resmetirom (Rezdiffra™)

Policy # 00884
Original Effective Date: 08/12/2024
Current Effective Date: 08/12/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider resmetirom (Rezdiffra™)‡ for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for resmetirom (Rezdiffra) will be considered when the following criteria are met:

- Initial
    - Patient meets one of the following:
        - Patient has a diagnosis of noncirrhotic nonalcoholic steatohepatitis (NASH) or noncirrhotic metabolic dysfunction–associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (stage F2 to F3 fibrosis) confirmed by biopsy; OR
        - Patient has a diagnosis of noncirrhotic nonalcoholic steatohepatitis (NASH) or noncirrhotic metabolic dysfunction–associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (stage F2 to F3 fibrosis) based on noninvasive testing (e.g., Fibrosis-4 Index [FIB-4], vibration-controlled elastography [VCTE], enhanced liver fibrosis [ELF], OR magnetic resonance elastography [MRE]; AND

- If the patient has had a liver biopsy, patient has a NAFLD Activity Score (NAS) of ≥ 4; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Patient does NOT have cirrhosis (F4) or hepatic decompensation; AND
- Patient is 18 years of age or older; AND
- Requested medication will be used in conjunction with lifestyle interventions, including diet and exercise; AND
- If the patient has BMI > 27, patient has had a trial of lifestyle interventions for at least 3 months, with a goal of at least 5% to 10% weight loss; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Patient's concomitant related conditions including dyslipidemia, type II diabetes, and hypertension are managed according to standard of care; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Patient does not have excessive alcohol use defined as more than 20 g per day for women and more than 30 g per day for men. (Note that one standard drink [or one alcoholic drink equivalent] contains roughly 14 grams of pure alcohol, which is found in 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of distilled spirits.)
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*

- Continuation
  - Patient has an initial authorization for Rezdiffra; AND
  - Patient does not have cirrhosis (F4) or hepatic decompensation; AND
  - Patient has been adherent to treatment with Rezdiffra; AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
  - Patient is responding adequately to treatment (as confirmed in laboratory tests and other noninvasive tests (NITs); AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*

- Patient's concomitant related conditions including dyslipidemia, type II diabetes, and hypertension are managed according to standard of care; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Patient does not have excessive alcohol use defined as more than 20 g per day for women and more than 30 g per day for men. (Note that one standard drink [or one alcoholic drink equivalent] contains roughly 14 grams of pure alcohol, which is found in 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of distilled spirits.)
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers resmetirom (Rezdiffra) when any of the following criteria are not met to be **not medically necessary.****

- For initial requests:
  - If the patient has had a liver biopsy, patient has a NAFLD Activity Score (NAS) of ≥ 4
  - If the patient has BMI > 27, patient has had a trial of lifestyle interventions for at least 3 months, with a goal of at least 5% to 10% weight loss
  - Patient's concomitant related conditions including dyslipidemia, type II diabetes, and hypertension are managed according to standard of care
  - Patient does not have excessive alcohol use defined as more than 20 g per day for women and more than 30 g per day for men
- For continuation requests:
  - Patient has been adherent to treatment with Rezdiffra
  - Patient is responding adequately to treatment (as confirmed in laboratory tests and other noninvasive tests (NITs)
  - Patient's concomitant related conditions including dyslipidemia, type II diabetes, and hypertension are managed according to standard of care
  - Patient does not have excessive alcohol use defined as more than 20 g per day for women and more than 30 g per day for men

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of resmetirom (Rezdiffra) when the patient selection criteria are not met (with the exception of those denoted above as **not medically necessary****) to be **investigational.***

Policy Guidelines

In June 2023, the nomenclature describing NAFLD and NASH was changed to metabolic dysfunction–associated steatotic liver disease (MASLD) and metabolic dysfunction–associated steatohepatitis (MASH), respectively. This policy uses the older nomenclature, as this is what is used in the prescribing information for Rezdiffra.

Background/Overview

Rezdiffra is indicated in conjunction with diet and exercise for the treatment of adults with non-cirrhotic non-alcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis). Rezdiffra, a thyroid hormone receptor beta (THR-β) agonist, is the first therapy approved for the treatment of NASH. In patients with NASH, THR-β function in the liver is impaired, leading to a reduction in mitochondrial function and β-oxidation of fatty acids with an increase in fibrosis. Rezdiffra stimulates THR-β in the liver to reduce intrahepatic triglycerides, improve mitochondrial function and subsequently reduce fibrosis.

The recommended dose of Rezdiffra is based on actual body weight. For patients < 100 kg the dose is 80 mg once daily and for patients ≥ 100 kg the dose is 100 mg once daily. Concomitant use of Rezdiffra with strong CYP2C8 inhibitors is not recommended. If Rezdiffra is used concomitantly with a moderate CYP2C8 inhibitor, it is recommended that the dose of Rezdiffra be reduced to 60 mg once daily (if weight is < 100 kg) or 80 mg once daily (if weight is ≥ 100 kg). The use of Rezdiffra in patients with decompensated cirrhosis (consistent with moderate to severe hepatic impairment) should be avoided.

