

Rezdiffra (resmetirom)

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

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Summary

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), is a condition characterized by the presence of hepatic steatosis in conjunction with at least one cardiometabolic risk factor, such as obesity, type 2 diabetes, dyslipidemia, or hypertension. The presence of inflammation and hepatocellular injury, with or without fibrosis, defines the progressive form known as metabolic dysfunction-associated steatohepatitis (MASH), previously

called nonalcoholic steatohepatitis (NASH). Untreated MASH can lead to complications like cirrhosis, liver failure, and hepatocellular carcinoma.

The first-line treatment for MASLD and MASH is lifestyle modification through a hypocaloric diet, weight loss, and regular exercise. Medications may be considered for MASH, particularly in those with advanced fibrosis. Two therapies are FDA-approved for the treatment of MASH including Wegovy (semaglutide), and Rezdiffra (resmetirom). Rezdiffra (resmetirom) is a thyroid hormone receptor-beta agonist indicated for the treatment of adults with non-cirrhotic MASH (formerly known as nonalcoholic steatohepatitis [NASH]) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) in conjunction with diet and exercise.

- Limitation of Use: Avoid use of Rezdiffra in those with decompensated cirrhosis.

Definitions

“Apoptosis signal-regulating kinase 1 (ASK-1) inhibitors” refer to a new class of drugs which are intended to reduce inflammation, cell death and fibrosis. An example included selonsertib, which has not yet been approved by the FDA.

“Body Mass Index (BMI)” is a value that is calculated based on an individual’s weight and height and helps determine whether a person is underweight (BMI <18.5), overweight (BMI 25.0-29.9), obese (BMI ≥30.0) or normal weight (BMI 18.5-24.9) as defined by the World Health Organization.

“Caspase inhibitors” refer to a new class of drugs that inhibit the activity of caspase enzymes (initiation of programmed cell death and inflammation). There are no current FDA-approved products in this class at this time.

“Documentation” refers to written information, including but not limited to:

- Up-to-date chart notes, relevant test results, and/or relevant imaging reports to support diagnoses; or
- Prescription claims records, and/or prescription receipts to support prior trials of formulary alternatives.

“Fibrosis stage” refers to the degree of fibrosis present in the liver, graded on a 5-point scale from F0 (no fibrosis) to F4 (cirrhosis). Stages F2-F3 represent significant fibrosis.

“Farnesoid X receptor (FXR) agonists” refer to a new class of drugs that activate the FX-receptor, which plays a role in regulating bile, acid, lipids and glucose metabolism. An example includes obeticholic acid (Oclavia) for the management of primary biliary cholangitis. There are no current FXR agonists approved for the management of MASH/MASLD.

"MASH resolution" is defined as the absence of hepatocellular ballooning, minimal lobular inflammation (grade 0-1), and a decrease in NAFLD activity score (NAS) by at least 2 points.

"Metabolic dysfunction-associated steatotic liver disease (MASH)" refers to a progressive form of nonalcoholic fatty liver disease characterized by hepatic steatosis ($\geq 5\%$ of hepatocytes), inflammation, and hepatocellular injury, with or without fibrosis, that was formerly termed nonalcoholic steatohepatitis (NASH).

"Model for End-stage Liver Disease (MELD)" is a numerical rating system used to assess the severity of liver disease. It is often used to help determine priority of patients on a liver transplant waiting list. Higher scores indicate more severe illness.

"MRI-PDFF" is magnetic resonance imaging–proton density fat fraction, an imaging-based quantitative biomarker of liver fat content used to diagnose and monitor hepatic steatosis.

"Noninvasive tests (NITs)" refer to blood- or imaging-based tests used to diagnose and monitor MASH and fibrosis as an alternative to liver biopsy. Examples include the FIB-4 index, Enhanced Liver Fibrosis (ELF) test, vibration-controlled transient elastography (VCTE), and magnetic resonance elastography (MRE).

"[s]" indicates state mandates may apply.

Medical Necessity Criteria for Initial Clinical Review

Initial Indication-Specific Criteria

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASH)

The Plan considers Rezdiffra (resmetirom) medically necessary when recent (within the last 6-12 months) clinical chart documentation provided indicates ALL of the following criteria are met:

1. The medication is prescribed by or in consultation with a gastroenterologist, endocrinologist, or hepatologist; *AND*
2. The member is 18 years of age or older; *AND*
3. The member has a diagnosis of noncirrhotic metabolic dysfunction-associated steatotic liver disease (MASH)^s with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis), confirmed by ONE (1) or more of the following:
 - a. Liver biopsy showing MASH and significant fibrosis (F2 or F3) without cirrhosis; *and/or*
 - b. Transient elastography (e.g. FibroScan) with liver stiffness ≥ 8.0 kPa (F2) but < 20 kPa (cirrhosis) or as interpreted by healthcare provider findings consistent with intermediate or high risk (i.e., F2 or F3); *and/or*

