Clinical Policy: Resmetirom (Rezdiffra)

Reference Number: PA.CP.PHAR.647
Effective Date: 11/2024
Last Review Date: 10/2024

Description
Resmetirom (Rezdiffra™) is a thyroid receptor beta agonist.

FDA Approved Indication(s)
Rezdiffra is indicated 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).

This indication is approved under accelerated approval based on improvement of NASH and fibrosis. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Limitation(s) of use: Avoid use in patients with decompensated cirrhosis.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of PA Health & Wellness® that Rezdiffra is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Metabolic Dysfunction-Associated Steatohepatitis (must meet all)**:**

1. Diagnosis of metabolic dysfunction-associated steatohepatitis (MASH; formerly known as NASH);
2. Prescribed by or in consultation with a hepatologist or gastroenterologist;
3. Age ≥ 18 years;
4. MASH with stage F2 or F3 fibrosis is confirmed by one of the following within the last 6 months (a-e):
   a. Liver biopsy;
   b. Both of the following assessments (i and ii):
      i. Serum-based assessment (e.g., fibrosis-4 [FIB-4], NAFLD fibrosis score [NFS], enhanced liver fibrosis test [ELF]);
      ii. Imaging-based assessment (e.g., FibroScan, magnetic resonance-based elastography [MRE], magnetic resonance imaging–proton density fat fraction [MRI-PDFF])
   c. FAST score, as measured by FibroScan and serum aspartate aminotransferase (AST);
   d. MAST score, as measured by MRI-PDFF, MRE, and serum AST;
   e. MEFIB score, as measured by FIB-4 and MRE;

5. If body mass index (BMI) ≥ 25 kg/m^2, documentation of adherence based on the prescriber's assessment to lifestyle modification, including participation in a physician-directed diet and exercise program, for at least the last 6 months;
6. Prescriber attestation that member is currently receiving standard of care management for concomitant related conditions, including type 2 diabetes, dyslipidemia, and hypertension (*see Appendix D*);
7. Dose does not exceed the appropriate weight-based dose (a or b) and 1 tablet per day:
   a. Actual body weight < 100 kg: 80 mg per day;
   b. Actual body weight ≥ 100 kg: 100 mg per day.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

A. Metabolic Dysfunction-Associated Steatohepatitis (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in <u>any</u> of the following parameters:
   a. Improvement in fibrosis ≥ 1-stage from baseline with no worsening of MASH (i.e., no worsening of hepatocellular ballooning, lobular inflammation, or steatosis);
   b. Resolution of MASH with no worsening of fibrosis;
   c. No increase in fibrosis stage and no worsening of MASH from baseline;
3. If request is for a dose increase, new dose does not exceed the appropriate weight-based dose (a or b) and 1 tablet per day:
   a. Actual body weight < 100 kg: 80 mg per day;
   b. Actual body weight ≥ 100 kg: 100 mg per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – PA.CP.PMN.53

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ACE: angiotensin-converting enzyme
ARB: angiotensin receptor blocker
BMI: body mass index
DPP-4: dipeptidyl peptidase 4
ELF: enhanced liver fibrosis
FDA: Food and Drug Administration
FIB-4: fibrosis-4
GLP-1: glucagon-like peptide 1
MASH: metabolic dysfunction-associated steatohepatitis
MASLD: metabolic dysfunction–associated steatotic liver disease
NAFLD: nonalcoholic fatty liver disease
MRE: magnetic resonance elastography
NASH: non-alcoholic steatohepatitis
NFS: NAFLD fibrosis score
PCSK9: proprotein convertase subtilisin/kexin type 9
SGLT2: sodium-glucose co-transporter 2

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

None reported

Appendix D: General Information

- In June 2023, the nomenclature describing NASH and nonalcoholic fatty liver disease (NAFLD) was changed by an international liver disease societies consensus to MASH and metabolic dysfunction-associated steatotic liver disease (MASLD), respectively.
- MASH is defined by the presence of ≥ 5% hepatic steatosis with inflammation and hepatocyte injury (hepatocyte ballooning), with or without evidence of liver fibrosis.
- Standard of care management for concomitant related conditions:
  - Type 2 diabetes management may include metformin, glucagon-like peptide 1 (GLP-1) receptor agonist, sodium-glucose co-transporter 2 (SGLT2) inhibitor, sulfonylurea, dipeptidyl peptidase 4 (DPP-4) inhibitors, pioglitazone, or insulin.
  - Dyslipidemia management may include a statin, ezetimibe, fibrate, omega-3 fatty acids, or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.
  - Hypertension management may include an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), calcium channel blocker, or a thiazide diuretic.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
MASH	Recommended dose is based on actual body weight: • < 100 kg: 80 mg PO daily • ≥ 100 kg: 100 mg PO daily	See dosing regimen

VI. Product Availability

Oral tablets: 60 mg, 80 mg, 100 mg

VII. References

1. Rezdiffra Prescribing Information. West Conshohocken, PA: Madrigal Pharmaceuticals; March 2024. Available at: https://www.madrigalpharma.com/wp-content/uploads/2024/03/Prescribing-Information.pdf. Accessed July 15, 2024.
2. Harrison SA, Bedossa P, Guy CD, et al. A Phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. N Engl J Med. 2024;390(6):497-509.
3. American Diabetes Association Professional Practice Committee. 4. Comprehensive medical evaluation and assessment of comorbidities: Standards of Care in Diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S52-S76.
4. 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.
5. Cusi K, Isaacs S, Barb D, et al. American Association of Clinical Endocrinology (AACE) clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the American Association for the Study of Liver Diseases (AASLD). Endocr Pract. 2022;28(5):528-562.
6. Kanwal F, Shubrook JH, Adams LA, et al. Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. Gastroenterology. 2021;161(5):1657-1669.
7. Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Ann Hepatol. 2024;29(1):101133.
8. Sterling RK, Duarte-Rojo A, Patel K, et al. AASLD Practice Guideline on imaging-based noninvasive liver disease assessment of hepatic fibrosis and steatosis. Hepatology. Published online March 15, 2024.

Reviews, Revisions, and Approvals	Date
Policy created	10/2024