Drug Use Research & Management Program
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New Drug Evaluation: Obeticholic acid (Ocaliva®) film-coated oral tablet

Date of Review: January 2017
Generic Name: Obeticholic acid
PDL Class: unassigned

End Date of Literature Search: September 23, 2016
Brand Name (Manufacturer): Ocaliva® (Intercept Pharmaceuticals, Inc)
AMCP Dossier Received: Yes

Current Status of PDL Class: unassigned

Research Questions:

- What is the efficacy of obeticholic acid compared to currently available agents or is it superior to placebo for treatment of non-alcoholic steatohepatitis (NASH) and primary biliary cholangitis (PBC)?
- Is obeticholic acid safe for treatment of NASH or PBC?
- Are there any subgroups (i.e. age, gender, ethnicity, concomitant diabetes, disease duration or severity) that would particularly benefit or be harmed from treatment with obeticholic acid?

Conclusions:

- There is low quality evidence based on one phase 3 and one phase 2 clinical trial that obeticholic acid improves alkaline phosphatase (ALP) levels in patients with PBC and inadequate response to ursodeoxycholic acid (UDCA), also known as ursodiol. The majority of patients included in these trials were white females with normal bilirubin levels and a mean ALP of 323 units/L. Response to obeticholic acid (defined as ALP <1.67-times the upper limit of normal (ULN), ALP decrease >15%, and bilirubin level within normal limits) was achieved at 3 months in 41% (43/105) of patients taking obeticholic acid 10 mg daily in combination with ursodiol compared to 5% (5/106) of patients taking placebo (number needed-to-treat [NNT] =3).[1] Over 90% of participants remained on ursodiol during the trials.
- There is low quality evidence from a pooled analysis of clinical trial data conducted by the FDA that obeticholic acid improves ALP levels in patients with PBC intolerant to ursodiol. At 3 months, response to therapy (as defined above) was achieved in 35% (10/26) of patients taking obeticholic acid compared to 4% (1/28) of patients taking placebo.[1] Data is limited by the number of patients included in these trials and stringent criteria excluding patients with severe disease.
- Use of ursodiol at 13-15 mg/kg/day as first-line therapy for PBC has demonstrated decreased disease progression and increase time to liver transplantation.[2] There is insufficient evidence to evaluate long-term efficacy of obeticholic acid for PBC or evaluate efficacy in specific subgroups. The U.S. Food and Drug Administration (FDA) requires drug labeling to caution that continued approval for PBC may be contingent upon verification and description of clinical benefit in confirmatory trials.[3]
- There is insufficient evidence to evaluate efficacy or safety of obeticholic acid for off-label treatment of NASH. Clinical trial data are limited by small population sizes, use of un-validated surrogate endpoints, and lack of long-term outcomes.

Author: Sarah Servid, Pharm.D. Date: January 2016

- The FDA labeling includes warnings for severe pruritus and liver-related adverse effects. Severe pruritus occurred in 7%, 19%, and 23% of patients taking placebo, 5 to 10 mg of obeticholic acid, and 10 mg obeticholic acid, respectively.[1] Obeticholic acid use was also associated with a numerically greater number of liver-related adverse effects including new onset jaundice, ascites, PBC flares and biochemical changes typically indicative of hepatic injury.[1] Patients with complications from cirrhosis or hepatic decompensation were excluded from these trials. There is insufficient evidence to evaluate long-term safety of obeticholic acid for the treatment of PBC or NASH and long-term data are needed to determine the significance of harms observed in short-term phase 2 and 3 trials.

Recommendations:

- Incorporate the STC 05 Bile Therapy drugs (obeticholic acid, ursodiol, and cholic acid) into one PDL class.
- 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. No recommendations are made for other bile therapy medications at this time.
- Approve the proposed PA criteria 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 (**Appendix 2**).

Background:

Obeticholic acid is a drug which recently achieved accelerated approval by the FDA for treatment of primary biliary cholangitis (PBC; also known as primary biliary cirrhosis). It binds to the farnesoid X receptor in liver and intestinal cells which results in decreased production of bile and increased bile flow from the liver. Obeticholic acid currently does not have FDA approval for treatment of other liver conditions. However, it has been granted a breakthrough therapy designation from the FDA for nonalcoholic steatohepatitis (NASH).[4] Drugs may be designated as breakthrough therapy if preliminary evidence indicates they may demonstrate substantial improvement over available therapy for a serious condition.[5] Improvements can include clinically relevant endpoints, surrogate endpoints or change in pharmacodynamics biomarkers which indicate a potential for improved disease outcomes.[5] Because NASH is a common disease with few disease-altering treatment options, there is a large potential for off-label use of obeticholic acid. This review examines the evidence supporting efficacy and safety of obeticholic acid for treatment of PBC and for off-label treatment of NASH. Currently, bile therapies (including ursodiol, obeticholic acid, chenodiol, and cholic acid) have not been assigned to a preferred or non-preferred PDL status.

