



Drug Coverage Policy

Effective Date2/1/2026

Coverage Policy Number.....IP0642

Policy Title.....Rezdiffra

Hepatology – Rezdiffra

- Rezdiffra™ (resmetirom tablets - Madrigal Pharmaceuticals)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

OVERVIEW

Rezdiffra, a thyroid hormone receptor-beta (THR-β) agonist, is indicated in combination with diet and exercise for the treatment of **non-cirrhotic non-alcoholic steatohepatitis (NASH)** with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) in adults.¹

Limitations of Use: Avoid use in patients with decompensated cirrhosis.

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 trial.¹

Clinical Efficacy

The efficacy of Rezdiffra was evaluated in one ongoing, Phase III, randomized, double-blind, placebo-controlled, multicenter, pivotal study in adults with biopsy-confirmed NASH (MAESTRO-NASH) with fibrosis (F1B, F2, or F3) [n = 966].⁵ The dual primary endpoints at Week 52 were 1) NASH resolution (achievement of a hepatocellular ballooning score = 0, inflammation score = 0 or 1, and ≥ 2 point reduction in non-alcoholic fatty liver disease activity score [NAS]) with no worsening of fibrosis, and 2) ≥ 1 stage improvement in fibrosis with no worsening of NAS. Patients who reached the Week 52 analysis were eligible to continue to the open-label extension with a primary endpoint of 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). Eligible patients were ≥ 18 years of age, had at least three of five metabolic risk factors according to the International Diabetes Foundation criteria for metabolic syndrome³ (central obesity, elevated triglycerides [≥ 150 mg/dL], reduced high-density lipoprotein cholesterol [< 50 mg/dL in females or < 40 mg/dL in males], elevated blood pressure [$\geq 130/85$ mmHg], elevated fasting plasma glucose [≥ 100 mg/dL]), and had undergone prescreening vibration-controlled transient elastography (VCTE; FibroScan) within the past 3 months that showed a controlled attenuation parameter of ≥ 280 dB/meter and a liver stiffness measurement of ≥ 8.5 kPa (alternately, a liver biopsy that was performed within 6 months before randomization could be confirmed to be eligible as a baseline biopsy by the central pathologist of the trial). Additional key inclusion criteria were histologic evidence of NASH and an NAS of ≥ 4 (on a scale of 0 to 8 with higher scores indicating more severe disease), with a score of ≥ 1 for each component (steatosis [on a scale of 0 to 3], lobular inflammation [on a scale from 0 to 3], and hepatocellular ballooning [on a scale from 0 to 2]). Key exclusion criteria were alcohol consumption of > 20 g/day for women and > 30 g/day for men for a period of ≥ 3 consecutive months within 1 year of screening and causes of chronic liver disease other than non-cirrhotic NASH.

The mean age was 57 years, the mean body mass index was 35.7 kg/m², 67% of patients had type 2 diabetes, 78% of patients had hypertension, and 71% of patients had dyslipidemia.² Glucagon-like receptor-1 agonist use was reported in approximately 15% of patients. Most patients had a fibrosis stage of F3 (62%), 33% of patients had F2, and 5% of patients had F1B. All patients underwent lifestyle modification consisting of diet and exercise.

At Week 52, NASH resolution associated with a ≥ 2 point reduction in NAS without worsening of fibrosis stage was reported for 29.9% and 25.9% of patients in the Rezdiffra 100 mg and 80 mg groups, respectively vs. 9.7% of patients in the placebo group (P < 0.0001 for Rezdiffra doses vs. placebo).⁵ The proportion of patients with ≥ 1 stage fibrosis improvement with no worsening in NAS at Week 52 was 25.9% and 24.2% for Rezdiffra 100 mg and 80 mg, respectively vs. 14.2% for placebo (P < 0.0001 for Rezdiffra doses vs. placebo). Fewer patients treated with Rezdiffra vs. placebo with F1B or F2 at baseline progressed to $\geq F3$ (18% to 19% vs. 34%, respectively) and more patients treated with Rezdiffra vs. placebo with F1B or F2 at baseline had an improved fibrosis stage (31% to 33% vs. 15%, respectively). A similar proportion of patients treated with Rezdiffra and placebo with F1B or F2 at baseline had no change (stable) in fibrosis stage at Week 52 (48% to 51% vs. 51%, respectively).

