVA (obeticholic acid) oral tablet Prescribing Information. New York, NY; Intercept Pharmaceuticals, Inc. May 2021.

P&T / DUR Review: *12/21 (DM); 01/17 (SS)*
Implementation: *4/1/17*