Primary biliary cholangitis is a relatively rare disease thought to be autoimmune in origin. PBC affects approximately 1.91 to 40.2 per 100,000 people and is most common in women.[1] It is characterized by anti-mitochondrial auto-antibodies which target biliary epithelial cells and cause antibody-mediated destruction of intrahepatic bile ducts and liver cells.[2] Clinically, elevation of a group of enzymes called alkaline phosphatase (ALP) is associated with biliary disease.[6] These enzymes are found in many body tissues including liver, bone, small intestine, kidneys, placenta and leukocytes.[6] In adults, about 80% of ALP found in serum comes from liver and bone tissue.[6] The mechanism of hepatic ALP release into circulation in patients with cholestatic disease is unclear but bile accumulation appears to increase hepatocyte synthesis of ALP.[6] Elevations of ALP more than 4-times ULN suggests a cholestatic disorder but lesser elevations (around 3-fold ULN) are relatively nonspecific and can occur in all types of liver disease, while mild elevations less than 1.5-times normal can be seen in normal patients without disease.[6] Diagnosis is based on presence of at least 2 of the following factors: evidence of chronic cholestasis such as persistently elevated ALP greater than 1.5-times ULN for more than 6 months, presence of anti-mitochondrial antibodies, or histological evidence of PBC upon biopsy.[2] Without treatment, progressive damage to biliary cells causes inflammation and eventually leads to fibrosis and liver failure. Prognosis varies depending on disease severity and duration. In patients with early stage disease, approximately 50% develop cirrhosis within 4 years and 15-25% develop liver failure within 5 years.[2] In another study of asymptomatic patients with PBC, the 10-year survival rate ranged from 50-70%.[2] In symptomatic patients, median survival time was 5 to 8 years after symptom

onset.[2] Factors that increase risk of progressive cirrhosis include bilirubin levels greater than 1 mg/dL and moderate to severe lymphocytic piecemeal necrosis upon biopsy.[2]

Prior to 2016, the only FDA approved medication for treatment of PBC was ursodiol. Use of ursodiol at 13-15 mg/kg/day has demonstrated decreased disease progression and increase time to liver transplantation.[2] Guidelines from the American Association for the Study of Liver Disease recommend ursodiol as a first-line therapy regardless of histologic stage.[2] Typically, improvement in liver function tests (LFTs) is seen within 2 weeks of starting therapy.[2] Further improvement can be observed over 6-9 months, though in some patients LFTs may continue to improve over the course of 2-5 years.[2] Common adverse effects of ursodiol include loose stools, headache and mild weight gain. Approximately 3% of patients are intolerant to therapy.[2,7] In addition, approximately 40% of patients have an inadequate response to ursodiol.[7] Inadequate or lack of response has previously been defined using multiple parameters. The current FDA-recommended definition of inadequate or non-response in PBC is less than 40% reduction in ALP levels at 12 months if baseline ALP levels are greater than 2-times ULN or a reduction less than 15% at 12 months if baseline ALP levels are between 1.67- and 2-times ULN.[1,7] These patients have a higher risk of disease progression and may benefit from further therapy to lower ALP levels and prevent long-term outcomes.[7] Standard therapy for patients with PBC also includes immunizations against hepatitis A and B, alcohol avoidance, symptom management, and prevention or treatment of cirrhosis complications.[2]

Obeticholic acid is indicated for PBC in combination with ursodiol in patients with inadequate response to therapy or as monotherapy in patients unable to tolerate ursodiol due to unacceptable adverse effects. It was approved on the basis of 2 phase 2 and one phase 3 RCT examining reduction in ALP levels. Validity of ALP as a surrogate endpoint can vary depending on the type and stage of liver disease, and correlation in later stages of PBC remains unclear.[7] In a retrospective analysis of patients taking ursodiol for PBC, patients with higher ALP levels one year after diagnosis were correlated with decreased survival at 10 years (84% in patients with ALP ≤2-times ULN vs. 64% in patients with ALP >2-times ULN).[8] Bilirubin levels above ULN are also correlated with reduced transplant-free survival at 10 years (86% with normal bilirubin vs. 41% bilirubin >ULN).[8] However, optimum reduction of ALP levels with treatment of PBC remains unclear and the minimum clinically important reduction in ALP has not been established for PBC. Criteria used in the phase 3 trial were based on the FDA-recommended definition of response (ALPO <1.67x ULN, ALP decrease >15%, and bilirubin ≤ULN). These levels were chosen based on retrospective analyses of ursodiol-treated patients which demonstrated that these specific ALP levels had greatest correlation with transplant-free survival.[1] Direct data evaluating clinically relevant outcomes such as mortality or liver disease progression has not been evaluated. Continued approval for PBC may be contingent upon future studies examining these outcomes.[3]

