

PRIOR AUTHORIZATION POLICY

POLICY: Hepatology – Rezdiffra Prior Authorization Policy

- Rezdiffra™ (resmetirom tablets – Madrigal Pharmaceuticals)

REVIEW DATE: 04/03/2024; selected revision 05/08/2024 and 12/04/2024

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

Disease Overview

NASH, also known as metabolic-dysfunction associated steatohepatitis (MASH), is a progressive liver disease characterized by the presence of $\geq 5\%$ hepatic steatosis with hepatocellular damage and inflammation in the absence of readily identified alternative cause of steatosis (e.g., medications, starvation, monogenic disorders) in individuals who drink little or no alcohol (defined as < 20 g/day for women and < 30 g/day for men).² Once NASH progresses to clinically meaningful fibrosis (stages F2 and F3), the risk of adverse clinical outcomes increases. In the US, it is estimated that 1.5% to 6.5% of adults have NASH.³ The estimated prevalence of high-risk NASH (defined as non-alcoholic fatty liver disease activity score [NAS] ≥ 4 and fibrosis stage ≥ 2 [F2]) in the US is 5.8%. The risk of NASH is two- to three-fold higher in individuals with obesity (25% to 30%) and/or type 2 diabetes (30% to 40%).⁴ In the US, NASH is among the top causes of hepatocellular carcinoma and the second most common indication for liver transplantation after hepatitis C.

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. The key secondary endpoint was the percent reduction in low-density lipoprotein cholesterol (LDL-C) at Week 24. 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 syndrome⁹ (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

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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/m^2 , 67% of patients had type 2 diabetes, 78% of patients had hypertension, and 71% of patients had dyslipidemia (approximately 50% of patients were taking a statin).⁵ 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). At Week 24, LDL-C was reduced by -16.3% and -13.6% with Rezdiffra 100 mg and 80 mg, respectively, vs. +0.7% with placebo ($P = 0.0001$ Rezdiffra doses vs. placebo) [key secondary endpoint]. 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

An update to the American Association for the Study of Liver Diseases (AASLD) Practice Guidance on the Clinical Management of non-alcoholic fatty liver disease (NAFLD) was published in October 2024 to address the approval of Rezdiffra.¹⁰ It is recognized that although MASH can only be definitively diagnosed by histologic exam (biopsy), in practice, patient selection is based on evidence of steatosis and fibrosis as determined by non-invasive liver disease assessments (NILDAs) in patients with cardiometabolic risk factors without other causes of steatosis, notably, alcohol consumption of > 20 g/day for women and > 30 g/day in men. There are no FDA-approved NILDAs to diagnose MASH with stage F2 to F3 fibrosis or to monitor the response to pharmacotherapy. In general imaging-based NILDAs such as liver stiffness measurement (LSM) by VCTE or magnetic resonance elastography (MRE) have better accuracy in assessing fibrosis vs. blood-based tests. In general, magnetic resonance spectroscopy and magnetic resonance imaging proton fat density fat fraction (MRI-PDFF) are considered the most accurate quantitative measures of hepatic steatosis, followed by VCTE-controlled attenuation parameter score and gray scale ultrasound. However, for the purpose of selecting patients for treatment with Rezdiffra, non-quantitative imaging evidence of hepatic steatosis (e.g., ultrasonographic evidence) in individuals with at least one cardiometabolic risk factor and F2 or F3 fibrosis may be sufficient. Liver biopsy is not typically recommended for fibrosis staging in current clinical practice; however, histologic exam remains the gold standard to quantify fibrosis if performed previously (historical biopsy obtained reasonably recently, e.g., within 3 years). Since NILDAs 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 with Rezdiffra. Regardless of treatment, the management of metabolic-dysfunction associated steatotic liver disease (MASLD) should include comprehensive lifestyle modification (e.g., nutrition, exercise, and behavior modification) and optimal control of comorbid metabolic conditions. Further, given

the comorbidity profile of individuals with MASLD, cardiovascular risk management is an important aspect of medical management.