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Non-cirrhotic non-alcoholic steatohepatitis (NASH)
Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver condition, characterized by pathophysiological fatty liver changes unrelated to alcohol intake, and is associated with insulin resistance, obesity, weight gain, and diabetes. Most patients with NAFLD are asymptomatic and are often diagnosed through an ultrasound ordered for unrelated reasons or during a work-up performed secondary to abnormal liver enzymes on routine blood tests. Nonalcoholic steatohepatitis (NASH) is a severe, subset form of NAFLD.

NASH, also known as metabolic dysfunction-associated steatohepatitis (MASH), is a progressive liver disease defined by the presence of ≥ 5% hepatic steatosis with hepatocellular damage and inflammation. NASH can progress to advanced liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) which are associated with significant morbidity and mortality. In the US, NASH is among the top causes of HCC and the second most common indication for liver transplantation after hepatitis C. Once NASH progresses to clinically meaningful fibrosis (stages F2 and F3), the risk of adverse clinical outcomes increases.

It is estimated that about 25% of the U.S. population is affected by NAFLD while 1.5% to 6.5% of the U.S. population is affected by NASH. The risk of NASH is two- to three-fold higher in individuals with obesity (25% to 30%) and/or type II diabetes (30% to 40%). Until the approval of Rezdiffra, management of NASH included lifestyle modifications through diet and exercise and treating associated disease states such as hypertension, dyslipidemia, diabetes, and obesity. Weight loss of ≥ 10% results in a resolution of NASH in the majority of patients and improves fibrosis and portal inflammation.

Biomarkers and noninvasive tests (NITs) can be used clinically to either exclude advanced diseases or identify those with a high probability of cirrhosis. In addition, NITs can be used to assess the likelihood of significant fibrosis, predict risk of disease progression and decompensation, make management decisions, and aid in assessing response to treatment. Noninvasive tests for NASH [e.g., FIB-4, vibration-controlled elastography (VCTE), magnetic resonance elastography (MRE)] are used for screening and risk stratification and may be used for disease staging by specialists but can be inconclusive, requiring liver biopsy. Although liver biopsy is considered the reference standard for grading and staging hepatic disease as it provides information on anatomic complications (e.g., cellular injury, inflammation, fibrosis) and aids in ruling out other causes of liver disease, it has

significant limitations related to risk and cost, and is therefore not consistently performed in clinical practice.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Rezdiffra is approved for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) in conjunction with diet and exercise. 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 a confirmatory trial.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Rezdiffra was evaluated based on an efficacy analysis at Month 12 in MAESTRO NASH, a Phase 3, 54-month, randomized, double-blind, placebo-controlled trial. Enrolled patients had metabolic risk factors and a baseline or recent liver biopsy showing NASH with fibrosis stage 2 or 3 and a NAFLD Activity Score (NAS) of at least 4. NAS is an unweighted composite of steatosis (scored 0 to 3), lobular inflammation (scored 0 to 3), and ballooning degeneration (scored 0 to 2). Key trial exclusion criteria were alcohol consumption of > 20 grams/day for women and > 30 grams per day for men, hemoglobin A1c (HbA1c) > 9.0% at screening, and causes of chronic liver disease other than non-cirrhotic NASH. Efficacy determination was based on the effect of Rezdiffra on resolution of steatohepatitis without worsening of fibrosis and ≥ 1 stage improvement in fibrosis without worsening of steatohepatitis, on post-baseline liver biopsies collected at 12 months. The month 12 analysis included 888 F2 and F3 (at eligibility) patients 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.

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Efficacy findings reported in the prescribing information were based on the percentage of patients meeting clinical endpoints based on biopsy readings performed by two pathologists (Pathologist A and Pathologist B). Results for the NASH resolution endpoint based on Pathologist A's readings were 27%, 36%, and 13% for Rezdiffra 80 mg, Rezdiffra 100 mg, and placebo, respectively. For the same endpoint, results based on Pathologist B's readings were 26%, 24%, and 9% for Rezdiffra 80 mg, Rezdiffra 100 mg, and placebo, respectively. Results for the fibrosis endpoint based on Pathologist A's readings were 23%, 28%, and 15% for Rezdiffra 80 mg, Rezdiffra 100 mg, and placebo, respectively. For the same endpoint, results based on Pathologist B's readings were 23%, 24%, and 13% for Rezdiffra 80 mg, Rezdiffra 100 mg, and placebo, respectively.

Although Rezdiffra met both primary endpoints 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.

MAESTRO-NASH, which will serve as the confirmatory trial, is anticipated to be completed in August 2028, with the final report submitted to the FDA in March 2029.

References

1. Rezdiffra [package insert]. Madrigal Pharmaceuticals, Inc. West Conshohocken,PA. March 2024.
2. Rezdiffra Drug Evaluation. Express Scripts. April 3, 2024.
3. Rezdiffra (resmetirom) New Drug Review. IPD Analytics. March 2024.
4. Clinical features and diagnosis of metabolic dysfunction-associated steatotic liver disease (nonalcoholic fatty liver disease) in adults. UpToDate. Updated February 28, 2024.
5. Rinella, M. E., Neuschwander-Tetri, B. A., Siddiqui, M. S., Abdelmalek, M. F., Caldwell, S., Barb, D., Kleiner, D. E., & Loomba, R. (2023). AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology, 77(5), 1797–1835. https://doi.org/10.1097/hep.0000000000000323

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07/02/2024 Medical Policy Committee review
07/10/2024 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 07/2025

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.