Nonalcoholic steatohepatitis is a form of nonalcoholic fatty liver disease (NAFLD) caused by an accumulation of triglycerides in the liver. NASH is estimated to be present in approximately 5% of the United States (U.S.) population and is strongly correlated with obesity.[9] Without treatment, approximately 11% of patients will develop cirrhosis over 15 years.[9] NASH is the also the most common cause of hepatocellular carcinoma in the U.S., and an estimated 7% of patients with cirrhosis due to NASH will develop carcinoma within 6.5 years.[9] Current standard of care for NASH includes lifestyle interventions, control of metabolic diseases such as diabetes, and use of vitamin E. However, current pharmacotherapy has not demonstrated improvement in disease progression or other long-term outcomes. Obeticholic acid represents one therapy which has the potential to modify disease progression, but current evidence is limited to 2 phase 2 trials. The primary outcomes examined in these trials were insulin sensitivity in patients with concomitant diabetes and the NAFLD activity score. The NAFLD activity score evaluates NASH severity based on histological assessment with scores ranging from 0 to 8.[10] Scores are assigned based on the following categories: steatosis (0-3), lobular inflammation (0-3), and hepatocellular ballooning (0-2).[9] Fibrosis stage is not included in the NAFLD activity score and is determined separately. The NAFLD activity score has not been correlated with long-term outcomes in PBC, and the minimally important clinically significant difference has not been determined.

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See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Primary Biliary Cholangitis

Obeticholic acid for treatment of PBC was approved on the basis a 12-month phase 3 placebo-controlled trial and 2 supporting 3-month phase 2 dose-response trials. Response to obeticholic acid was defined as a composite endpoint of ALP less than or equal to 1.67-times ULN, a total bilirubin within normal limits, and an ALP decrease of at least 15% from baseline.[1] Criteria were chosen based on retrospective analyses demonstrating these specific ALP levels had greatest correlation with clinical outcomes of transplant-free survival.[1] Secondary outcomes for these trials included evaluation of other liver function tests and adverse effects associated with therapy.

The majority of patients enrolled in these trials were white females taking concomitant ursodiol therapy. Of the patients enrolled in the phase 3 trial (n=216), only 16 patients (7%) were taking obeticholic acid as monotherapy.[11] Phase 2 trials included an additional 59 patients who took obeticholic acid as monotherapy. Due to stringent inclusion and exclusion criteria, the majority of patients enrolled in these trials had mild or early disease.[11] Patients with bilirubin greater than 2-times ULN, decompensated liver disease or complications of cirrhosis, were excluded from the trials.[11,12] Mean baseline ALP in the phase 3 trial was 323 units/L (less than 3-times ULN), and 92% of patients had a bilirubin level within normal limits.[1,11] Patients enrolled in phase 2 trials had similar baseline disease severity.

Overall, the phase 3 study used for FDA approval had low risk of bias. The study was adequately randomized and blinded with balanced baseline characteristics. Overall, attrition was low but was more common in treatment groups.[11] Missing data in the phase 3 trial were classified as non-responders providing a more conservative estimate of treatment effect.[11] Risk of reporting bias was low, and data analyses were performed by a contracted research company. Phase 2 trials were similarly designed.[12] One phase 2 trial evaluating monotherapy for obeticholic acid remains unpublished. Data from this unpublished trial were included in the FDA summary review but limited information concerning trial design was available from the literature.[1] The phase 2 trials also had higher attrition rates with more frequent discontinuations associated with higher doses of obeticholic acid.[12] Data available from the published phase 2 trial were also imputed using last observation carried forward which may increase risk of bias by overestimating the treatment effect of obeticholic acid.[12]

FDA analysis for efficacy included only patients taking the approved dose of 5 or 10 mg.[1] In phase 2 and 3 trials, response to therapy was achieved at 3 months in 41% (43/105) of patients taking obeticholic acid 10 mg once daily in combination with ursodiol compared to 5% (5/106) of patients taking placebo and ursodiol.[1] In patients taking obeticholic acid 10 mg as monotherapy, 35% (10/26) of patients responded to treatment (see definition above) compared to 4% (1/28) of patients taking placebo.[1] A similar effect was observed at 12 months, with 46-47% of patients achieving a response with obeticholic acid 10 mg daily monotherapy compared to 10% of patients taking placebo.[1,11] Sensitivity analyses using worse case scenarios and more stringent thresholds of response demonstrated similar benefits with obeticholic acid.[1] Because the majority of patients enrolled in these trials had a normal bilirubin level at baseline, the composite outcome was primarily driven by the change in ALP. Similar reductions were observed with gamma-glutamyl transpeptidase (GGT) and aspartate aminotransferase (AST) levels compared to baseline.[1] Because the majority of patients enrolled in these trials had early or mild disease, the applicability of this evidence to patients with more severe disease is limited. In a systematic review conducted by the Institute for Clinical and Economic Review including data from these 3 trials, subgroup analyses based on disease severity were conducted.[7] Results from these analyses indicate that patients with abnormal bilirubin at baseline (n=21) had significant reductions compared to placebo at 12 months (-0.5 mg/dL vs. 0.04 mg/dL, respectively; $p<0.05$) though differences were not observed initially at 3 months.[7] In addition, stratification based on ALP levels demonstrated persistent ALP reduction in patients with baseline ALP levels

