



## Obeticholic acid (Ocaliva™) New Drug Update

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June 2016

<b>Drug Name:</b>	<b>obeticholic acid (OCA)</b>
<b>Trade Name (Manufacturer):</b>	<b>Ocaliva (Intercept)</b>
<b>Form:</b>	Oral tablet
<b>Strength:</b>	5 mg and 10 mg
<b>FDA Approval:</b>	May 27, 2016
<b>Market Availability:</b>	Available via a specialty pharmacy network
<b>FDA Approval Classification:</b>	Priority review; Fast track designation; Orphan drug designation
<b>Classification:</b>	Specific Therapeutic Class (HIC3) – Farnesoid X receptor agonist, bile acid analog (D7E)

### INDICATION<sup>1</sup>

Obeticholic acid (Ocaliva) is a farnesoid X receptor (FXR) agonist approved for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA (defined as a trial of at least 1 year), or as a single therapy in adults unable to tolerate UDCA.

The 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.

### DISEASE BACKGROUND<sup>2</sup>

Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is a rare, chronic autoimmune disease characterized by chronic cholestasis and progressive impaired bile acid secretion from the liver. PBC is typically diagnosed between the ages of 40 and 60. It affects more women than men and is the second leading cause of liver transplant in women in the United States. 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. The presence of antimitochondrial antibodies (AMA) is also a common feature of PBC, occurring in approximately 90% of patients. Probable PBC can be diagnosed based on serum ALP and AMA levels. Liver biopsy is not required for diagnosis according to the American Association for the Study of Liver Diseases (AASLD).<sup>3</sup>

The FXR is found in the nucleus of cells primarily in the liver and intestine.<sup>4</sup> Activation of FXR regulates bile acid homeostasis enterohepatically, as well as inflammation and fibrosis in response to liver injury. Obeticholic acid is a semisynthetic derivative of the primary human bile acid chenodeoxycholic acid (CDCA), the natural agonist of FXR.<sup>5</sup> Obeticholic acid 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.

## CONTRAINDICATIONS/WARNINGS

Obeticholic acid is contraindicated in patients with complete biliary obstruction.

Liver-related adverse reactions including jaundice, worsening ascites and primary biliary cholangitis flare were reported in clinical trials with daily doses of obeticholic acid of at least 10 mg. Liver function tests should be monitored during treatment with obeticholic acid. Discontinue if complete biliary obstruction occurs.

Severe widespread pruritus, typically requiring medical attention, has been reported in clinical trials. Mean onset was 11 days in patients taking obeticholic acid 10 mg, 158 days in those titrated from 5 mg to 10 mg, and 75 days for patients taking placebo. 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, with varying incidence and severity reported; symptoms may subside spontaneously with progression to cirrhosis and hepatic decompensation. Other therapies include rifampin, and in resistant cases, biliary drainage may be considered.<sup>6</sup>

Dose-dependent reductions in high-density lipoprotein cholesterol (HDL-C) were reported. In clinical trials, this occurred in 20% of patients in the obeticholic acid 10 mg arm, 9% in the obeticholic acid titration arm, and 2% in the placebo arm; at 12-months the proportion of patients in each arm remained relatively unchanged. Serum lipid levels should be monitored during treatment. The potential risk versus benefits of continued treatment should be considered in patients who experience reductions in HDL-C and have not had an adequate response to obeticholic acid therapy. It is important to note that hyperlipidemia, with increases in both HDL-C and low-density lipoprotein cholesterol (LDL-C), is a common feature of PBC.

## DRUG INTERACTIONS

Bile acid resins (cholestyramine, colestipol, colesevelam) may reduce the absorption and efficacy of obeticholic acid. Timing of dosing of obeticholic acid and a bile acid resin should be separated by at least 4 hours.

Coadministration of warfarin and obeticholic acid may result in decreased international normalized ratio (INR). Monitor INR and adjust warfarin dose as needed.

Obeticholic acid may increase the exposure of CYP1A2 substrates when taken concomitantly; therefore, therapeutic monitoring of a CYP1A2 substrate with a narrow therapeutic index should be performed.

## COMMON ADVERSE EFFECTS

The most common adverse events reported in clinical trials ( $\geq 10\%$ ) are pruritus (56% to 70%; 38% for placebo), fatigue (19% to 25%; 15% for placebo), abdominal pain (10% to 19%; 14% for placebo), rash (7% to 10%; 8% for placebo), and arthralgia (6% to 10%; 4% for placebo).

## SPECIAL POPULATIONS

### Pregnancy

There are limited available human data regarding obeticholic acid use in pregnant women to inform users of drug-associated risks. There were no developmental abnormalities or fetal harm observed in animal studies.

### Pediatrics

The safety and effectiveness has not been established in pediatric patients.

### Geriatrics

No adjustment in dosage is required.

### Hepatic Impairment

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. Monitor patients for elevated liver function tests and development of liver-related adverse reactions.

### Renal Impairment

Obeticholic acid has not been studied in patients with moderate and severe renal impairment.

## DOSAGES

The recommended initial dose is 5 mg taken orally once daily with or without food. After 3 months, if an inadequate reduction in ALP and/or total bilirubin has not been achieved, and therapy is tolerated, the dose can be increased to 10 mg once daily, if tolerated. The daily dose should not exceed 10 mg.

For management of patients with intolerable pruritus due to obeticholic acid therapy, consider one of the following:

- addition of an antihistamine or bile acid binding resin
- reduction of obeticholic acid dose – doses of 5 mg every other day may be given to patients intolerant to daily doses of 5 mg
- temporary disruption of obeticholic acid for up to 2 weeks, with a dose reduction upon restarting therapy
- discontinuation of obeticholic acid therapy if intolerable pruritus persists

For patients with moderate to severe hepatic impairment (Child-Pugh B and C), the recommended starting dose is 5 mg once weekly. After 3 months, the dosage may be increased to 5 mg twice weekly,

and subsequently to 10 mg twice weekly in patients who have an inadequate reduction in ALP and/or total bilirubin and tolerate therapy. Dosages should be separated by at least 3 days.

