**09-J4000-85**

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# Subject: Resmetirom (Rezdiffra) tablets

**THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.**



## DESCRIPTION:

Nonalcoholic fatty liver disease (NAFLD) is the most common hepatic disease, with 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 identified during a work-up for abnormal liver enzymes or ultrasound as part of a diagnosis of exclusion for other hepatic diseases. Nonalcoholic steatohepatitis (NASH) is a severe, subset form of NAFLD. 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. 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. NASH/MASH is characterized by an accumulation of fat in the liver and is defined as the presence of greater than or equal to 5% hepatic steatosis with inflammation and hepatocyte injury (e.g., hepatocyte ballooning), with or without evidence of liver fibrosis. Advanced stages of NASH may progress to hepatic cirrhosis, requiring liver transplantation, and/or hepatocellular carcinoma. Noninvasive tests for NASH [e.g., FIB-4, liver stiffness measurement, magnetic resonance elastography) are used for screening and risk stratification, including triage to specialty providers (i.e., gastroenterologist, hepatologist), and may be used for disease staging by specialists but can be inconclusive, requiring liver biopsy. In general, liver biopsy is considered the 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 (e.g., autoimmune hepatitis).

Until recently, management strategies for NAFLD and NASH included lifestyle modifications (i.e., diet, exercise) and treating associated disease states such as hypertension, dyslipidemia, diabetes, and obesity. On March 14, 2024, the FDA approved for resmetirom (Rezdiffra) as the first medication for the treatment of adults with NASH/MASH with moderate to advanced liver fibrosis (i.e., stages F2 to F3 fibrosis) in conjunction with diet and exercise, and its accelerated approval may be contingent upon

verification of clinical benefit in confirmatory trials. Resmetirom (Rezdiffra) is a partial agonist of the thyroid hormone receptor-beta (THR-β). THR-β is the major form of THR in the liver, and its function is impaired for patients with NASH. The impaired THR-β function leads to a reduction in mitochondrial function and β-oxidation of fatty acids in association with an increase in fibrosis. Resmetirom (Rezdiffra) stimulates THR-β in the liver to reduce intrahepatic triglycerides, improves mitochondrial function and subsequently reduces fibrosis.

Resmetirom (Rezdiffra) was evaluated in a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial (MAESTRO-NASH; NCT03900429). Enrolled patients included those 18 years of age and older with metabolic risk factors (e.g., hypertension, dyslipidemia, type 2 diabetes) with a baseline liver biopsy showing stage F2 or F3 fibrosis, and a NAFLD Activity Score (NAS) of 4 or greater (Note: NAS is a composite histological score based on steatosis, lobular inflammation, and ballooning; see Definitions). Exclusion criteria included significant alcohol consumption (more than 20 g per day for women and more than 30 g per day for men), presence of cirrhosis on liver biopsy (stage F4), diagnosis of hepatocellular carcinoma; Model for End-Stage Liver Disease (MELD) score greater than or equal to 12 (unless due to therapeutic anticoagulation); hepatic decompensation, chronic liver disease other than NASH, active autoimmune disease, serum ALT >250 U/L, regular use of drugs historically associated with NAFLD (e.g. amiodarone, methotrexate, tetracyclines), thyroid disease including active/untreated hypothyroidism (TSH >7 IU/L with symptoms of hypothyroidism or >10 IU/L without symptoms), history of bariatric surgery, intestinal bypass surgery within 5 years, recent significant weight gain/loss, HbA1c greater than or equal to 9%, and taking a GLP-1 agonist, high-dose vitamin E (>400 IU/day), or pioglitazone therapy unless stable dose for 24 weeks prior to biopsy. A total of 888 patients who were on stable doses of medications for diabetes, dyslipidemia, and hypertension were randomized 1:1:1 to receive resmetirom 80 mg daily (n = 298), resmetirom 100 mg daily (n = 296) or placebo daily (n = 294). Demographic and baseline characteristics were similar between the treatment and placebo groups. The primary efficacy endpoint was based on the effect of resmetirom on resolution of steatohepatitis without worsening of fibrosis and greater than or equal to 1-stage improvement in fibrosis without worsening of steatohepatitis. Results were evaluated by two different pathologists and reported in Table 1.