between 1-2-times ULN up to values greater than 4-times ULN.[7] These results must be interpreted with caution because of the limited number of patients included in these analyses and because data were primarily drawn from unpublished conference abstracts and poster presentations. In addition, these trials enrolled a limited number of patients who were taking obeticholic acid as monotherapy. The FDA notes that the results from these trials provide preliminary data supporting use of obeticholic acid as monotherapy in PBC but that additional confirmatory trials should be conducted.[1] Recommended post-marketing requirements for the drug include trials to confirm efficacy and safety as monotherapy for PBC, analysis of efficacy and safety in patients with more severe liver disease or hepatic impairment, and confirmation of an association with long-term clinical outcomes such as disease progression, complications of cirrhosis, transplantation, and mortality.[1] Further post-marketing requirements include development of a daily dose formulation for patients with hepatic impairment and participation in the Risk Evaluation and Mitigation Strategies program.[1]

Nonalcoholic Steatohepatitis

The majority of evidence to support the off-label use of obeticholic acid 25 mg daily for treatment of NASH comes from one phase 2, randomized, double-blind placebo-controlled trial (FLINT) that examined improvement in liver histology over the course of 72 weeks (n=238).[10] Results from a smaller phase 2 trial in patients with NASH and diabetes also provide supporting evidence for off-label use of obeticholic acid for NASH.[9] The primary endpoint in the FLINT trial was improvement in the NAFLD activity score of at least 2 points without worsening of fibrosis.[10] Other secondary, clinically-relevant endpoints included improvement in fibrosis stage, liver function tests, health-related quality of life, and adverse effects.[10]

Patients included in the FLINT trial were an average age of 52 years; 80% had a definite diagnosis of NASH, 53.5% had diabetes and more than 60% had hypertension and hyperlipidemia.[10] Patients were included in the trial if they had a total NAFLD activity score of at least 4 of 8 total points with at least 1 point in each category of steatosis, lobular inflammation, and hepatocellular ballooning.[10] Mean fibrosis stage at baseline was 1.9 (SD 1.1) and approximately 22% of patients evaluated had stage 3 fibrosis. Patients were excluded if they had other liver or biliary disease, alcohol or substance abuse, hepatic decompensation, HIV, or diabetes with a hemoglobin A1c greater than 9.5%.[10]

Risk of bias in this trial was low with adequate randomization, blinding and reporting. Risk of attrition bias was high because positive results at an interim analysis resulted in early discontinuation of biopsies for the primary outcome. Biopsies to assess histological improvement of NASH were not performed in 64 patients.[10] Exclusion of these patients from the analysis may result in more favorable efficacy outcomes for the drug. However, of the patients with a biopsy upon study completion, more patients treated with obeticholic acid had improved liver histology (measured by NAFLD activity score) compared with placebo (RR 2.2, 95% CI 1.4 to 3.3, p=0.0002; ARR 24%; NNT 4).[10] Clinical implications of this change are unclear as the NAFLD activity score has not been correlated with clinical outcomes and a minimum clinical important difference has not been determined. Similarly, fibrosis scores improved in patients treated with obeticholic acid compared to placebo (RR 2.0, 95% CI 1.2 to 3.4; p=0.004; NNT=6).[10] However, resolution of NASH with persistent NAFLD or resolution of NAFLD failed to reach statistical significance (RR 1.7, 95% CI 0.9 to 3.2; p=0.08), and there was no difference in health-related quality of life scores between groups.[10]

Overall, these results demonstrate obeticholic acid may be a potential therapy for improvement of NASH. However, evidence is limited by limited a sample size, short duration, and lack of long-term clinical outcomes of cirrhosis. Discontinuations due to adverse events were not reported in the FLINT trial, but other studies have demonstrated higher rates of pruritus with higher doses. These adverse effects may be especially important when determining long-term adherence to therapy. Though these early trials demonstrate potential for use of obeticholic acid for treatment of NASH, many questions remain regarding the long-term efficacy and adverse effects. In addition, use of surrogate endpoints limits applicability of current evidence. Further trials will need to be conducted to establish efficacy in NASH and better evaluate safety of this therapy in NASH.