When selecting appropriate patients for treatment, Rezdiffra can be considered in adults with MASH and moderate to advanced liver fibrosis (consistent with F2 or F3 fibrosis).¹⁰ The diagnosis should be assessed by one of the following: 1) NILDA, preferably imaging-based test results, consistent with MASH with stage F2 or F3 fibrosis; or 2) Historical liver biopsy demonstrating MASH with stage F2 or F3 fibrosis (and without evidence of concomitant, histologically active autoimmune liver disease). Rezdiffra is not recommended in patients with the following: compensated or decompensated cirrhosis, concomitant uncontrolled active liver diseases (e.g., autoimmune hepatitis, primary biliary cholangitis), or alcohol consumption > 20 grams/day (women) or > 30 grams/day (men), or symptomatic gallstone-related conditions (e.g., acute cholecystitis). While some values for NILDAs (VCTE and MRE) are cited within the update, for choosing patients appropriate for treatment with Rezdiffra, they are not completely aligned with the MAESTRO-NASH trials, and the AASLD notes that clinicians may consider expanded non-invasive criteria in making treatment decisions.

The updated guidance also addresses efficacy and futility of Rezdiffra treatment based on the Week 52 data with Rezdiffra from MAESTRO-NASH.¹⁰ However, it is recognized that these recommendations may change when longer-term data become available. The decision to continue treatment beyond 12 months should be based on evidence of improvement, worsening, or treatment failure, or disease stabilization. Although the guidance provides recommendations for continuing/re-evaluating treatment with Rezdiffra based on LSM values for VCTE or MRE, reliable evidence to correlate LSM data with histologic changes in liver fibrosis is lacking. Continuation of Rezdiffra in patients with significant fibrosis improvement is recommended. In patients with evidence of worsening of liver disease at Month 12, discontinuation of Rezdiffra should be considered. Worsening liver disease can be identified by clinical data suggestive of worsening liver disease including consistent increase in alanine aminotransferase or fibrosis progression as assessed by NILDA. In patients without clear evidence of liver disease improvement or worsening, the decision to continue therapy (pending longer-term data) should be based on holistic patient assessment considering baseline fibrosis status and potential benefit of slowing or stabilizing liver fibrosis even if no regression is noted; individual comorbidity profile associated with progressive liver disease; concomitant therapy including adherence and response to lifestyle interventions; changes in liver biochemical and NILDA parameters; and adverse effects (if any) during treatment with Rezdiffra.

Other available guidelines do not address Rezdiffra. The 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.^{4,6,7} The goal of liver-directed treatment is to reverse steatohepatitis and fibrosis, or to at least halt the progression of fibrosis.⁷ Importantly, the presence of steatosis serves largely as a biomarker or risk factor of steatohepatitis with fibrosis; however, the presence of steatosis does not necessarily imply severe disease. In general, in patients with NASH with \geq F2 fibrosis, agents approved for other indications that have shown benefit for NASH in clinical trials should be considered under specific circumstances (e.g., diabetes, obesity).^{4,6,7} A healthy diet and regular exercise are the foundation of treatment. Weight loss of \geq 10% is generally required to improve NASH and fibrosis. Management of comorbid conditions (e.g., cardiovascular disease, obesity, diabetes) should be done in-line with the standard of care and encourage use of agents that have shown benefit in NASH (e.g., liraglutide, semaglutide, pioglitazone, vitamin E).

