Pharmacy Management Drug Policy

SUBJECT: Rezdiffra (resmetirom)
POLICY NUMBER: PHARMACY-121
EFFECTIVE DATE: 05/2024
LAST REVIEW DATE: 12/19/2024

If the member's subscriber contract excludes coverage for a specific service or prescription drug, it is not covered under that contract. In such cases, medical or drug policy criteria are not applied. This drug policy applies to the following line/s of business:

Policy Application

Category:	☒ Commercial Group (e.g., EPO, HMO, POS, PPO)	☐ Medicare Advantage
	☒ On Exchange Qualified Health Plans (QHP)	☐ Medicare Part D
	☒ Off Exchange Direct Pay	☒ Essential Plan (EP)
	☐ Medicaid & Health and Recovery Plans (MMC/HARP)	☒ Child Health Plus (CHP)
	☐ Federal Employee Program (FEP)	☐ Ancillary Services
	☐ Dual Eligible Special Needs Plan (D-SNP)	

DESCRIPTION:

Non-alcoholic fatty liver disease (NAFLD), also known as metabolic dysfunction-associated fatty liver disease (MAFLD), is the most common chronic liver condition in Western populations and is most often associated with comorbid obesity and type 2 diabetes (T2D). Nonalcoholic steatohepatitis (NASH), also known as metabolic dysfunction-associated steatohepatitis (MASH), is the most severe form of NAFLD and is characterized by an accumulation of fat in the liver. It is defined as the presence of ≥5% hepatic steatosis with inflammation and hepatocellular injury (also known as hepatocyte ballooning), with or without fibrosis.[3] Once NASH progresses to clinically significant fibrosis (stage F2 or higher), patients are at a higher risk for adverse clinical outcomes. NASH affects an estimated 1.5% to 6.5% of U.S. adults.[5] The prevalence of NASH is rising worldwide in parallel with increases in the prevalence of obesity and metabolic comorbid disease (insulin resistance, dyslipidemia, central obesity, and hypertension).[2]

The American Association for the Study of Liver Diseases (AASLD) [2023], American Association of Clinical Endocrinology (2022), and American Gastroenterological Association (AGA) [2021] provide guidelines and/or guidance on the overall management of NAFLD and NASH. In patients with NASH, the goal of liver-directed treatment is to reverse steatohepatitis and fibrosis, or at least halt fibrosis progression.[9] A healthy diet and regular exercise form the foundation of treatment for the vast majority of those with NAFLD. Weight loss of 3%-5% improves steatosis, but greater weight loss (> 10%) is generally required to improve NASH and fibrosis.[2] Aggressive lifestyle changes aimed at long-term weight loss are recommended for NASH patients at a high risk for advanced fibrosis.[9] Management of cardiovascular risk factors, such as hypertension and dyslipidemia, as well as diabetes should follow recommended standards of care.

On March 14,2024 the Food and Drug Administration (FDA) granted accelerated approval for Rezdiffra (resmetirom), a once-daily, oral, thyroid hormone receptor-beta (THR-β) agonist, in conjunction with diet and exercise, for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis). Rezdiffra is the first FDA-approved treatment for NASH.

The accelerated approval of Rezdiffra was based on an efficacy analysis at Month 12 from the 54 month Phase 3, randomized, double-blind, placebo-controlled MAESTRO-NASH trial.[1] Enrolled patients were required to have 3 or more metabolic risk factors, biopsy-proven NASH with fibrosis stage 1B, 2, or 3 and a NAFLD activity score (NAS) ≥ 4 with at least 1 in each NAS component (steatosis [on a scale from 0 to 3], lobular inflammation [on a scale from 0 to 3], and hepatocellular ballooning [on a scale from 0 to 2].[8] The month 12 analysis included 888 biopsy confirmed NASH patients with F2 and F3 (at eligibility) randomized 1:1:1 to receive placebo (n = 294), Rezdiffra 80 mg once daily (n = 298), or Rezdiffra 100 mg once daily (n = 296), in addition to lifestyle counseling on nutrition and exercise. Patients were on stable doses of medications for diabetes, dyslipidemia, and hypertension.

The two primary endpoints at week 52 were NASH resolution (achievement of a hepatocellular ballooning score of 0, a lobular inflammation score of 0 or 1, and a reduction in the NAFLD activity score by ≥ 2 points) with no worsening of fibrosis, and an improvement (reduction) in fibrosis by at least one stage with no worsening of the NAFLD activity score based on biopsy readings. The key secondary end point was the percent change from baseline in the low-density lipoprotein (LDL) cholesterol level at week 24. At Week 52, NASH resolution associated with a ≥ 2 point reduction in NAS with no worsening of fibrosis stage was reported for 29.9% of patients in the Rezdiffra 100 mg and 25.9% in the 80 mg groups vs. 9.7% of patients in the placebo group (P < 0.0001 for Rezdiffra doses vs. placebo).[8] The proportion of patients with ≥ 1 stage fibrosis improvement with no worsening in NAS at Week 52 was 25.9% for Rezdiffra 100 mg and 24.2% in the 80 mg group vs. 14.2% for placebo (P < 0.0001 for Rezdiffra doses vs. placebo). At Week 24, LDL-C was reduced by -16.3% in the Rezdiffra 100 mg and -13.6% in the 80 mg group and not in those who received placebo (0.1%) (P < 0.0001 Rezdiffra doses vs. placebo). At week 52, trial discontinuations due to adverse events were more common in the 100-mg resmetirom group than in the other two trial groups (6.8 % in the 100-mg resmetirom group, 1.9% in the 80-mg group, and 2.2% in the placebo groups). The most frequent adverse events were gastrointestinal (diarrhea and nausea).