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Clinical Safety:

Safety analyses included all patients from phase 2 and 3 trials with supporting data from trials in healthy volunteers, extension studies, and studies for treatment of NASH. The most common adverse event observed in clinical trials was pruritus occurring in 38% of placebo patients, 56% in patients titrated from 5 mg to 10mg obeticholic acid, and 68% in patients given 10 mg obeticholic acid.[13] Severe pruritus occurred in 7%, 19%, and 23% of patients in the placebo group, obeticholic acid titration group, and 10 mg obeticholic acid group, respectively.[13] Management strategies employed in these trials included use of bile acid sequestrants, anti-pruritic agents, drug holidays, dose reductions and gradual titrations.[1] Pruritus was also the most common reason for treatment discontinuation. A dose dependent decrease in high density lipoprotein (HDL-C) was also observed with obeticholic acid.[13] Mean decrease in HDL-C in 10 mg treatment groups was approximately 10-20 mg/dL from a baseline of 70-80 mg/dL.[1] The clinical implications of this decrease remain uncertain as cardiovascular adverse events were not compared in these short-term trials. However, given the large change in HDL-C, further monitoring and evaluation may be warranted. Serious adverse events were also more common in patients taking obeticholic acid compared to placebo. In patients taking 10 mg obeticholic acid, the rate of serious adverse events was 5.2 events per 100 patient years compared to 2.4 events in the placebo group.[3] In addition, incidence of hepatic adverse events was more common in patients taking obeticholic acid compared to placebo. Rates of hepatic adverse events for placebo, 5 to 10 mg titration, and 10 mg groups were 2.4%, 4.5% and 5.2%, respectively.[13] These events even more frequently at higher doses of 25 mg and 50 mg (above approved 5 and 10 mg dose).[1] Events included new onset jaundice, ascites, PBC flares, and biochemical changes typically indicative of hepatic injury.[13] These events may be due to progressive disease though the imbalance between treatment and placebo groups indicates these adverse events could be drug-related. These adverse liver events are especially noteworthy as correlation to long-term clinical outcomes has not been established. In addition patients with complications of cirrhosis and hepatic decompensation were excluded from these clinical trials. A warning for adverse hepatic events is included in the labeling.[1] Recommendations also include dose adjustment in patients with moderate or severe hepatic impairment and a post-marketing trial confirming efficacy and safety in this population. Further data from long-term safety extension studies found similar rates of serious adverse events between treatment groups without any obvious trends or underlying pathology. Only 2 deaths occurred during the course of the clinical trials in patients takin obeticholic acid, both of which were thought to be unrelated to study treatment.[1]

Pharmacology and Pharmacokinetic Properties:[3]

Parameter	
Mechanism of Action	Obeticholic acid is an agonist at the farnesoid X receptor, a nuclear receptor located in liver and intestinal cells. Activation of this receptor results in decreased levels of bile via suppression of bile production from *de novo* cholesterol synthesis and increased biliary transport out of the liver.
Absorption	T_{max}: parent drug = 1.5 hours; active metabolites = 10 hours Food has no effect on bioavailability
Distribution and Protein Binding	Protein binding >99% V_d=618 liters
Metabolism	Conjugation with glycine or taurine in the liver to form active metabolites which undergo enterohepatic circulation.
Elimination	87% feces <3% urine

Abbreviations: T_{max}=time to maximal concentration, V_d=volume of distribution

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Mortality
2) Liver disease progression (fibrosis) or time to liver failure
3) Complications of cirrhosis (liver transplant, hospitalizations, hepatic encephalopathy, hepatorenal syndrome)
4) Health-related quality of life
5) Early discontinuation due to adverse events
6) Serious adverse events

Primary Study Endpoint:
1) "Response" to treatment defined as: ALP < 1.67-times ULN; reduction of ALP ≥15% from baseline; AND total bilirubin level within normal limits.

