FDA Drug Safety Communication

This information is an update to the FDA Drug Safety Communication: Due to risk of serious liver injury, FDA restricts use of Ocaliva (obeticholic acid) in primary biliary cholangitis (PBC) patients with advanced cirrhosis issued on May 26, 2021.

Serious liver injury being observed in patients without cirrhosis taking Ocaliva (obeticholic acid) to treat primary biliary cholangitis

Monitor liver tests often for early identification of worsening liver function

12-12-2024 FDA Drug Safety Communication

Based on its review of postmarket clinical trial data, the U.S. Food and Drug Administration (FDA) identified cases of serious liver injury among patients being treated for primary biliary cholangitis (PBC) with Ocaliva (obeticholic acid) who did not have cirrhosis of the liver. We previously identified that PBC patients with advanced cirrhosis were at risk of serious liver injury when taking Ocaliva and updated the prescribing information to restrict its use in these patients. FDA's review of this required clinical trial found that some cases of liver injury in patients without cirrhosis resulted in liver transplant. This risk was notably higher for patients taking Ocaliva compared with a placebo, a pill without any active medicine.

FDA restricted the use of Ocaliva in patients who have PBC with advanced cirrhosis of the liver in 2021 because it can cause serious harm in those patients, adding a new *Contraindication* to the Ocaliva prescribing information and patient Medication Guide. However, our recent review of case reports submitted to FDA* found that some patients with PBC and advanced cirrhosis were still taking the medicine despite these restrictions.

We are notifying health care professionals and patients of this new safety information, and that frequent liver test monitoring is necessary to identify worsening liver function and ensure appropriate discontinuation of Ocaliva. The agency will continue to monitor the medicine's safety and will follow up if additional information becomes available.

Health care professionals should monitor liver tests frequently in patients being treated with Ocaliva to detect and address worsening liver function early. Based on the current data, it is not clear if this monitoring will be sufficient to address the risk of serious liver injury. Discontinue Ocaliva treatment with any evidence of liver disease progression or if efficacy is not established. Explain the signs and symptoms of worsening liver injury to patients receiving Ocaliva and direct them to contact you immediately if they develop any signs or symptoms of worsening liver injury.

Patients should talk to your health care professional about this safety risk and the benefits of continuing treatment with Ocaliva. Discuss any concerns you may have, including about possible alternative treatments. Contact your health care professional immediately if you develop any of the following symptoms, which may indicate worsening liver injury:

Any of these specific symptoms

- Swollen belly
- Yellow eyes or skin
- Bloody or black stools
- Coughing up or vomiting blood
- Mental status changes such as confusion, slurred speech, mood swings, changes in personality, or increased sleepiness or difficulty waking up

Any of these general symptoms if they are severe or do not go away after a few days

- Belly pain
- Nausea, vomiting, or diarrhea
- Loss of appetite or weight loss
- New or worsening tiredness
- Weakness
- Fever and chills
- Lightheadedness
- Less frequent urination

Ocaliva is a prescription medicine approved in May 2016 that has been shown to improve a certain liver test called alkaline phosphatase (ALP) in patients with PBC who have not responded well enough to another medicine called ursodeoxycholic acid (UDCA). The original clinical trial showed a decrease in ALP that supported FDA accelerated approval. FDA required the additional postmarket clinical trial to verify the clinical benefit of Ocaliva.

FDA evaluated liver safety in the postmarket clinical trial in patients who were appropriate for Ocaliva treatment based on the approved indication in the prescribing information. Among these patients, the risk of both liver transplant and death were higher in patients receiving Ocaliva compared with those receiving placebo. Specifically, among patients for whom Ocaliva was indicated, which were those with a lower risk of progression to liver transplant or death, 7 of 81 who received Ocaliva needed a liver transplant compared to 1 of 68 patients who received placebo.[1] An additional four patients receiving Ocaliva died, compared to one receiving placebo. Analyses evaluating the risk of liver transplant and death resulted in a hazard ratio of 4.77 (95% confidence interval: 1.03, 22.09) for patients without advanced cirrhosis and not contraindicated from receiving the drug.

Following the addition of the contraindication for PBC patients with advanced cirrhosis in May 2021, we identified 20 cases (domestic, n=13; foreign, n=7) received by FDA* between May 26, 2021, and September 18, 2024, reporting one or more of the following events in patients treated with Ocaliva: liver transplant (n=7), evaluation or listing for liver transplant (n=8), or liver-related death (n=6). Although we were not able to assess the appropriateness of Ocaliva use for most of these cases because of limited information, we identified three U.S. cases of liver-related events that occurred in patients for whom Ocaliva should have been discontinued based on progression of their liver disease as indicated in the 2021 safety labeling changes. This shows the importance of ongoing monitoring of liver tests and prompt action to withdraw Ocaliva if there is evidence of progression towards cirrhosis.

*The cases were reported to the FDA Adverse Event Reporting System (FAERS) database.

[1]The liver transplant case in the placebo group occurred after the patient switched to commercially available Ocaliva and was dosed with Ocaliva for two years prior to liver transplant; this case may also be related to Ocaliva treatment.

We previously communicated about the risk of serious liver injury associated with Ocaliva in May 2021 (restriction of Ocaliva use in PBC patients with advanced cirrhosis). Additional communications about related safety issues for Ocaliva occurred in February 2018 (addition of *Boxed Warning* to highlight correct dosing of Ocaliva) and September 2017 (warning about serious liver injury with incorrect dosing).

We encourage health care professionals and patients to report side effects involving Ocaliva or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Health care professionals, patients, and consumers can sign up for email alerts about Drug Safety Communications on medicines or medical specialties of interest to you.

Related Information

- National Institute of Diabetes and Digestive and Kidney Diseases: Primary Biliary Cholangitis (Primary Biliary Cirrhosis)
- Gastrointestinal Drugs Advisory Committee Meeting on Ocaliva (September 13, 2024, Meeting Information)
- Most Recent Ocaliva Drug Label (2022)
- The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective
- Think It Through: Managing the Benefits and Risks of Medicines