Guidelines

The American Association for the Study of Liver Diseases (AASLD) Practice Guidance on the Clinical Management of NAFLD (2023) was updated in October 2024 to address the approval of

Rezdiffra and in November 2025 to address approval of Wegovy (semaglutide subcutaneous injection) for MASH.^{4,5} Best practices in the management of MASH include comprehensive lifestyle modification (nutrition, exercise, behavioral modification), and optimal control of comorbid metabolic conditions.⁴ MASH can only be definitively diagnosed by histologic exam (biopsy); however, in practice, patient selection is based on evidence of steatosis and fibrosis as determined by non-invasive tests in patients with cardiometabolic risk factors without other causes of steatosis, notably, alcohol consumption of > 20 g/day for women and > 30 g/day for men. Specifically, fibrosis can be estimated using imaging and/or blood-based non-invasive tests with reasonable to high accuracy.⁵ There are no FDA-approved non-invasive tests to diagnose MASH with stage F2 to F3 fibrosis or to monitor the response to pharmacotherapy.⁴ Although liver biopsy is not typically recommended for fibrosis staging in current clinical practice, histologic exam remains the gold standard to quantify fibrosis if performed previously (historical biopsy obtained reasonably recently, e.g., within 3 years). Since non-invasive tests are more readily available than liver biopsy, it is recommended that more current data (e.g., within 6 to 12 months) be utilized to determine patients who are appropriate candidates for treatment. Three non-invasive tests are supported in the guidance: VCTE, magnetic resonance elastography (MRE), and the blood-based biomarker Enhanced Liver Fibrosis™ (ELF) score.⁵ For the blood-based ELF score, a cutoff of 9.2 provides optimal sensitivity and specificity for detecting \geq F2 fibrosis. To guide the selection of appropriate candidates for treatment with MASH therapy, the ELF score range of 9.2 to 10.5 is recommended. While the range serves as guidance, in those with values outside of the upper range, exclusion of cirrhosis and portal hypertension should be considered using another non-invasive test such as VCTE or MRE. Rezdiffra is not recommended in patients with cirrhosis.⁴

Coverage Policy

POLICY STATEMENT

Prior Authorization is required for benefit coverage of Rezdiffra. All approvals are provided for the duration noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a male, regardless of the individual's gender identity or gender expression; females are defined as individuals with the biological traits of a female, regardless of the individual's gender identity or gender expression. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rezdiffra as well as the monitoring required for adverse events and long-term efficacy, approval requires Rezdiffra to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Rezdiffra as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory results, medical test results, claims records, prescription receipts, and/or other information. All documentation must include patient-specific identifying information.

Rezdiffra is considered medically necessary when the following is met:

FDA-Approved Indication

- 1. Metabolic-Dysfunction Associated Steatohepatitis (MASH)/Non-Alcoholic Steatohepatitis (NASH).** Approve for 1 year if the patient meets ONE of the following (A or B):
 - A) Initial Therapy:** Approve if the patient meets ALL of the following (i, ii, iii, iv, v, vi):
 - i.** Patient is \geq 18 years of age; AND
 - ii.** Patient has stage F2 or F3 fibrosis prior to initiating treatment with Rezdiffra or Wegovy **[documentation required]** identified by ONE of the following (a, b, c, or d):

- a) Liver biopsy performed within the 3 years preceding treatment with Rezdifra or Wegovy **[documentation required]**; OR
 - b) Vibration-controlled transient elastography (VCTE) performed within the 6 months preceding treatment with Rezdifra or Wegovy **[documentation required]**; OR
 - c) Magnetic resonance elastography (MRE) performed within the 6 months preceding treatment with Rezdifra or Wegovy **[documentation required]**; OR
 - d) Enhanced Liver Fibrosis™ (ELF) test performed within the 6 months preceding treatment with Rezdifra or Wegovy **[documentation required]** with a score of ≥ 9.2 to ≤ 10.5 **[documentation required]**; AND
- iii. According to the prescriber, the patient has ONE or more of the following metabolic risk factors that are managed according to standard of care (a, b, c, d, e):
- a) Central obesity;
 - b) Hypertriglyceridemia;
 - c) Reduced high-density lipoprotein cholesterol;
 - d) Hypertension;
 - e) Elevated fasting plasma glucose indicative of diabetes or pre-diabetes; AND
- iv. According to the prescriber, patient meets ONE of the following (a or b):
- a) Female* patient: Alcohol consumption is < 20 grams/day; OR
Note: 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.
 - b) Male* patient: Alcohol consumption < 30 grams/day; AND
Note: 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.
- v. The medication will be used in combination with appropriate diet and exercise therapy; AND
- vi. The medication is prescribed by or in consultation with an endocrinologist, gastroenterologist, or hepatologist.
- B) Patient is Currently Receiving Rezdifra**: Approve if the patient meets ALL of the following (i, ii, iii, iv, v, and vi):
- Note: A patient who has received < 1 year of therapy or who is restarting therapy should be considered under criterion A (Initial Therapy).
- i. Patient has completed ≥ 1 year of therapy with Rezdifra AND according to the prescriber, the patient has not had worsening of fibrosis or MASH/NASH; AND
Note: This applies to a patient starting their second (or more) year of therapy with Rezdifra (i.e., the patient has already completed 1 year or more of therapy with Rezdifra).
 - ii. According to the prescriber, the patient does not have cirrhosis (F4); AND
 - iii. According to the prescriber, metabolic risk factors are managed according to standard of care; AND
 - iv. According to the prescriber, patient meets ONE of the following (a or b):
 - a) Female* patient: Alcohol consumption is < 20 grams/day; OR
Note: 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.
 - b) Male* patient: Alcohol consumption < 30 grams/day; AND
Note: 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.
 - v. The medication will be used in in combination with appropriate diet and exercise therapy; AND