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Nevens, et al.[11] Phase 3, DB, PC, PG, RCT	1. OCA 10 mg daily 2. OCA 5 mg daily titrated to 10 mg daily at 6 months if lacking ADE with inadequate treatment response 3. PBO 1:1:1 12 months	Demographics: - Mean age: 56 years - Female: 91% - White: 94% - Ursodiol use: 93% - Mean ALP 323 units/L - Bilirubin <ULN: 92% Key Inclusion Criteria: - PBC diagnosis consistent with AASLD and EASL guidelines* - Adults ≥18 years of age - ALP ≥1.67x ULN or bilirubin >ULN - Baseline ursodiol therapy x12 months or intolerance to ursodiol (off ursodiol for ≥3 months) Key Exclusion Criteria: - H/o other liver disease - Bilirubin >2x ULN - Complications of cirrhosis or hepatic decompensation (MELD ≥15, awaiting transplant, portal hypertension, hepatorenal syndrome) - H/o severe pruritus - Concurrent fibrates, antibody therapy or immunosuppressants, other hepatotoxic medications - Prolonged QTc >500ms	ITT: 1. 73 2. 71 3. 73 mITT (all patients receiving at least 1 dose): 1. 73 2. 70 3. 73 Attrition: 1. 9 (12%) 2. 7 (10%) 3. 3 (4%)	Primary Endpoint: Response to treatment (ALP <1.67x ULN, ALP decrease >15%, and bilirubin ≤ULN) 1. 34 (47%); OR 9.4 (95% CI 3.7 to 23.9) vs. PBO 2. 32 (46%); OR 9.1 (95% CI 3.6 to 23.2) vs. PBO 3. 7 (10%); p<0.001 for both groups vs. PBO Secondary Endpoints at 12 months: Change in AST (units/L) 1. -14.0 (SD 99.3) LSMD -16.0 (SE 3.9) 2. -12.5 (SD 14.1) LSMD -14.1 (SE 3.8) 3. 3.0 (SD 31.7) p<0.001 for both groups vs. PBO Change in ALT (units/L) 1. -24.4 (SD 26.6) LSMD -20.4 (SE 3.1) 2. -22.3 (SD 21.2) LSMD -16.3 (SE 3.0) 3. -3.9 (SD 20.0) p<0.001 for both groups vs. PBO Change in ALP (units/L) 1. -117.7 (SD 73.3) LSMD -115.5 (SE 13.2) 2. -103.5 (SD 87.0) LSMD -98.1 (SE 13.1) 3. -7.7 (SD 88.0) p<0.001 for both groups vs. PBO	1. ARR: 37% NNT: 3 2. ARR: 36% NNT: 3 NA NA NA	Serious AE: 1. 8 (11%) 2. 11 (16%) 3. 3 (4%) p-value NR DC due to AE: 1. 8 (11%) 2. 4 (6%) 3. 2 (3%) p-value NR Pruritus 1. 50 (68%) 2. 39 (56%) 3. 28 (38%) p-value NR	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Randomization via IWRS; stratified by risk criteria (ALP, AST, bilirubin levels) and ursodiol use. Balanced baseline characteristics. Performance Bias: LOW. Patient and investigators blinded via matching placebo. Blinding of assessors not stated. Use of objective laboratory outcomes minimizes bias. Detection Bias: LOW. Blinding of assessors was not stated, but use of objective laboratory outcomes minimizes risk of bias. Study appeared adequately powered for defined endpoint. Attrition Bias: LOW. Overall attrition was low, but was higher in treatment groups (10-12% vs. 4%). Data analyzed using mITT with missing data classified as non-responders giving a more conservative estimate of effect. Reporting Bias: LOW. All specified outcomes reported. Study was funded by Intercept who was involved in trial design, data collection, and writing the manuscript. Data management and statistical analysis performed by third-party. **Applicability**: Patient: moderate/ severe disease, decompensation or complications of cirrhosis were excluded. Majority of patients were white limiting applicability to other populations. Intervention: 93% of patients on ursodiol; 50% in group #2 increased to 10 mg at 6 months. Comparator: Placebo appropriate. Outcomes: Composite surrogate outcomes used to define treatment response. Individual components of the composite NR individually. Unclear if decrease of ALP observed (~100 units/L) would be associated with long-term outcomes. Minimum important changes in ALP has not been established for PBC. Setting: 59 sites in 13 countries from March 2012 to December 2013. 15 sites were in the

				Change in total bilirubin (mg/dL) 1. -0.07 (SD 0.25) LSMD -0.17 (SE 0.04) 2. -0.03 (SD 0.20) LSMD -0.13 (SE 0.04) 3. 0.08 (SD 0.24) P<0.001 for both groups vs. PBO	NA			United States but the exact percent of US patients was not reported.
2. Hirschfield, et al.[12] Phase 2, DB, PC, dose-response, RCT	1. OCA 10mg daily 2. OCA 25 mg daily 3. OCA 50 mg daily 4. Placebo 1:1:1:1 3 months Upon completion patients could enroll in an open-label extension study for up to 12 months	Demographics: - Female: 95% - White: 96% - Mean age: 55 years - Mean bilirubin 0.2 mg/dL - Mean ALP 287 units/L - Mean ursodiol dose 15.6-16.3 mg/kg/day Key Inclusion Criteria: - Age: 18-75 years - Diagnosis of PBC consistent with AASLD and EASL guidelines* - Stable dose of ursodiol for at least 6 months - ALP of 1.5-10x ULN Key Exclusion Criteria: - AST or ALT >5x ULN - Bilirubin >2x ULN - SCr > 1.5 mg/dL - H/o or presence of hepatic decompensation - Other liver diseases - Concurrent use of colchicine, methotrexate, azathioprine or systemic corticosteroids	ITT: 1. 38 2. 48 3. 41 4. 38 mITT (all patients who had a post-baseline ALP <7 days after last dose): 1. 38 2. 47 3. 39 4. 37 Attrition: 1. 6 (16%) 2. 6 (13%) 3. 16 (39%) 4. 1 (3%)	Primary Endpoint: Mean % change in ALP from baseline to 3 months 1. 24% (95% CI -30% to -18%) 2. 25% (95% CI -30% to -20%) 3. 21% (95% CI -30% to -12%) 4. 3% (95% CI -7% to 2%) RR not reported; p-value <0.0001 for all groups vs. PBO	NA	SAE: 1. 0 (0%) 2. 1 (2.1%) 3. 5 (12.2%) 4. 1 (2.6%) p-value NR DC due to AE: 1. 5 (13.2%) 2. 5 (10.4%) 3. 15 (36.6%) 4. 1 (2.6%) p-value NR Pruritus 1. 47% p=NS 2. 85% p<0.0003 3. 80% p<0.006 4. 50%	NA NA 1. NA 2. ARR: 0.35 NNH: 3 3. ARR: 0.30 NNH: 3	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Computer randomization using a block size of 4 for each center. Allocation concealment was not stated. Performance Bias: LOW. Patients and providers blinded with use of matching placebo. Detection Bias: LOW. Blinding of assessors not stated. Use of objective laboratory outcomes limits risk of bias. Attrition Bias: HIGH. More patients in OCA groups discontinued treatment (13-39%) vs placebo (2.6%). P-values not reported. Missing values imputed using last observation carried forward which may overestimate treatment effect. Study appeared appropriately powered. Reporting Bias: HIGH. Funded by Intercept Pharmaceuticals who assisted with finalization of analysis, data presentation, and manuscript submission. **Applicability**: Patient: Inclusion of only patients with mild disease limits applicability to patients with moderate or severe disease. Limited inclusion of minority populations and male gender. Intervention: Patients maintained ursodiol therapy throughout trial. FDA approved dose was only studied in 38 patients. Comparator: Placebo appropriate to establish efficacy. Outcomes: Use of ALP as surrogate for response to treatment. Limited duration of 3 months may not capture full therapeutic effect. Effect on long-term clinical outcomes is unclear. Setting: 41 centers in North America and Europe from November 2007 to May 2009.

