January 25, 2017

Dave Compana
UNITED STATES

Dear Dave Compana:

Thank you for your recent medical information inquiry regarding the Academy of Managed Care Pharmacy (AMCP) dossier for OCALIVA® (obeticholic acid).

INDICATIONS AND USAGE

OCALIVA, a farnesoid X receptor (FXR) agonist, is indicated for the treatment of primary biliary cholangitis (PBC), formerly known as 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 achieved accelerated approval based on an improvement in the reduction of alkaline phosphatase (ALP) levels. Increased survival or reduction in disease-related symptoms has not been established. Continued approval of this indication may be contingent upon verification and description of clinical benefits in confirmatory trials.

IMPORTANT SAFETY INFORMATION

Contraindications

OCALIVA is contraindicated in patients with complete biliary obstruction.

Warnings and Precautions

Liver-Related Adverse Reactions

In two 3-month, placebo-controlled clinical trials a dose-response relationship was observed for the occurrence of liver-related adverse reactions including jaundice, ascites and primary biliary cholangitis flare with dosages of OCALIVA of 10 mg once daily to 50 mg once daily (up to 5-times the highest recommended dosage), as early as one month after starting treatment with OCALIVA.

In a pooled analysis of three placebo-controlled trials in patients with PBC, the exposure-adjusted incidence rates for all serious and otherwise clinically significant liver-related adverse reactions, and isolated elevations in liver biochemical tests, per 100 patient exposure years (PEY) were: 5.2 in the OCALIVA 10 mg group (highest recommended dosage), 19.8 in the OCALIVA 25 mg group (2.5 times the highest recommended dosage) and 54.5 in the OCALIVA 50 mg group (5 times the highest recommended dosage) compared to 2.4 in the placebo group.
Monitor patients during treatment with OCALIVA for elevations in liver biochemical tests and for the development of liver-related adverse reactions. Weigh the potential risks against the benefits of continuing treatment with OCALIVA in patients who have experienced clinically significant liver-related adverse reactions. The maximum recommended dosage of OCALIVA is 10 mg once daily. Adjust the dosage for patients with moderate or severe hepatic impairment.

Discontinue OCALIVA in patients who develop complete biliary obstruction.

Severe Pruritus

Severe pruritus was reported in 23% of patients in the OCALIVA 10 mg arm, 19% of patients in the OCALIVA titration arm and 7% of patients in the placebo arm in the POISE trial, a 12-month double-blind randomized controlled trial of 216 patients. Severe pruritus was defined as intense or widespread itching, interfering with activities of daily living, or causing severe sleep disturbance, or intolerable discomfort, and typically requiring medical interventions. In the subgroup of patients in the OCALIVA titration arm who increased their dosage from 5 mg once daily to 10 mg once daily after 6 months of treatment (n=33), the incidence of severe pruritus was 0% from months 0 to 6 and 15% from months 6 to 12. The median time to onset of severe pruritus was 11, 158 and 75 days for patients in the OCALIVA 10 mg, OCALIVA titration and placebo arms, respectively.

Management strategies include the addition of bile acid resins or antihistamines, OCALIVA dosage reduction and/or temporary interruption of OCALIVA dosing.

Reduction in HDL-C

Patients with PBC generally exhibit hyperlipidemia characterized by a significant elevation in total cholesterol primarily due to increased levels of high density lipoprotein-cholesterol (HDL-C). In the POISE trial, dose-dependent reductions from baseline in mean HDL-C levels were observed at 2 weeks in OCALIVA-treated patients, 20% and 9% in the 10 mg and titration arms, respectively, compared to 2% in the placebo arm. At month 12, the reduction from baseline in mean HDL-C level was 19% in the OCALIVA 10 mg arm, 12% in the OCALIVA titration arm and 2% in the placebo arm. Nine patients in the OCALIVA 10 mg arm and six patients in the OCALIVA titration arm, versus three patients in the placebo arm had reductions in HDL-C to less than 40 mg/dL.

Monitor patients for changes in serum lipid levels during treatment. For patients who do not respond to OCALIVA after one year at the highest recommended dosage that can be tolerated (maximum of 10 mg once daily), and who experience a reduction in HDL-C, weigh the potential risks against the benefits of continuing treatment.

Adverse Reactions

The most common adverse reactions from subjects taking OCALIVA (≥5%) were pruritus, fatigue, abdominal pain and discomfort, rash, oropharyngeal pain, dizziness, constipation, arthralgia thyroid function abnormality and eczema.

Drug Interaction

Bile Acid Binding Resins
Bile acid binding resins such as cholestyramine, colestipol or colesevelam absorb and reduce bile acid absorption and may reduce the absorption, systemic exposure and efficacy of OCALIVA. If taking bile acid binding resins, take OCALIVA at least 4 hours before or 4 hours after (or at as great an interval as possible) taking a bile acid binding resin.

We are pleased to provide you with comprehensive clinical and economic evidence for OCALIVA in this AMCP dossier.

The US Full Prescribing Information for OCALIVA (obeticholic acid) 5 mg and 10 mg tablets can be found here: https://ocaliva.com/ocaliva_pi.pdf

The information provided is supplied as a professional courtesy in response to your inquiry and is intended for educational purposes only. Should you have any questions or need additional information please contact us at medinfo@interceptpharma.com.

Sincerely,

Juan Carlos Lopez-Talavera, MD, PhD
Senior Vice President, Global Medical Affairs

Case Number: US17-00036

Enclosures:
OCALIVA US Prescribing Information