# PDL DRUG REVIEW

**Proprietary Name: Ocaliva®**
**Common Name: obeticholic acid**
**PDL Category: GI. Misc.**

| Comparable Products | Preferred Drug List Status |
|---|---|
| Ursodiol | Preferred |

## Summary


**Pharmacology:** Obeticholic acid, the active ingredient of Ocaliva®, is a farnesoid X receptor (FXR) agonist. FXR is a nuclear receptor expressed in the liver and intestine and is a main regulator of bile acid, inflammatory, fibrotic, and metabolic pathways. FXR activation decreases the intracellular hepatocyte concentrations of bile acids. The overall size of the circulating bile acid pool becomes limited while promoting choleresis (bile acid secretion from the liver), thus reducing hepatic exposure to bile acids.

**Indications and Usage:** For the treatment of primary biliary cholangitis (PBC; formerly called primary biliary cirrhosis), 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.

There is no pregnancy category with this product; however, the risk summary indicates the limited available human data on the use of obeticholic acid during pregnancy are not sufficient to inform a drug-associated risk. The safety and efficacy of use in the pediatric population have not been established.

**Dosage Forms:** Tablets: 5mg, 10mg

**Recommended Dosage:** 5mg PO QD in those who have not achieved an adequate biochemical response to an appropriate dosage of UDCA for at least 1 year or are intolerant to UDCA. If an adequate reduction in ALP and/or total bilirubin has not been achieved after 3 months of Ocaliva® 5mg and the dose is tolerated, it is recommended to increase the dose to 10mg QD (the maximum recommended dose).

If intolerable pruritus develops, it is recommended to consider one or more of the following: Add an antihistamine or bile acid binding resin; reduce the dose of Ovaliva® to 5mg QOD (if intolerant to 5mg QD dose) or 5mg QD (if intolerant to 10mg QD dose); temporarily interrupt treatment for up to 2 weeks, then restart at a reduced dose.

Treatment with Ocaliva® in patients with moderate and severe hepatic impairment should be started and monitored by a healthcare provider with experience managing PBC. Dose adjustments are not required with mild hepatic impairment. If moderate to severe hepatic impairment, the recommended starting dose is 5mg once weekly. If an

adequate reduction in ALP and/or total bilirubin has not been achieved after 3 months and the dose is tolerated, increase the dose to 5mg twice weekly and subsequently 10mg twice weekly per response and tolerability. It is also recommended to monitor for the occurrence of liver-related adverse reactions. Weigh the risk/benefits of continuing treatment if clinically significant liver-related adverse reactions occur.

**Drug Interactions:** It is recommended to 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. It is recommended to monitor the INR and adjust the dosage of warfarin if used concomitantly with Ocaliva®. Last, the concomitant use of Ocaliva® with CYP1A2 substrates with narrow therapeutic index may increase the exposure to the CYP1A2 substrates. Therapeutic monitoring is recommended.

**Common Adverse Drug Reactions:** *Listed % incidence for adverse drug reactions= reported % incidence for drug (Ocaliva® 10mg) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than its comparator.* The most frequently reported adverse events included pruritus (32%), fatigue (10%), abdominal pain & discomfort (0%), rash (2%), arthralgia (6%), oropharyngeal pain (7%), dizziness (2%), constipation (2%), peripheral edema (4%), palpitations (6%), pyrexia (6%), thyroid function abnormality (1%), and eczema (3%).

**Contraindications:** In patients with complete biliary obstruction

**Manufacturer:** Intercept Pharmaceuticals Inc

**Analysis:** There was one randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of Ovaliva® in patients with PBC (N=216) who had been taking UDCA for at least 12 months or who were unable to tolerate UDCA and did not receive UDCA for at least 3 months. Ocaliva® and placebo treatment arms were given in combination with UDCA in 93% of patients during the trial and as monotherapy in 7% of patients who were not able to tolerate UDCA. The primary endpoint was a responder analysis at month 12, where response was defined as a composite of 3 criteria; ALP <1.67 times the upper limit of normal (ULN), total bilirubin ≤ ULN, and an ALP decrease of ≥15%. (The ULN for ALP was defined as 118 U/L for females and 124U/L for males; the ULN for total bilirubin was defined as 1.1mg/dl for females and 1.5mg/dl for males).

The following table includes the % the patients by treatment arm who achieved a response to the primary composite endpoint at month 12, as well as the individual components of the primary endpoint. There were 33 in the Ocaliva® titration arm who did not achieve a response at 6 months and they tolerated Ocaliva®. Therefore, their dose increased from 5mg to 10mg once daily. Of these 33 patients, 13 (39%) achieved the primary composite endpoint. Ocaliva® 10mg and Ocaliva® titration treatment arms had statistically significantly better responder rates as compared with placebo (p<0.0001).

| | Ocaliva® 10mg (N=73) | Ocaliva® titration (N=70) | Placebo (N=73) |
|---|---|---|---|
| Primary Composite Endpoint | | | |
| Responder Rate | 48% | 46% | 10% |
| Components of Primary Endpoint | | | |
| ALP <1.67-times ULN | 55% (N=40) | 47% (N=33) | 16% (N=12) |
| Decrease in ALP of ≥15% | 78% (N=57) | 77% (N=54) | 29% (N=21) |
| Total bilirubin ≤ULN | 82% (N=60) | 89% (N=62) | 78% (N=57) |

In the Ocaliva® monotherapy group, 38% (N=9) achieved a response to the composite endpoint at month 3 as compared with 4% (N=1) in the placebo group. The mean reduction in ALP in the Ocaliva® group was 246U/L as compared to an increase of 17U/L in the placebo group.

**Place in Therapy:** PBC is "...characterized by an ongoing immunologic attack on the intralobular bile ducts that eventually leads to cirrhosis and liver failure."[2] One reference source recommends that all patients with PBC be treated with UDCA.[2] Obeticholic acid (Ocaliva®) 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.

It is recommended that Ocaliva® require prior authorization to verify diagnosis and concurrent use of UDCA or intolerance of UDCA.

**PDL Placement:** ☐ **Preferred**
☒ **Non-Preferred**

## References


[1] Ocaliva [package insert]. New York, NY: Intercept Pharmaceuticals, Inc; 2016.

[2] UpToDate desktop reference. Overview of the treatment of primary biliary cholangitis (primary biliary cirrhosis). Accessed August 2016.