3. Neuschwander-Tetri, et al.[10] Phase 2, MC, PC, RCT	1. OCA 25 mg daily 2. Placebo 1:1 72 weeks with 24 weeks follow-up	Demographics: - Mean age: 51.5 years - HLD: 62.5% - HTN: 61% - DM: 53.5% - Definite NASH: 80% - Mean fibrosis stage: 1.9 - Stage 3 fibrosis: 22% - Mean NAFLD activity score: 5.2 Key Inclusion Criteria: - Histological evidence of definite or borderline NASH - Histological NAFLD total activity score ≥ 4 and ≥1 in individual categories Key Exclusion Criteria: - Cirrhosis or clinical evidence of hepatic decompensation - Other cause of liver disease - Alcohol consumption > 20 g/day for women or >30 g/day for men - Confounding conditions (Bile duct obstruction, PBC, ALT > 300 U/L, SCr >2 mg/dL, DM with A1C >9.5%, HIV, life expectancy <5 years, substance abuse)	ITT: 1. 141 2. 142 PP (included patients with a final biopsy): 1. 110 2. 109 Attrition: 1. 8 (7.3%) 2. 11 (10.1%)	Primary Endpoint: Improvement in liver histology (decrease in NAFLD activity score ≥2 without worsening of fibrosis) 1. 50 (45%) 2. 23 (21%) RR 2.2 (95% CI 1.4 to 3.3) p=0.0002 Secondary Endpoints: Resolution of NAFLD OR resolution of NASH with persistent NAFLD in patients w/definite NASH at baseline 1. 22 (22%) 2. 13 (13%) RR 1.7 (95% CI 0.9 to 3.2) p=0.08 Improvement in fibrosis score: 1. 36 (35%) 2. 19 (19%) RR 2.0 (95% CI 1.2 to 3.4) P=0.004	ARR: 24% NNT: 4 NA ARR: 16% NNT: 6	Serious AE: 1. 30 (27.3%) 2. 21 (19.3%) p-value NR DC due to AE: NR Mortality 1. 2 (1.8%) 2. 0 (0%) p-value NR Pruritus 1. 33 (23%) 2. 9 (6%) p<0.0001	NA NA NA ARR: 0.17 NNH: 6	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Randomized centrally by computer generated procedure; stratified by site and diabetes status and blocked by date. Baseline characteristics generally balanced. Performance Bias: LOW. Use of matching placebo. Patients, investigators, clinical staff and pathologists were blinded. Detection Bias: LOW. Biopsies centrally assessed by blinded committee of pathologists that scored NAFLD activity, fibrosis stage and NASH. Attrition Bias: HIGH. Biopsy analysis d/c'd early because an interim analysis achieved superiority (64 patients did not have final biopsies and were excluded from the analysis). Overall attrition was similar between groups. Missing values imputed as non-responders providing a more conservative estimate of effect. Reporting Bias: LOW. Study funded by Intercept Pharmaceuticals and the National Institute of Diabetes, Digestive and Kidney Diseases. Intercept provided comments on the protocol but was not involved in the study design, analyses or publication. **Applicability**: Patient: Patients with hepatic decompensation were excluded. Mean fibrosis stage was 1.9. Intervention: Currently only 5 and 10 mg tablets are marketed. Comparator: Placebo appropriate to determine efficacy. Outcomes: NAFLD activity score has not been correlated with clinical outcomes and a minimum clinically important difference has not been determined. Limited duration trial with no data on long-term outcomes of cirrhosis. Setting: 8 sites in the USA from March 2011 to December 2012.

