08 September 2017

IMPORTANT PRESCRIBING INFORMATION

SUBJECT: Liver injury, liver decompensation, liver failure, and death have been reported in primary biliary cholangitis (PBC) patients with moderate or severe hepatic impairment (Child-Pugh B and C) when OCALIVA® was dosed more frequently than recommended

Dear Health Care Provider:

Introduction

The purpose of this letter is to highlight important prescriber information for OCALIVA® (obeticholic acid), a farnesoid X receptor (FXR) agonist and a modified bile acid approved 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.

Postmarketing Cases

Liver injury, liver decompensation, liver failure, and death have been reported in patients with moderate to severe hepatic impairment when OCALIVA was dosed more frequently than recommended in labeling for such patients. In addition, serious liver adverse events have been reported in patients initiating therapy without cirrhosis or with mild liver impairment. Liver-related adverse events have occurred both early in treatment and after months of treatment.

Signs and symptoms reported in patients experiencing liver-related adverse outcomes include: increases in bilirubin and other liver enzymes, new or worsening pruritus, new or worsening fatigue, vague neuropsychiatric symptoms (such as dysphoria), abdominal pain, nausea, vomiting, diarrhea, dehydration, jaundice and liver decompensation.

In PBC clinical trials, a dose-response relationship was observed for the occurrence of liver-related adverse reactions with OCALIVA. Systemic and hepatic concentrations of OCALIVA increase significantly in patients with moderate to severe hepatic impairment. Consequently, the current US Package Insert recommends a longer dosing interval (i.e., 5 mg once weekly) for PBC patients with moderate to severe hepatic impairment (Child-Pugh B and C).

Current Dosing Recommendations

The current OCALIVA label states the starting dose in moderate and severe hepatic impairment (Child-Pugh B and C) is 5 mg once **weekly**. If an adequate reduction in ALP and/or total bilirubin has not been achieved after 3 months of OCALIVA 5 mg once **weekly**, and the patient is tolerating the drug, the dose of OCALIVA should be increased to 5 mg twice **weekly** (at least three days apart) and subsequently to 10 mg twice **weekly** (at least three days apart) depending on response and tolerability.

Recommendations for Monitoring/Treatment of Patients with Adverse Events

Considering the risk for liver injury associated with incorrect dosing of patients with advanced stage PBC, it is important for prescribers to:

- identify patients with impaired hepatic function at the start of OCALIVA treatment and ensure these patients are prescribed the recommended approved starting dosage regimen (i.e., 5 mg once weekly).
- monitor patients during treatment with OCALIVA for progression of their PBC disease and reduce the dosing frequency to once weekly for patients who progress to moderate hepatic impairment (Child-Pugh Class B).

During treatment with OCALIVA, patients should be monitored closely for the occurrence of liver-related adverse reactions and a thorough evaluation of causality should be performed. OCALIVA and other drugs associated with potential liver toxicity should be discontinued in patients with laboratory or clinical evidence of toxicity.

Health care providers should exercise a low threshold for drug discontinuation or interruption, based on laboratory, imaging and/or clinical evidence of toxicities. There is no immediate risk in temporary discontinuation of OCALIVA, but there is potentially significant risk associated with continuing treatment without a complete evaluation of physical and biochemical parameters for evidence of liver injury.

Contact Information

Health care providers and patients are encouraged to report adverse events in patients taking OCALIVA to Intercept Pharmaceuticals, Inc. at 1-844-782-ICPT. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088. You also may contact our medical information department via phone (1-844-782-ICPT), email medinfo@interceptpharma.com or at https://interceptpharma.com/about/medical-information-requests/ if you have any questions about the information contained in this letter or the safe and effective use of OCALIVA.

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