resmetirom (Rezdiffra™)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO289

Description

Resmetirom (Rezdiffra) is a liver-targeted thyroid hormone receptor-beta (THR-β) selective agonist pending FDA-approval for the treatment of adults with nonalcoholic steatohepatitis (NASH) with liver fibrosis.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
resmetirom (Rezdiffra)	nonalcoholic steatohepatitis (NASH)	For weight < 100kg: 80 mg tablets	30 tablets/30 days
		For weight ≥100kg: 100 mg tablets	

Initial Evaluation

I. **Resmetirom (Rezdiffra)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hepatologist or gastroenterologist; **AND**
   C. Member has a diagnosis of **nonalcoholic steatohepatitis (NASH)** when the following are met:
      1. Diagnosis is biopsy confirmed; **AND**
      2. Documented liver fibrosis stage F2 or F3; **AND**
      3. Other causes of liver disease or hepatic steatosis have been ruled out (e.g., alcoholic steatohepatitis, acute fatty liver, autoimmune hepatitis, Hepatitis A, B or C, hemochromatosis, drug-induced liver disease, etc.); **AND**
   D. Provider attestation member has adopted liver-protective lifestyle interventions such as optimizing weight loss, dietary changes, and exercise; **AND**
   E. Provider attestation member is optimizing standard of care pharmacologic treatment to manage comorbid diseases, including, but not limited to cardiovascular disease, dyslipidemia, diabetes, hypertension; **AND**
   F. Member does not have evidence of cirrhosis, hepatic decompensation, or hepatocellular carcinoma (HCC)

II. Resmetirom (Rezdiffra) is considered investigational when used for all other conditions, including but not limited to:
   A. Heterozygous Familial Hypercholesterolemia
   B. Evidence of cirrhosis (F4), hepatic decompensation, or hepatocellular carcinoma (HCC)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Disease response to treatment defined by improvement in fibrosis or stabilization/no worsening of fibrosis as determined by non-invasive tests (e.g., transient elastography (e.g., FibroScan), magnetic resonance elastography (MRE), etc.); **AND**
IV. Member has not progressed to cirrhosis, experienced hepatic decompensation events, or hepatocellular carcinoma (HCC)

Supporting Evidence

I. Resmetirom (Rezdiffra) is a liver-targeted thyroid hormone receptor-beta (THR-β) selective agonist for the treatment of adults with nonalcoholic steatohepatitis (NASH) with liver fibrosis. When activated in the liver, THR-β leads to the breakdown of stored fat.
II. Non-alcoholic fatty liver disease (NAFLD) is characterized by an abnormal accumulation of fat in the liver. NAFLD can be subcategorized as nonalcoholic fatty liver (NAFL), in which there is hepatic steatosis (HS) but no injury to liver cells, and as nonalcoholic steatohepatitis (NASH), in which HS is accompanied by hepatocellular injury.
III. NASH can progress to liver fibrosis, and liver fibrosis can progress to irreversible cirrhosis and hepatocellular carcinoma (HCC). NASH and alcoholism are the top two indications for liver transplantations and is the leading indication for liver transplantation in adults 65 years of age and older and women of all ages. NAFLD is closely linked to and often precedes the development of metabolic abnormalities (insulin resistance, dyslipidemia, obesity, and hypertension). Having several metabolic abnormalities confers an even greater risk of histological progression of NASH and all-cause mortality.
IV. In 2023, it was proposed by hepatology medical societies that the naming for these conditions be updated to metabolic-associated fatty liver disease (MAFLD) and metabolic steatohepatitis (MASH).

V. Diagnosis of suspected disease in most patients is based on clinical and laboratory data as well as imaging with appropriate exclusion of other liver conditions, but NASH is also a diagnosis of exclusion, which includes excluding: other causes of hepatic steatosis [alcoholic steatohepatitis, acute fatty liver, autoimmune hepatitis, Hepatitis A, B and C, hemochromatosis, drug-induced liver disease, etc.), absence of coexisting chronic liver disease, and exclusion of significant alcohol consumption.

VI. Abnormal laboratory results indicating liver injury (e.g., aminotransferase levels (AST, ALT, etc.) may be detected and managed by primary care practitioners (PCPs), but should not be used in isolation to make a definitive NASH diagnosis. Individuals with intermediate to high-risk NASH or cirrhosis should be referred to hepatology or gastroenterology to undergo additional monitoring and confirmatory tests.

VII. Liver biopsy is regarded as the gold standard to diagnose NASH. Several noninvasive testing (NIT) methods to detect fibrosis in patients with liver disease have been established as alternatives to biopsy, however may not provide accurate diagnostic specificity. Degree of steatohepatitis may only be detected with a liver biopsy. When there is diagnostic uncertainty in patients with indeterminate, unreliable, or conflicting NITs, diagnosis via liver biopsy remains the most reliable method to confirm advanced fibrosis and progression of NASH.