A current limitation in the data from the MAESTRO-NASH trial is the lack of clinical-outcomes data to correlate with histological data.[8] The safety of long-term resmetirom has not yet been assessed. Data from the ongoing 54-month MAESTRO-NASH trial will be used to confirm clinical benefit and potentially support full approval of Rezdiffra (resmetirom). The primary endpoint will be a composite 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 modified end-stage liver disease [MELD] score from < 12 to ≥ 15. It is anticipated to be completed in August 2028 with final reports submitted to the FDA in March 2029. Although Rezdiffra met both primary endpoints at week 52 in the trial, the placebo-subtracted effect was modest overall (~14 to 23 percentage points for NASH resolution and ~10 to 13 percentage points for fibrosis improvement), indicating that about 2 of 10 patients treated with Rezdiffra will have NASH resolution and 1 of 10 patients treated will have fibrosis improvement. [7]

The Institute for Clinical and Economic Review (ICER) is a non-profit research organization that evaluates clinical and economic evidence for the value of prescription drugs, medical tests, devices, and health system innovations. In May 2023, ICER published a final evidence report for resmetirom for NASH. By a one-vote majority, the panel voted that the evidence is adequate to demonstrate that the net health benefit of resmetirom is superior to that provided by lifestyle management alone. Panel members who voted “yes” found that there is adequate evidence to show improvements in fibrosis stage with no worsening of NASH. Others concluded that resmetirom could potentially reduce the need for liver transplants. Alternatively, voting panel members who voted that there is no adequate evidence adequate to demonstrate that the net health benefit of resmetirom is superior to that

provided by lifestyle management alone concluded that there are not enough long-term data available at this time. Others suggested that the clinical benefits are uncertain, and that there are no published data on patient quality of life. The report concludes that in NASH with F2 or F3 fibrosis there is moderate certainty of comparable to substantial net health benefits with high certainty of at least comparable benefits compared with standard of care (rating C++). The report states "It remains unclear whether changes in the primary outcomes will translate into reduction in cirrhosis, decompensated liver failure, HCC, liver transplantation and death or into improvements in quality of life. Long-term follow-up of the randomized trials should be able to answer these questions."[10]

POLICY:

Commercial/Essential/Child Health Plus criteria:

Based upon our criteria and assessment of the peer-reviewed evidence, the use of Rezdiffra (resmetirom) has not been medically proven to be effective and, therefore, is considered **experimental/investigational** for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis).

The justification for Rezdiffra (resmetirom) to be considered **experimental/investigational** is as follows:

A. Based on our assessment of the peer-reviewed literature, there is inconclusive evidence that the drug has a definite positive effect on health outcomes.

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services

POLICY GUIDELINES:

1. Prior-authorization is contract dependent.
2. This policy does not apply to Medicare Part D. The drugs in this policy may apply to the following formularies: Commercial, Exchange, Child Health Plus, and Essential Plan. If a drug referenced in this policy is non-formulary, please reference Non-Formulary Medication Exception Review Policy for all Lines of Business policy (Pharmacy-69)
3. Clinical documentation must be submitted for each request (initial and recertification) unless otherwise specified (e.g., provider attestation required). Supporting documentation includes, but is not limited to, progress notes documenting previous treatments/treatment history, diagnostic testing, laboratory test results, genetic testing/biomarker results, and imaging.
    - Continued approval at time of recertification will require documentation that the drug is providing ongoing benefit to the patient in terms of improvement or stability in disease state or condition.
4. All requests will be reviewed to ensure they are being used for an appropriate indication and may be subject to an off-label review in accordance with our Off-Label Use of FDA Approved Drugs Policy (Pharmacy-32).

CODES:

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

Code Key:
Experimental/Investigational = (E/I),
Not medically necessary/ appropriate = (NMN).

HCPCS:

UPDATES:

Date	Revision
12/19/2024	Revised
09/13/2024	Revised
09/11/2024	Policy Posted
05/13/2024	Created and Implemented
05/09/2024	P&T Committee Review/Approval

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10. ICER Final Evidence Report – Remetirom and Obeticholic Acid for NASH. NASH-Final-Report_For-Publication_053023.pdf (icer.org). Published May 25,2023. Accessed May 13,2024.