- vi. The medication is prescribed by or in consultation with an endocrinologist, gastroenterologist, or hepatologist.

*Refer to the Policy Statement

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Rezdiffra for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

- 1. Metabolic-Dysfunction Associated Steatotic Liver Disease (MASLD)/Non-Alcoholic Fatty Liver Disease (NAFLD).** Resmetirom is indicated in patients with non-cirrhotic NASH with moderate to advanced liver fibrosis.¹ NAFLD and NASH include the presence of steatosis; however, NASH additionally involves inflammation and injury to liver cells.²
- 2. Metabolic-Dysfunction Associated Steatohepatitis (MASH)/Non-Alcoholic Steatohepatitis (NASH) with Cirrhosis (F4).** Resmetirom is indicated in patients with non-cirrhotic NASH with moderate to advanced liver fibrosis.¹ The safety and effectiveness of Rezdiffra have not been established in patients with NASH cirrhosis. MEASTRO-NASH-OUTCOMES is an ongoing trial to assess the efficacy of Rezdiffra in adults with NASH with well-compensated cirrhosis (Child-Pugh A) [n = 700].⁸ Results are anticipated in 2025.

References

1. Rezdiffra™ tablets [prescribing information]. West Conshohocken, PA: Madrigal Pharmaceuticals; March 2024.
2. Harrison SA, Bedossa P, Guy CD, et al; for the MAESTRO-NASH Investigators. A Phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. *N Engl J Med.* 2024;390:497-509. 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;77:1797-1835.
3. International diabetes foundation. The IDF consensus worldwide definition of the metabolic syndrome. Available at: <https://idf.org/media/uploads/2023/05/attachments-30.pdf>. Accessed on: March 20, 2024.
4. Chen VL, Morgan TR, Rotman Y, et al. Resmetirom therapy for metabolic dysfunction-associated steatotic liver disease: October 2024 updates to AASLD Practice Guidance. *Hepatology.* 2025;81(1):312-320.
5. Bansal MB, Patton H, Morgan TR, et al. Semaglutide therapy for metabolic dysfunction-associated steatohepatitis: November 2025 updates to AASLD practice guidance. *Hepatology.* 2025 Nov 7. [Online ahead of print].

