Clinical Policy: Resmetirom (Rezdiffra)

Reference Number: CP.PHAR.647
Effective Date: 03.14.24
Last Review Date: 05.24
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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 health plans affiliated with Centene Corporation® 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 biomarkers (i and ii):
      i. Serum biomarker (e.g., fibrosis-4 [FIB-4], NAFLD fibrosis score [NFS], enhanced liver fibrosis test [ELF]);
      ii. Imaging biomarker (e.g., FibroScan, 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, magnetic resonance elastography (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 to lifestyle modification, including participation in a physician-directed diet and exercise program, for at least the last 6 months;
6. For members with type 2 diabetes: Failure of a 6-month trial of pioglitazone at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
7. 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*);
8. 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 (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B)*;
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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

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
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
pioglitazone	30-45 mg PO daily	45 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

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 (also known as 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 March 14, 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.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	08.25.23	11.23
RT1: Drug is now FDA-approved – criteria updated per FDA labeling: added new MASH terminology; added MASH fibrosis diagnostic test options and timeframe from within the last 6 months; updated criterion for BMI lower limit requiring documentation of adherence to lifestyle modification from 27 kg/m^2 to 25 kg/m^2 per overweight range of BMI index; added prescriber attestation that member is currently receiving standard of care management for concomitant related conditions; updated maximum FDA-labeled dosing; for positive response criteria, added option of MASH resolution with no worsening of fibrosis; references reviewed and updated.	04.09.24	05.24

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.