Seladelpar Gets Accelerated Approval for Autoimmune Liver Disease

The PPAR agonist decreased liver disease biomarkers and improved itching in people with primary biliary cholangitis.

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The Food and Drug Administration (FDA) this week granted accelerated approval of seladelpar (brand name Livdelzi) for primary biliary cholangitis (PBC), a rare autoimmune disease affecting the bile ducts and liver. Another medication in the same class, elafibranor (brand name Iqirvo), received accelerated approval in June.

PBC is characterized by chronic inflammation and progressive destruction of the bile ducts, which carry bile from the liver and gallbladder to the small intestine to aid digestion. Symptoms include fatigue and itching (pruritus). If left untreated, PBC can lead to cirrhosis, liver cancer and the need for a liver transplant. Before the recent approvals, the treatment options were ursodeoxycholic acid (UDCA; Actigall and other brand names) or obeticholic acid (Ocaliva), but there is no cure.

"Those living with PBC share common symptoms, including incessant itching or skin-crawling sensations, as well as debilitating fatigue that is made worse by the itching at night," said Carol Roberts, president of PBCers, said in a Gilead news release. "The availability of a new treatment option that can help reduce this intense itching while also improving biomarkers of active liver disease is a milestone for our community."

Seladelpar (developed by CymaBay, which was recently acquired by Gilead Sciences) and elafibranor (developed by Genfit and marketed by Ipsen) are peroxisome proliferator-activated receptor (PPAR) agonists that activate proteins that play a role in bile acid synthesis, fat metabolism, inflammation and fibrosis. Both therapies have also been evaluated for metabolic dysfunction-associated steatohepatitis (MASH), but they did not meet the FDA's high bar of MASH improvement without worsening fibrosis and fibrosis improvement without worsening MASH.

Seladelpar was approved in combination with UDCA for people with an inadequate response to the older drug and for those who cannot tolerate UDCA. It is not recommended for people with decompensated cirrhosis, or liver failure.

The approval is supported by data from the Phase III RESPONSE study (NCT04620733), which were

presented at EASL Congress 2024 and published in The New England Journal of Medicine.

The study included nearly 200 people with PBC who had an inadequate response or unacceptable side effects on UDCA. They were randomly assigned to receive once-daily oral seladelpar or a placebo. The primary endpoint was biochemical response, defined as a substantial decrease in alkaline phosphatase (ALP) and normal bilirubin after a year of treatment.

At 52 weeks, 62% of people who received seladelpar met this endpoint, compared with 20% in the placebo group. What's more, one quarter of participants assigned to seladelpar achieved ALP normalization, compared with none in the placebo group. People in the seladelpar group also saw a significantly greater reduction in itching. Treatment was safe and generally well tolerated, and there were no treatment-related serious adverse events.

Another study presented at the EASL Congress, called ASSURE (NCT03301506), looked at long-term outcomes among people who participated in earlier trials of seladelpar for PBC. The analysis included 158 people from the RESPONSE trial and 179 participants from other legacy studies. They received once-daily seladelpar on an open-label basis for up to three years. Biochemical response rates remained stable or increased over time, and treatment continued to be well tolerated with longer follow-up.

A third study looked at a subset of ASSURE participants who had already progressed to compensated liver cirrhosis. Here, too, a majority saw improvements in biochemical markers of bile blockage and liver damage. Even in this sicker group, there were no treatment-related serious drug-related adverse events.

Elafibranor also led to significant decreases in ALP and bilirubin levels in the Phase III ELATIVE trial, but the improvement in itching did not reach the threshold for statistical significance. UCDA generally does not relieve itching, and obeticholic acid can make it worse.

Studies have not yet determined whether seladelpar or elafibranor can prevent liver decompensation or improve survival. Obeticholic acid, which has longer follow-up, has been shown to prolong survival.

Drugs that receive accelerated approval based on surrogate endpoints, such as biomarkers, are expected to undergo further testing to confirm that they offer clinical benefits, and the FDA can rescind the approval if they fail to measure up. The confirmatory AFFIRM trial (NCT06051617), evaluating clinical outcomes among people with compensated cirrhosis due to PBC, is currently underway.

Seladelpar is priced at about $150,000 per year. The Gilead Support Path Program offers information and resources to help patients understand coverage and financial options. Gilead already has a successful track record in the liver disease field with its treatments for hepatitis B, C and D.

“Livdelzi stands out in the therapeutic landscape for its unique ability to address multiple aspects of PBC with a single medication,” the Global Liver Institute said in a statement. “It not only enhances liver function markers, such as fibrosis and ALP scores, but it also alleviates common and debilitating symptoms such as pruritus (chronic itch) and fatigue.”

The approval provides flexibility for people who do not tolerate UDCA or do not respond to it. “This flexibility ensures that patients have access to a treatment that aligns with their individual needs and preferences, a significant advancement in personalized care for PBC,” said Kristin Hatcher, GLI’s Program Director of Pediatric and Rare Liver Diseases.

Click here for full prescribing information for seladelpar (Livdelzi).

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