## CLINICAL TRIALS<sup>7,8</sup>

*A literature search was performed using “obeticholic acid” plus “primary biliary cirrhosis” or “primary biliary cholangitis”.*

A 12-month, double-blind, parallel-group, phase 3 study, evaluated the efficacy of obeticholic acid (OCA) in 216 adults with PBC were taking UDCA or unable to tolerate UDCA. Patients were randomized (1:1:1) to receive once daily OCA 10 mg, OCA titration, or placebo. Patients in the titration group received OCA 5 mg daily for 6 months and increased to 10 mg if they tolerated the drug, but did not achieve the primary endpoint. The majority (93%) of patients received OCA combination with UDCA (at pre-study doses) and a small number (7%) who were unable to tolerate UDCA received OCA as monotherapy.

Inclusion criteria were treatment with UDCA for at least 12 months (stable dose for at least 3 months) or intolerant to UDCA (no UDCA for at least 3 months) and ALP  $\geq 1.67$  x upper limit of normal (ULN) and/or total bilirubin  $> ULN$  but  $< 2x ULN$ .

The primary composite endpoint was the proportion of patients achieving ALP  $< 1.67x ULN$  (with a  $\geq 15\%$  reduction) and bilirubin  $\leq ULN$ . Significant reductions in ALP were seen within 2 weeks and were maintained throughout the study. After 12 months, 47%, 46% and 10% of patients in the OCA 10 mg, OCA titration, and placebo arms achieved the primary endpoint, respectively (both OCA groups  $p < 0.0001$  compared to placebo). In the study drug groups combined, 77% of patients achieved at least a 15% reduction in ALP compared to only 29% in the placebo group; in addition, 36% of those in the placebo group experienced an increase in ALP compared to only 3% of patients treated with OCA. The mean bilirubin levels did not change from baseline in the OCA groups, while it increased in the placebo group; suggestive of a slowing of disease progression with OCA. In the OCA titration group, 36 (52%) patients remained at 5 mg for the duration of the 12-month treatment period and 33 (48%) patients were titrated to 10 mg for the last 6 months of the 12-month period. Secondary endpoints measurements showed clinically meaningful and statistically significant reductions in gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which support a potential improvement of hepatic cell injury with OCA.

Other results of secondary endpoints and sub-group/post hoc analyses found:

- In pre-specified key subgroup analyses, younger age at PBC diagnosis and male patients are associated with a worse prognosis.
- A post hoc analysis of OCA-treated patients, found that a similar proportion of patients with advanced disease achieved the primary endpoint as compared to those with non-advanced disease.
- OCA treatment was associated with improvements in markers of immunomodulatory (IgM) and inflammatory response (C-reactive protein) compared with placebo.
- In a small subset of patients, there was a statistically significant reduction in progression of fibrosis (assessed by percentage increase in transient elastography) in the 10 mg OCA group (2.9%) compared to the placebo group (21.7%;  $p < 0.05$ ), but not in the OCA titration group (22.1%).

- Most patients included in the study were earlier in disease stage and clinical outcomes such as death; liver transplant; hospitalization for variceal bleed or encephalopathy; uncontrolled ascites; and hepatocellular carcinoma were low, as expected.

Three open-label long-term extension studies, including phase 2 and 3 trials, reported that ALP and bilirubin response was maintained after 2 years on therapy. In addition, placebo-treated patients who crossed over to OCA treatment experienced improvements in ALP and bilirubin after 1 year of therapy.

## OTHER DRUGS USED FOR CONDITION<sup>9,10,11</sup>

Ursodeoxycholic acid (UDCA), also known as ursodiol (Urso®), is an isomer of the primary human bile acid chenodeoxycholic acid (CDCA), but has no activity at FXR. Oral administration of UDCA 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. Therapy with UDCA improves serum ALP and bilirubin levels and delays histological progression of the disease, thereby increasing liver transplant-free survival. As expected, it is recommended as first-line therapy for patients with PBC by the American Association for the Study of Liver Diseases (AASLD).

## PLACE IN THERAPY<sup>12</sup>

Ursodeoxycholic acid (UDCA) was FDA approved in 1997, and until now, was the only drug indicated to treat PBC. Unfortunately, up to 50% of patients fail to adequately respond to UDCA, and 5% to 10% of patients cannot tolerate it. Patients left untreated, or who have not responded to UDCA, 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 UDCA, either as monotherapy or in combination with UDCA.

## SUGGESTED UTILIZATION MANAGEMENT

<b>Anticipated Therapeutic Class Review (TCR) Placement</b>	Bile Salts
<b>Clinical Edit</b>	Confirmation of the following: <ul style="list-style-type: none"> <li>• Diagnosis of primary biliary cholangitis based on 2 of the following: <ul style="list-style-type: none"> <li>- Alkaline phosphatase (ALP) <math>\geq 1.5 \times</math> ULN</li> <li>- Presence of antimitochondrial antibodies (AMA)</li> <li>- Histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts</li> </ul> </li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Contraindication/unable to tolerate ursodeoxycholic acid <b>OR</b></li> <li>• Trial of ursodeoxycholic acid for at least 1 year</li> </ul>
<b>Quantity Limit</b>	30 tablets per 30 days
<b>Duration of Approval</b>	1 year
<b>Drug to Disease Hard Edit</b>	Complete biliary obstruction

## REFERENCES

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