FDA Approves First-Ever Drug for Fatty Liver Disease

People who used resmetirom (Rezdiffra) in a late-stage clinical trial experienced both MASH resolution and fibrosis improvement.

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On March 14, the Food and Drug Administration (FDA) granted accelerated approval of Madrigal Pharmaceuticals' resmetirom (brand name Rezdiffra) as the first medication for metabolic dysfunction-associated steatohepatitis (MASH), or advanced fatty liver disease.

Resmetirom, a once-daily pill, was approved along with diet and exercise for adults with MASH who have moderate to advanced (Stage F2 or F3) liver fibrosis but have not yet progressed to cirrhosis (Stage F4). Patients will not need a liver biopsy to be eligible for the new treatment. The approval is supported by results from a late-stage clinical trial which showed that resmetirom is the first drug to both reduce liver fat accumulation and improve fibrosis.

"This is a day of celebration for patients with [MASH] who have been waiting many years for the first approved therapy," said Wayne Eskridge, CEO of the Fatty Liver Foundation.

MASH, the new name for non-alcoholic steatohepatitis (NASH), and its earlier stage, metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), is a leading cause of advanced liver disease. Over time, fat buildup in the liver can trigger inflammation and fibrosis, or development of scar tissue that impairs organ function. Now that hepatitis B can be prevented with a vaccine and hepatitis C can be easily cured, fatty liver disease is responsible for a growing share of cirrhosis, liver cancer and liver transplants. People with MASLD or MASH are also at greater risk for cardiovascular disease.

Estimates suggest that around a third of people in the United States have MASLD, and about 5% have MASH. What's more, the prevalence is increasing worldwide, including among children. The new terminology emphasizes the link with obesity, type 2 diabetes and other metabolic abnormalities, but even lean people can develop MASLD. Until now, with no approved medical therapies, management has relied on lifestyle changes such as weight loss, exercise and, in some cases, bariatric surgery.

"Previously, patients with [MASH] who also have notable liver scarring did not have a medication that could directly address their liver damage," Nikolay Nikolov, MD, acting director of the FDA's

Office of Immunology and Inflammation, said in a news release. “Today’s approval of Rezdiffra will, for the first time, provide a treatment option for these patients, in addition to diet and exercise.”

A Long Road to Approval

Developing treatments for fatty liver disease has proved challenging, as the FDA’s dual benchmark of MASH improvement without worsening fibrosis and fibrosis improvement without worsening MASH has been difficult to meet. Numerous drug candidates that work by various mechanisms have looked promising in early and mid-stage clinical trials, only to fail in larger studies. Madrigal CEO Bill Sibold has called MASH a “graveyard of drug development.”

Last year, it looked like Intercept Pharmaceuticals’ obeticholic acid (Ocaliva) could be the front-runner. That drug led to fibrosis improvement without worsening MASH, but it failed to meet the second endpoint of MASH improvement without worsening fibrosis. Last June, the FDA decided against approval because the modest benefits did not appear to outweigh safety concerns.

Resmetirom (formerly known as MGL-3196) is a selective thyroid hormone receptor-beta agonist that mimics the action of hormones that play a role in fat metabolism. Activation of this receptor can lower blood lipid levels and reduce liver fat accumulation.

The safety and effectiveness of resmetirom were evaluated in the Phase III MAESTRO-NASH trial (NCT03900429). The main study analysis included nearly 1,000 people with biopsy-confirmed MASH, moderate to advanced fibrosis and metabolic risk factors. They were randomly assigned to receive once-daily oral resmetirom at a dose of 80 or 100 milligrams or a placebo. After 52 weeks, they had a follow-up liver biopsy. (The FDA approved the 80 mg dose for people weighing less than 220 pounds and the 100 mg dose for those weighing more.)

The results, previously presented at last year’s EASL Congress and recently published in The New England Journal of Medicine, showed that resmetirom met both endpoints after a year of treatment. About 30% of participants who received resmetirom experienced MASH resolution without worsening fibrosis, compared with 10% of placebo recipients. A quarter experienced at least a one-stage improvement in fibrosis without worsening MASH, compared with 14% in the placebo group. Participants taking resmetirom also saw improvements in fibrosis biomarkers, liver stiffness (a noninvasive measure of fibrosis), liver enzyme levels and LDL cholesterol levels.

Without a biopsy, it can be difficult to determine the exact stage of fatty liver disease, and some people with less advanced disease could be prescribed resmetirom. Study results from the MAESTRO-NAFLD1 study, presented in 2021, showed that treatment also benefited people with MASLD, reducing liver fat and fibrosis according to biomarkers and noninvasive imaging.

Resmetirom is generally safe and well tolerated. The most common side effects are diarrhea, nausea, vomiting, itching, abdominal pain, constipation and dizziness. Rates of serious adverse events in MAESTRO-NASH were statistically similar in all three treatment groups (approximately 12%). The product label includes warnings about liver toxicity and gallbladder-related side effects. Resmetirom can potentially interact with other drugs, including statins for lowering

cholesterol. People with decompensated cirrhosis should not use resmetirom.

Drugs that receive accelerated approval based on biomarkers and other surrogate endpoints 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. Follow-up in MAESTRO-NASH will continue for more than four years to see whether resmetirom helps prevent complications of advanced liver disease. Another ongoing trial, MAESTRO-NASH-OUTCOMES (NCT05500222) is evaluating resmetirom for people with compensated cirrhosis.

“The approval of the first medication for [MASH] is a true game-changer for health care providers, the research community and, most importantly, patients living with this serious liver condition,” MAESTRO-NASH lead investigator Stephen Harrison, MD, of Pinnacle Clinical Research and Oxford University, said in a news release. “Importantly, we continue to study Rezdiffra to determine if the positive results observed in the MAESTRO studies will lead to reduced risk of progression to cirrhosis, liver failure, need for liver transplant and premature mortality.”

Approval of the first MASH medication is welcome news, but, as was the case when the first direct-acting antivirals for hepatitis C were approved, high cost and limited access could be a concern for MASH treatment as well. Madrigal set the wholesale price at $47,400 per year, Fierce Pharma reported.

Resmetirom will be available in April through a limited specialty pharmacy network, and initial marketing will target people with advanced MASH who are already under the care of a liver disease specialist, according to the company. Madrigal has established a patient support program to help people navigate insurance and affordability challenges, co-pay support for eligible patients and a patient assistance program for those without insurance.

After such a long wait, resmetirom might not remain the sole MASH treatment for long. GLP-1 agonists and related diabetes and weight-loss medications, for example, may also be able to treat fatty liver disease. Studies of semaglutide (Ozempic or Wegovy) have yielded mixed results, but tirzepatide (Mounjaro or Zepbound) and the experimental drugs retatrutide, efinopegdutide and survodutide look promising. Approval of more MASH medications will both offer patients more options and should ultimately make treatment more affordable.

Click here for full prescribing information for Rezdiffra.

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