According to the AASLD, targeted screening of populations at increased risk for advanced liver disease is advised to identify and manage those with clinically significant fibrosis (stage \geq F2).² The primary goal in the specialty care setting (gastroenterology, hepatology) is the identification of patients with “at-risk” NASH or advanced fibrosis. Such patients require further assessment and may benefit from targeted interventions. The AGA recommends that at-risk patients be screened for alcohol use and have liver tests

as well as a complete blood count as part of the initial screening process.⁷ Results from standard laboratory tests can allow calculation of simple fibrosis scores using non-invasive tests for fibrosis (e.g., Fibrosis-4 [FIB-4] or NAS). Patients with a FIB-4 of ≥ 1.3 to ≤ 2.67 are considered to be at indeterminate risk and should undergo an LSM, ultrasound is acceptable if VCTE (Fibroscan) is unavailable. Other methods such as bidimensional shear wave elastography or point shear wave elastography can also be used to measure LSM. If the LSM by VCTE is ≥ 8 kPa to ≤ 12 kPa, patients are considered to be at indeterminate risk, and referral to a hepatologist for liver biopsy or MRE or monitoring with re-evaluation in 2 to 3 years is recommended. Of note, an LSM of ≥ 8.0 equates to clinically significant fibrosis (\geq F2); an LSM < 8.0 is considered low risk for clinically significant fibrosis and can be managed with repeat surveillance testing in 2 to 3 years. Patients with a FIB-4 > 2.67 are considered high risk and should be referred to a hepatologist. Additionally, patients with a LSM > 12 kPa or a liver biopsy showing F2 to F4 fibrosis are also considered high risk.

POLICY STATEMENT

Prior Authorization is recommended for prescription 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rezdiffra is recommended in those who meet the following:

FDA-Approved Indication

1. Metabolic-Dysfunction Associated Steatohepatitis (MASH)/Non-Alcoholic Steatohepatitis (NASH), with Moderate to Advanced Liver Fibrosis. Approve for 1 year if the patient meets the 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, and vii):
- i. Patient is ≥ 18 years of age; AND
 - ii. Prior to treatment with Rezdiffra, the diagnosis of MASH/NASH is confirmed by ONE of the following (a or b):
 - a) Patient has had a liver biopsy AND meets BOTH of the following [(1) and (2)]:
 - (1) Liver biopsy has been performed within the 3 years preceding treatment with Rezdiffra **[documentation required]**; AND
 - (2) Liver biopsy shows non-alcoholic fatty liver disease activity score of ≥ 4 with a score of > 1 in ALL of the following ([i], [ii], and [iii]) **[documentation required]**:
 - (i) Steatosis; AND
 - (ii) Ballooning; 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 to 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

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rezdiffra is not recommended in the following situations:

- 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.** 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.
- 3.** Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Rezdiffra™ tablets [prescribing information]. West Conshohocken, PA: Madrigal Pharmaceuticals; March 2024.
2. Rinella ME, Neuschwander-Tetri BA, Siddigui MS, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology*. 2023;77:1797-1835.
3. National Institute of Diabetes Digestive and Kidney Diseases. Nonalcoholic fatty liver disease (NAFLD) and NASH. Last reviewed April 2021. Available at: <https://www.niddk.nih.gov/health-information/liver-disease/nafl-d-nash/definition-facts#:~:text=Experts%20estimate%20about%2024%25%20of,of%20U.S.%20adults%20have%20NASH>. Accessed on: February 9, 2024
4. Cusi K, Isaacs S, Barb D, et al. American Association of Clinical Endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology settings. Co-sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocrine Pract*. 2022;28:528-562
5. 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, Siddigui MS, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology*. 2023;77:1797-1835.
6. Rinella ME, Neuschwander-Tetri BA, Siddigui MS, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology*. 2023;77:1797-1835.
7. Kanwal F, Shubrook JH, Adams LA, et al. Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. *Gastroenterol*. 2021;161:1657-1669.
8. Madrigal Pharmaceuticals. A Phase 3 study to evaluate the effect of resmetirom on clinical outcomes in patients with well-compensated NASH cirrhosis (MAESTRO-NASH-OUTCOMES) In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2024 March 19]. Available at: <https://clinicaltrials.gov/study/NCT05500222?tab=table>. NLM Identifier: NCT05500222.
9. 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.
10. American Association for the Study of Liver Diseases. Resmetirom therapy for metabolic dysfunction-associated steatotic liver disease: October 2024 updates to AASLD Practice Guidance. *Hepatology*. 2024 Oct 18 [Epub ahead of Print].