VIII. Patients with hepatic steatosis or clinically suspected NAFLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with a fibrosis risk stratification by the fibrosis-4 (FIB-4 index), which is a common noninvasive test to help estimate the amount of scarring in the liver. The score calculates age, AST and ALT levels, and platelet count.

IX. The 2023 American Association for the Study of Liver Diseases (AASLD) and 2022 American Association of Clinical Endocrinology (AACE) guidelines provide guidance on the clinical care pathway for initial risk stratification and management of patients with NASH:

a. Low risk of advanced fibrosis is defined as an FIB-4 score < 1.3, LSM < 8.0 kPa by transient elastography (TE) or a liver biopsy fibrosis stage of F0–F1.
b. Intermediate/Indeterminate risk is defined as an FIB-4 score between ≥ 1.3 and 2.67 and/or an LSM between 8.0 and 12.0 kPa on TE, and in those patients who are unable or unwilling to obtain a liver biopsy.
c. High risk is defined as an FIB-4 score > 2.67, LSM > 12.0 kPa by TE, or a liver biopsy that shows clinically significant liver fibrosis (F2–F4).

X. There is no single or specific NIT that is recommended; however, liver-specific imaging, including vibration-controlled transient elastography (VCTE) (e.g., FibroScan®) are commonly used to assess liver stiffness and can be used to exclude significant hepatic fibrosis. VCTE can assess the presence of liver disease through a combination of controlled attenuation parameter (CAP) and liver stiffness measurement (LSM), which assess hepatic fat and liver stiffness, respectively. Changes in liver stiffness may be useful in identifying

disease progression. Hepatic fat may also be assessed using magnetic resonance imaging-proton density fat fraction (MRI-PDFF), which determines fat content via the difference in resonance frequencies between fat and water and can additionally quantify steatosis. Other common NITs used in clinical practice include magnetic resonance elastography (MRE), enhanced liver fibrosis test (ELF), and acoustic radiation force impulse imaging (ARFI) (Virtual Touch™ tissue quantification, ElastPQ).

XI. Patients with NASH and at least stage 2 fibrosis (F2), referred to as "at-risk" NASH, have a demonstrably higher risk of liver-related morbidity and mortality.

XII. Lifestyle intervention is the key therapeutic intervention for patients with NAFLD. The American Association for the Study of Liver Diseases (AASLD) guidance on the management of NAFLD endorse dietary modification, increased physical activity, and weight loss. A weight loss of 5% to 10% of body weight can reverse hepatic steatosis and stabilize or diminish NASH in many patients, but this goal is frequently difficult to achieve. AASLD emphasizes optimizing glucose control for patients with diabetes, lipid-lowering therapy for patients with hyperlipidemia, and abstinence from alcohol for patients with clinically significant hepatic fibrosis.

XIII. Goal of pharmacologic therapy for NASH is to slow the progress of, halt, or reverse fibrosis while patients are still pre-cirrhotic. As of December 2023, resmetirom (Rezdiffra) is anticipated to be the first FDA-approved therapy for NASH. Vitamin E and pioglitazone have been used historically and may improve the histologic changes of NASH, but data are limited. Some of the medications approved for commonly associated comorbidities such as T2DM and obesity have been studied in the context of NASH and may reduce liver enzymes or steatosis or improve liver histology. Therefore, medications with possible liver-related benefits should be optimized when managing comorbidities.

XIV. MAESTRO-NASH is an ongoing randomized, double-blind, placebo-controlled Phase 3 trial in patients with NASH and liver fibrosis. This study incorporates a 52-week serial liver biopsy analysis in 966 patients with biopsy-confirmed NASH and significant fibrosis (stage F1b, F2, F3). Patients were randomly assigned to placebo, resmetirom 80 mg, or resmetirom 100 mg once daily. Baseline characteristics were balanced across treatment arms and include BMI 36 kg/m^2, type 2 diabetes (67%), hypertension (78%), dyslipidemia (71%; LDL 99 mg/dL); baseline liver biopsy nonalcoholic fatty liver disease activity score (NAS) ≥ 5 (84%); baseline fibrosis stage: F3 (62%), F2 (33%), F1B (5%). The NAS is a validated scoring system with scores ranging from 0–8 and are composed of the unweighted sum of semi-quantitative steatosis (0–3), ballooning (0–2), and lobular inflammation scores (0–3).

XV. Dual primary endpoints evaluated the proportion of patients with NASH resolution with at least 2 points reduction in without worsening of fibrosis at least 1 point improvement in the fibrosis stage with no worsening of NAS. Key secondary endpoint included percent change from baseline in LDL-C (after 24 weeks). The 52-week dual primary endpoint and the key secondary endpoint were met for both the 80 mg and 100 mg dose of resmetirom

(Rezdiffra). 26% (80 mg) and 30% (100 mg) of patients randomized to resmetirom had NASH resolution without worsening of fibrosis stage compared to 10% of the placebo group ($p < 0.0001$ for both comparisons). Additionally, 24% (80 mg) and 26% (100 mg) of patients randomized to resmetirom had ≥ 1 stage improvement in fibrosis without worsening of NASH compared with 14% for the placebo group ($p < 0.0001$ for both comparisons).

