FDA Issues Liver Injury Safety Alert for PBC Drug Ocaliva

Obeticholic acid can cause drug-induced liver injury in people with primary biliary cholangitis, whether or not they have cirrhosis.

December 20, 2024 By Liz Highleyman

On December 12, the Food and Drug Administration (FDA) issued a safety alert warning of the potential for serious liver injury among people without cirrhosis who use Ocaliva (obeticholic acid) to treat primary biliary cholangitis (PBC). In some cases, liver injury was serious enough to require a liver transplant or led to death.

PBC is a rare condition characterized by chronic inflammation and progressive destruction of the bile ducts, which carry bile from the liver and gallbladder to the small intestine. Symptoms include fatigue and pruritus (itching). If left untreated, PBC can lead to liver fibrosis, cirrhosis, liver cancer and the need for a liver transplant.

Ocaliva, a farnesoid X receptor agonist from Intercept Pharmaceuticals, received FDA accelerated approval for the treatment of PBC in 2016, after a randomized clinical trial showed that the drug improved alkaline phosphatase liver enzyme levels more than a placebo in patients who did not respond to an older medication, ursodeoxycholic acid (UDCA). A pair of real-world studies found that it appeared to reduce the risk of liver decompensation, liver transplantation and liver-related death.

However, a confirmatory post-marketing trial showed that patients appropriately treated with Ocaliva according to the prescribing information were at higher risk for liver transplantation and death compared with those who received a placebo.

In November, the FDA declined to grant traditional full approval of Ocaliva for second-line treatment of PBC after an expert advisory committee voted 13 to 1 that its clinical benefits were not clear, and a majority were not convinced that its benefits outweigh its risks. Intercept indicated that it still believes in the "totality of evidence supporting Ocaliva" and would work with the FDA on next steps.

In 2021, the agency restricted use of Ocaliva by PBC patients with advanced cirrhosis due to their higher risk for drug-induced liver injury. Now, the warning has been extended to people without cirrhosis, although the FDA so far has not withdrawn the accelerated approval of Ocaliva for this

population.

Some patients who experienced severe liver injury in the post-marketing trial did not have cirrhosis. What's more, the agency identified 20 cases of liver transplantation, wait-listing for a transplant or death reported to the FDA Adverse Event Reporting System after the 2021 contraindication for advanced cirrhosis was added. In a few cases, severe liver injury occurred in people with progressive liver disease who should no longer have been using Ocaliva.

The FDA urges frequent liver test monitoring for people taking Ocaliva so providers can identify worsening liver function early and stop the treatment. "Based on the current data, it is not clear if this monitoring will be sufficient to address the risk of serious liver injury," stated the safety alert.

"Discontinue Ocaliva treatment with any evidence of liver disease progression or if efficacy is not established," the FDA advised providers. "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."

The agency advised patients to contact a health care professional immediately if they develop 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.

Fortunately, people with PBC now have more options. The FDA this year granted accelerated approval of two new drugs, Ipsen's Iqirvo (elafibranor) and Gilead Sciences' Livdelzi (seladelpar). These are peroxisome proliferator-activated receptor (PPAR) agonists that activate proteins that play a role in bile acid synthesis, fat metabolism, inflammation and fibrosis. Both are indicated for use in combination with UDCA for PBC patients who have an inadequate response to UDCA alone or who are unable to tolerate it. Iqirvo and Livdelzi are not recommended for people with decompensated cirrhosis, or liver failure.

Ocaliva has also been studied as a treatment for metabolic dysfunction-associated steatohepatitis (MASH; formerly known as non-alcoholic steatohepatitis, or NASH), but the FDA denied approval twice, determining that the drug's modest benefits do not appear to outweigh the risk for drug-induced liver injury.

Iqirvo and Livdelzi, too, have been evaluated for fatty liver disease, but they did not meet the FDA's criteria of MASH improvement without worsening fibrosis and fibrosis improvement without worsening MASH.

Only one medication, Madrigal Pharmaceuticals' Rezdiffra (resmetirom), is currently approved for MASH. Several other therapies that work by different mechanisms—including GLP-1 agonists, such as semaglutide (Ozempic or Wegovy), currently used to treat type 2 diabetes and obesity—show promise in ongoing studies.

Click here for more news about primary biliary cholangitis.
Click here for more news about fatty liver disease.