Revision Details

Type of Revision	Summary of Changes	Date
New	New policy	08/15/2024
Selected Revision	<p>For Metabolic-Dysfunction Associated Steatohepatitis (MASH)/Non-Alcoholic Steatohepatitis (NASH), with Moderate to Advanced Liver Fibrosis, for Initial Therapy, the timeframe requirement for a patient with a liver biopsy was changed to be within the 3 years preceding treatment with Rezdifra, previously within the past 6 months preceding treatment with Rezdifra. For a Patient Currently Receiving Rezdifra, the criteria that the patient has completed ≥ 1 year and < 2 years of therapy with Rezdifra and has derived benefit from treatment with Rezdifra as demonstrated by one of the following, according to the prescriber: 1) MASH/NASH resolution AND no worsening of fibrosis; OR No worsening of MASH/NASH AND improvement in fibrosis by ≥ 1 stage, was removed. A patient who has completed ≥ 1 year of therapy with Rezdifra is now reviewed under the same criterion that was previously applied for a patient who has completed ≥ 2 years of therapy. As revised, a patient who has completed ≥ 1 year of therapy with Rezdifra AND according to the prescriber has not had worsening of fibrosis or MASH/NASH may be approved if other criteria are met.</p>	3/15/2025
Annual Revision	<p>Metabolic Dysfunction-Associated Steatohepatitis (MASH)/Non-Alcoholic Steatohepatitis (NASH), with Moderate to Advanced Liver Fibrosis. <u>Initial Therapy.</u> The criterion that the liver biopsy shows non-alcoholic fatty liver disease activity score of ≥ 4 with a score of > 1 in ALL of the following [documentation required]: Steatosis, ballooning, and lobular inflammation; was modified such that a score of ≥ 1 is required in ALL of the following [documentation required]: Steatosis, ballooning, and lobular inflammation. The timeframe within the criterion for an imaging exam was changed from within the 3 months preceding treatment with Rezdifra to within the 6 months preceding treatment with Rezdifra.</p>	6/15/2025
Selected Revision	<p>Metabolic-Dysfunction Associated Steatohepatitis (MASH)/Non-Alcoholic Steatohepatitis (NASH). The condition for approval was updated to remove "with moderate to advanced liver fibrosis" to match the intent of the criteria. For initial therapy, a patient is still required to demonstrate moderate or advanced fibrosis.</p>	8/15/2025

Selected Revision	<p>Metabolic-Dysfunction Associated Steatohepatitis (MASH)/Non-Alcoholic Steatohepatitis (NASH). <u>Initial Therapy.</u> For the criterion regarding confirmation of the diagnosis of MASH/NASH, the requirement that the diagnosis be “prior to treatment with Rezdifra” was removed. The number of metabolic risk factors in the following criterion was changed to ONE or more (previously THREE or more): According to the prescriber, the patient has ONE or more of the following metabolic risk factors that are managed according to standard of care: central obesity, hypertriglyceridemia, reduced high-density lipoprotein cholesterol, hypertension, elevated fasting plasma glucose indicative of diabetes or pre-diabetes.</p>	10/16/2025
Selected Revision	<p>Metabolic Dysfunction-Associated Steatohepatitis (MASH)/Non-Alcoholic Steatohepatitis (NASH). Initial Therapy. Criteria for the diagnosis of MASH/NASH were updated such that the patient must have documentation of stage F2 or F3 fibrosis prior to initiating treatment with Rezdifra or Wegovy confirmed by ONE of the following: Liver biopsy performed within 3 years preceding treatment with Rezdifra or Wegovy [documentation required], vibration-controlled elastography (VCTE) performed within 6 months preceding treatment with Rezdifra or Wegovy [documentation required], magnetic resonance imaging (MRE) performed within 6 months preceding treatment with Rezdifra or Wegovy [documentation required], or Enhanced Liver Fibrosis (ELF) test performed within 6 months preceding treatment with Rezdifra or Wegovy [documentation required] with a score of ≥ 9.2 to ≤ 10.5 [documentation required]. Previously, the diagnosis of MASH/NASH was confirmed by a either a liver biopsy within 3 years preceding treatment with Rezdifra [documentation required] that showed a non-alcoholic fatty liver disease activity score of ≥ 4 with a score of ≥ 1 in steatosis, ballooning, and lobular inflammation [documentation required] OR an imaging exam (i.e., elastography, computed tomography, or magnetic resonance imaging) performed within 6 months preceding treatment with Wegovy [documentation required]. The separate criterion that the patient have stage F2 or F3 fibrosis [documentation required] was removed (this is part of the updated criterion outlined above; patients must still have documentation of F2 or F3 fibrosis). Reference to prior to initiating therapy throughout criteria were updated to include Wegovy</p>	2/1/2026

	<p>(i.e., prior to initiating treatment with Rezdifra "or Wegovy"); previously only Rezdifra. Patient is Currently Receiving Rezdifra. The criterion requiring that according to the prescriber the patient has not progressed to stage F4 (cirrhosis) was modified to state, according to the prescriber, patient does not have cirrhosis (F4).</p> <p>Metabolic Dysfunction-Associated Steatohepatitis (MASH)/Non-Alcoholic Steatohepatitis (NASH) with Cirrhosis (F4). This condition not recommended for approval was updated to add "(F4)" in reference to cirrhosis.</p>	
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The policy effective date is in force until updated or retired.

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