PRIOR AUTHORIZATION POLICY

POLICY: Hepatology – Rezdiffra Prior Authorization Policy
- Rezdiffra™ (resmetirom tablets – Madrigal Pharmaceuticals)

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

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 AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. 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.

CIGNA NATIONAL FORMULARY COVERAGE:

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 ≥ 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 syndrome[9] (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 [≥ 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/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 ≥ 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

Rezdiffra is not addressed in available guidelines; no therapies for NASH were approved at the time available guidelines were written. The American Association for the Study of Liver Diseases (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 ≥ 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 ≥ 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 ≥ 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 a liver stiffness measurement (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 (≥ 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.

- **Rezdiffra™ (resmetirom tablets - Madrigal Pharmaceuticals) is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):**

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 6 months 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

(iii) Lobular inflammation; OR

b) Patient has had ONE of the following imaging exams performed within the 3 months preceding treatment with Rezdiffra [(1), (2), or (3)] **[documentation required]**:

(1) Elastography; OR

Note: Examples of elastography include, but are not imputed to vibration-controlled transient elastography (e.g., FibroScan), transient elastography, magnetic resonance elastography, acoustic radiation force impulse imaging, shear wave elastography.

(2) Computed tomography; OR

(3) Magnetic resonance imaging; OR

iii. Patient meets ONE of the following prior to treatment with Rezdiffra (a or b) **[documentation required]**:

a) Patient has stage F2 fibrosis; OR

b) Patient has stage F3 fibrosis; AND

iv. According to the prescriber, the patient has THREE 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

v. 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.

vi. The medication will be used in combination with appropriate diet and exercise therapy; AND

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

B) Patient is Currently Receiving Rezdiffra: 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 meets ONE of the following (a or b):
  a) Patient has completed ≥ 1 year and < 2 years of therapy with Rezdiffra AND patient has derived benefit from treatment with Rezdiffra as demonstrated by at least ONE of the following, according to the prescriber [(1) or (2)]:
  Note: This applies to a patient starting their second year of therapy with Rezdiffra.
    (1) MASH/NASH resolution AND no worsening of fibrosis; OR
    (2) No worsening of MASH/NASH AND improvement in fibrosis by ≥ 1 stage; OR
  b) Patient has completed ≥ 2 years of therapy with Rezdiffra 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 third year (or more) of therapy with Rezdiffra (i.e., the patient has already completed at least 2 years of therapy with Rezdiffra).

i. According to the prescriber, patient has not progressed to stage F4 (cirrhosis); AND

ii. According to the prescriber, metabolic risk factors are managed according to standard of care; AND

iii. 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.

iv. The medication will be used in in combination with to appropriate diet and exercise therapy; AND

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

*Refer to the Policy Statement

CONDITIONS NOT RECOMMENDED FOR APPROVAL

- **Rezdiffra™ (resmetirom tablets - Madrigal Pharmaceuticals) is(are) considered experimental, investigational, or unproven for ANY other use(s) 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.** 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

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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.
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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.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	04/03//2024
Selected Revision	**Metabolic-Dysfunction Associated Steatohepatitis (MASH)/Non-Alcoholic Steatohepatitis (NASH), with Moderate to Advanced Liver Fibrosis.** Initial Therapy. A requirement for documentation was added to the following criteria: Patient with a liver biopsy, liver biopsy has been performed within the 6 months preceding treatment with Rezdiffra [documentation required] AND liver biopsy shows non-alcoholic	05/08/2024

	fatty liver disease activity score of ≥ 4 with a score of > 1 in steatosis, ballooning, and lobular inflammation [documentation required]. Patient that has had an imaging exam, elastography, computed tomography, or magnetic resonance imaging has been performed within the 3 months preceding treatment with Rezdiffra [documentation required]. Prior to treatment with Rezdiffra, patient meets patient has stage F2 fibrosis or F3 fibrosis [documentation required]: Patient is Currently Taking Rezdiffra. Patient has not progressed to stage F4 (cirrhosis) was updated to state, according to the prescriber, patient has not progressed to stage F4 (cirrhosis).	