XVI. The onset of adverse events (AEs) were typically observed during the first weeks of treatment, and most treatment-related AEs were considered mild or moderate in severity, and transient. The overall incidence of AE was comparable between treatment groups, with most common AE (>10%) in resmetirom arm being diarrhea, nausea, vomiting, arthralgia, urinary tract infection, and COVID-19 infection. There were no instances of drug induced liver injury (DILI).

XVII. Framework recommendations are based on critical appraisal of the evidence for safety and efficacy and defines clinically meaningful endpoints/benefits inclusive of, but are not limited to morbidity, mortality, symptom control, physical/emotional functioning, and quality of life. Historically, several pharmacologic therapies have been studied for the treatment of patients with NASH, however, most trials have not been able to detect a clinically meaningful difference, had significant safety issues, and/or been too short to determine an impact on important patient-centered clinical outcomes. The quality of evidence is considered moderate, as resmetirom (Rezdiffra) met both dual primary endpoints and achieved greater rates of stabilization of fibrosis compared to placebo. Fibrosis histology is an accepted surrogate endpoint and one of the strongest predictors for clinical outcomes; however, uncertainty remains regarding the magnitude of the long-term benefits of resmetirom (Rezdiffra). The effects of resmetirom (Rezdiffra) on the ultimate progression of NASH to worsening fibrosis, cirrhosis, and the outcomes of liver failure, need for transplantation, and early mortality cannot be known from this relatively short-term pivotal trial.

XVIII. Data from the MAESTRO-NASH trial will be reinforced by the Phase 3 MAESTRO clinical development program, including the MAESTRO-NASH-OUTCOMES, MAESTRO-NAFLD-1 and MAESTRO-NAFLD-OLE safety clinical trials. Resmetirom (Rezdiffra) was approved under the accelerated approval pathway based on evaluating liver histological improvements predicted to slow the progression of NASH defined as resolution of NASH without worsening fibrosis stage or improvement in fibrosis stage with no worsening of NAS. Continued approval for the treatment of NASH is contingent upon verification and description of clinical benefit in confirmatory trials. The 54-month analysis of MAESTRO-NASH in approximately 1,700 patients is on-going and will include the following endpoints: a composite clinical outcome composed of all-cause mortality, liver transplant, and significant hepatic events (including hepatic decompensation events [ascites, encephalopathy, or variceal hemorrhage], histological progression to cirrhosis, and a confirmed increase of MELD score.

Investigational or Not Medically Necessary Uses

I. Resmetirom (Rezdiffra) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Heterozygous Familial Hypercholesterolemia (HeHF)
      i. Resmetirom (Rezdiffra) was evaluated in a 12-week, double-blind, randomized, placebo-controlled Phase 2 trial in patients with HeFH (NCT03038022). Resmetirom reduced LDL-C levels by 18.8% (95% CI: -27.8% to -9.8%; *P* < 0.0001) compared with placebo at Week 12, with a mean difference of -27 mg/dL (95% CI: -38.4 to -15.5 mg/dL; *P* < 0.0001). Study limitations included small sample size, short treatment and follow-up duration, and inclusion of a homogeneous population. Additional studies are needed to further evaluate the potential role of resmetirom in the management of patients with HeFH.
   B. Cirrhosis, hepatic decompensation, or hepatocellular carcinoma (HCC)
      i. Patients with cirrhosis, patients with prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy), or in hepatocellular carcinoma (HCC) were excluded from participating in the MAESTRO-NASH clinical program. Reversal of cirrhosis in these patients may not be feasible and the efficacy and safety of resmetirom in this patient population is unknown.

References

1. Harrison SA, Ratziu V, Anstee QM, et al. Design of the phase 3 MAESTRO clinical program to evaluate resmetirom for the treatment of nonalcoholic steatohepatitis. *Aliment Pharmacol Ther*. 2024;59(1):51-63.
2. Resmetirom preapproval product dossier. Madrigal Pharmaceuticals. September 2023.
3. Juluri R, Vuppalanchi R, Olson J, et al. Generalizability of the nonalcoholic steatohepatitis Clinical Research Network histologic scoring system for nonalcoholic fatty liver disease. *J Clin Gastroenterol*. 2011;45(1):55-58. doi:10.1097/MCG.0b013e3181dd1348
4. Fahim SM, Tice JA, Suh K, et al. Resmetirom for nonalcoholic steatohepatitis. *J Manag Care Spec Pharm*. 2023;29(10):1169-1172. doi:10.18553/jmcp.2023.29.10.1169
5. Center for Drug Evaluation and Research. Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment Guidance for Industry. Updated December 2018. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/noncirrhotic-nonalcoholic-steatohepatitis-liver-fibrosis-developing-drugs-treatment
6. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology*. 2023;77(5):1797-1835.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
obeticholic acid (Ocaliva)	Primary Biliary Cholangitis (PBC)

Policy Implementation/Update

Action and Summary of Changes	Date
Policy created	02/2024