Abbreviations [alphabetical order]: AE = adverse effects; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ARR = absolute risk reduction; AST = aspartate aminotransferase; CI = confidence interval; DC = discontinuation; DB = double-blind; DM = diabetes mellitus; HIV = human immunodeficiency virus; H/o = history of; IWRS = interactive web response system; ITT = intention to treat; LSMD = least squares mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic steatohepatitis; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; OCA = obeticholic acid; PBC = primary biliary cirrhosis; PBO = placebo; PC = placebo-controlled; PG = parallel-group; QOL = quality of life; SAE = severe adverse effects; SCr = serum creatinine; SD = standard deviation; SE = standard error; ULN = upper limit of normal

*Diagnosis of PBC includes ≥2 of the following: increased ALP levels, positive antibody titers (anti-mitochondrial antibodies > 1:40 or PBC-specific antinuclear antibodies), or liver biopsy consistent with PBC.

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13. Obeticholic Acid Medical Review. US Food and Drug Administration Center for Drug Evaluation and Research. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/207999Orig1s000MedR.pdf. Accessed Sepetmber 22, 2016.

Appendix 1: Highlights of Prescribing Information

OCALIVA- obeticholic acid tablet, film coated
Intercept Pharmaceuticals Inc

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OCALIVA safely and effectively. See full prescribing information for OCALIVA.

OCALIVA (obeticholic acid) tablets, for oral use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

OCALIVA, a farnesoid X receptor (FXR) agonist, is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy 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 verification and description of clinical benefit in confirmatory trials. (1)

DOSAGE AND ADMINISTRATION

- Starting Dosage: The recommended starting dosage of OCALIVA is 5 mg orally once daily in adults who have not achieved an adequate response to an appropriate dosage of UDCA for at least 1 year or are intolerant to UDCA. (2.1)
- Dosage Titration: If adequate reduction in ALP and/or total bilirubin has not been achieved after 3 months of OCALIVA 5 mg once daily and the patient is tolerating OCALIVA, increase dosage to 10 mg once daily. (2.1)
- Maximum Dosage: 10 mg once daily (2.1, 5.1)
- Management of Patients with Intolerable Pruritus: See full prescribing information for management options. (2.2)
- Hepatic Impairment: See full prescribing information for dosage adjustment in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). (2.3)

Administration Instructions

- Take with or without food. (2.4)
- For patients taking bile acid binding resins, take OCALIVA at least 4 hours before or 4 hours after taking a bile acid binding resin, or at as great an interval as possible. (2.4, 7.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg, 10 mg (3)

CONTRAINDICATIONS

Patients with complete biliary obstruction (4)

WARNINGS AND PRECAUTIONS

- Liver-Related Adverse Reactions: Monitor for elevations in liver biochemical tests and development of liver-related adverse reactions; weigh the potential risk against the benefits of continuing treatment. Do not exceed 10 mg once daily. Adjust the dosage for patients with moderate or severe hepatic impairment. Discontinue in patients who develop complete biliary obstruction. (2.3, 4, 5.1)
- Severe Pruritus: Management strategies include the addition of bile acid binding resins or antihistamines; OCALIVA dosage reduction and/or temporary dosing interruption. (2.2, 5.2)
- Reduction in HDL-C: Monitor for changes in serum lipid levels during treatment. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (≥ 5%) are: pruritus, fatigue, abdominal pain and discomfort, rash, oropharyngeal pain, dizziness, constipation, arthralgia, thyroid function abnormality, and eczema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Intercept Pharmaceuticals at 1-844-782-ICPT or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Warfarin: Potential for decreased INR; monitor INR and adjust the dosage of warfarin, as needed, to maintain the target INR range. (7.2)
- CYP1A2 Substrates with Narrow Therapeutic Index (e.g., theophylline and tizanidine): Potential for increased exposure to CYP1A2 substrates; monitor drug concentrations of CYP1A2 substrates with narrow therapeutic index. (7.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2016

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
3. Is the treatment for primary biliary cholangitis?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have no evidence of complications from cirrhosis or hepatic decompensation (e.g., MELD score <15; not awaiting transplant; no portal hypertension; or no hepatorenal syndrome)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Is the total bilirubin level <2-times the upper limit of normal (ULN)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Does patient have a documented intolerance or contraindication to ursodiol?	**Yes:** Document symptoms of intolerance or contraindication and approve for up to 12 months	**No:** Go to #7
7. Has patient had a 12-month trial of ursodiol with inadequate response to therapy (ALP ≥1.67-times the ULN or total bilirubin greater than the ULN)?	**Yes**: Document baseline ALP and total bilirubin level and appprove for up to 12 months ALP:_____ units/L Total Bilirubin _____ mg/dL	**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 and approve for up to 12 months ALP:_____ units/L Total Bilirubin _____ mg/dL	**No**: Pass to RPh. Deny; medical appropriateness

P&T / DUR Review: *01/17*
Implementation: *TBD*