- c. Magnetic resonance elastography (MRE) with liver stiffness ≥ 3.1 kPa or as interpreted by a healthcare provider findings consistent with intermediate or high risk (i.e., F2 or F3); *and/or*
- d. Enhanced Liver Fibrosis (ELF) test ≥ 7.7 or as interpreted by healthcare provider or laboratory findings consistent with intermediate or high risk (i.e., F2 or F3); *and/or*
- e. Fibrosis-4 (FIB-4) index ≥ 1.3 PLUS one additional noninvasive test (transient elastography, MRE, or ELF) showing at least stage 2 fibrosis; *AND*
**formerly known as nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH), consistent with language used in the manufacturer's package insert.*
- 4. The member has attempted at least 6 months of intensive lifestyle intervention with diet and exercise aimed at weight loss of at least 5-10% (may not be applicable for those with a normal body mass index [BMI], or where a provider may consider it not medically appropriate), without sufficient improvement in MASH or fibrosis;^[5] *AND*
- 5. Rezdiffra (resmetirom) will be used in conjunction with diet and exercise aimed at weight loss; *AND*
- 6. The member is unable to use, or has tried and failed Wegovy (semaglutide) for MASH;^[5] *AND*
- 7. The member does NOT have cirrhosis or decompensated liver disease, as evidenced by any of the following:
 - a. Liver biopsy showing cirrhosis; *and/or*
 - b. Cirrhosis of the liver with portal hypertension; *and/or*
 - c. History of liver decompensation event (e.g., ascites, variceal bleeding, hepatic encephalopathy); *and/or*
 - d. Model for End-Stage Liver Disease (MELD) score > 15 ; *and/or*
 - e. Transient elastography (e.g. FibroScan) with liver stiffness measurement ≥ 20 kPa; *and/or*
 - f. MRE with liver stiffness measurement ≥ 5.0 kPa; *and/or*
 - g. ELF test > 11.3 ; *AND*
- 8. Rezdiffra (resmetirom) will NOT be used concurrently with other therapies indicated for NASH/MASH; *AND*
- 9. The requested dose does not exceed 100 mg per day.

If the above prior authorization criteria are met, the requested product will be authorized for up to 12-months.^[5]

Medical Necessity Criteria for Subsequent Clinical Review

Subsequent Indication-Specific Criteria

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASH)

The Plan considers Rezdiffra (resmetirom) medically necessary when recent (within the last 6 months) clinical chart documentation provided indicates ALL of the following criteria are met:

1. The member is currently receiving the medication through the Plan's benefit or has previously met applicable Initial Authorization criteria; *AND*
2. The member is responding positively to therapy as evidenced by ONE or more of the following:
 - a. Improvement in steatosis, inflammation, or fibrosis based on imaging (liver ultrasound or MRI) or non-invasive tests/scores, if available; *and/or*
 - b. Improvement in fibrosis stage based on available methods such as transient elastography, MRE, ELF, or clinical prediction scores (FIB-4, NAFLD fibrosis score); *and/or*
 - c. Lack of disease progression or stable disease state; *and/or*
 - d. Reduction in liver fat content on MRI-PDFF, if available; *AND*
3. The member has demonstrated ongoing engagement and efforts toward weight management through adherence to the recommended diet and exercise regimen; *AND*
4. When applicable [e.g., members without a history of trying Wegovy (semaglutide)], the member is unable to use, or has tried and failed Wegovy (semaglutide) for MASH; *AND*
5. The member has not developed cirrhosis or decompensated liver disease while on Rezdiffra (resmetirom), as evidenced by the absence of clinical signs or symptoms of decompensation (e.g., ascites, variceal bleeding, hepatic encephalopathy); *AND*
6. Rezdiffra (resmetirom) is NOT being used concurrently with other therapies indicated for NASH/MASH *AND* The requested dose does not exceed 100 mg per day.

If the above reauthorization criteria are met, the requested product will be authorized for up to 12 months.^[5]

Experimental or Investigational / Not Medically Necessary^[5]

Rezdiffra (resmetirom) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Treatment of NAFLD/MASH without significant fibrosis (stage F2-F3). Rezdiffra (resmetirom) was intentionally studied in those with stages F2 and F3 fibrosis, limited knowledge is available to support the safe and effective use of Rezdiffra (resmetirom) in those outside of this staging.
- Treatment of NASH/MASH in individuals with:
 - No fibrosis (stage F0) or mild fibrosis (stage F1).
 - Cirrhosis (stage F4) or decompensated liver disease.

- Other chronic liver diseases (e.g., hepatitis B, hepatitis C, autoimmune hepatitis, alcoholic liver disease, hemochromatosis, Wilson's disease).
- Treatment of pediatric NAFLD/MASH (age < 18 years). Resdiffra (remetirom) was only studied in those 18 years of age and older, the safety and efficacy in pediatrics has not been established.
- Prevention of NAFLD/MASH in individuals with fatty liver or metabolic risk factors.
- Use in combination with other off-label or investigational NASH/MASH therapies (e.g., vitamin E, pioglitazone, some GLP-1 RAs, FXR agonists, ASK-1 inhibitors, caspase inhibitors, etc.), outside of the context of a clinical trial.
- Use in individuals who have not first attempted at least 6 months of intensive lifestyle modification focusing on weight loss of $\geq 5\text{-}10\%$ through diet and exercise.
- Use in pre-transplant or post-transplant settings for the treatment or prevention of recurrent or de novo NASH/MASH in liver transplant recipients.

Applicable Billing Codes

Table 1	
ICD-10 diagnosis codes considered medically necessary for Metabolic Dysfunction-Associated Steatotic Liver Disease (MASH) if criteria are met:	
<i>Code</i>	<i>Description</i>
K75.81	Nonalcoholic Steatohepatitis (Nash)

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