### Table 1: Primary efficacy results for resmetirom (Rezdiffra) by pathologist

| | Placebo (N=294) | Resmetirom (Rezdiffra) 80 mg once daily (N=298) | Resmetirom (Rezdiffra) 100 mg once daily (N=296) |
|---|---|---|---|
| **Resolution of steatohepatitis and no worsening of liver fibrosis** | | | |
| Response rate, Pathologist A (%) | 13 | 27 | 36 |
| ➢ Difference in response rate vs. placebo (95% CI) | - | 14 (8, 20) | 23 (16, 30) |
| Response rate, Pathologist B (%) | 9 | 26 | 24 |
| ➢ Difference in response rate vs. placebo (95% CI) | - | 17 (11, 23) | 15 (9, 21) |

| Improvement in liver fibrosis and no worsening of steatohepatitis | | | |
|---|---|---|---|
| Response rate, Pathologist A (%) | 15 | 23 | 28 |
| ➢ Difference in response rate vs. placebo (95% CI) | - | 8 (2, 14) | 13 (7, 20) |
| Response rate, Pathologist B (%) | 13 | 23 | 24 |
| ➢ Difference in response rate vs. placebo (95% CI) | - | 11 (5, 17) | 11 (5, 17) |

Liver fibrosis was evaluated on the NASH Clinical Research Network (CRN) fibrosis score as 0 to 4. Resolution of steatohepatitis was defined as a score of 0 - 1 for inflammation, 0 for ballooning, and any value for steatosis. No worsening of steatohepatitis was defined as no increase in score for ballooning, inflammation, or steatosis. Estimated using the Mantel-Haenszel method stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3). 95% stratified Newcombe confidence intervals (CIs) are provided. Patients with missing liver biopsy at Month 12 are considered a non-responder.

As outlined in the prescribing information, the most common adverse reactions (reported in at least 5% of patients and higher compared to placebo) associated with resmetirom (Rezdiffra) are diarrhea, nausea, pruritus, vomiting, constipation, abdominal pain, and dizziness.

## POSITION STATEMENT:

**Comparative Effectiveness**

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of resmetirom (Rezdiffra) meets the definition of medical necessity when ALL of the following are met:

1. Diagnosis of noncirrhotic nonalcoholic steatohepatitis (NASH)/noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis with both of the following: – laboratory and/or medical documentation must be provided
    a. Stage F2 to F3 fibrosis
    b. **ONE** of the following (“i” or “ii”):
        i. Liver biopsy within the past 2 years
        ii. One of the following non-invasive liver tests within the past 1 year
            a. Vibration-controlled transient elastography (e.g., Fibroscan)
            b. Enhanced liver fibrosis (ELF)
            c. Magnetic resonance elastography (MRE)

2. Member is receiving drug therapy for any present metabolic risk factors (e.g., hypertension, dyslipidemia, diabetes) or has a documented intolerance/contraindication to therapy - laboratory and/or medical documentation must be provided
3. Member does NOT have any of the following: – laboratory and/or medical documentation must be provided
    a. Decompensated cirrhosis
    b. Moderate to severe hepatic impairment (i.e., Child-Pugh Class B or C)
    c. Other liver disease (e.g., Wilson's disease, hepatocelluar carcinoma, hepatitis)
4. Attestation that the medication will be administered in conjunction with a diet and exercise program
5. The medication will not be administered with any strong CYP2C8 inhibitors (e.g., gemfibrozil) or organic anion-transporting polypeptides [OATP1B1 or OATP1B3 inhibitors (e.g., cyclosporine)]
6. The medication is prescribed by a gastroenterologist or hepatologist.
7. The dose does not exceed 80 mg once daily for a weight less than 100 kg or 100 mg once daily for a weight equal to or greater than 100 kg

**Approval duration**: 1 year

Continuation of resmetirom (Rezdiffra) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization for the requested agent has been previously approved by Florida Blue or another health plan in the past 2 years (if another health plan, documentation of a health plan-paid claim during the 2 years before the authorization request must be submitted), OR the member currently meets all indication-specific initiation criteria
2. Member has experienced a clinically beneficial response (e.g., improved, stabilization, or slowed liver fibrosis and/or steatohepatitis) from resmetirom therapy without any clinically significant adverse effects (e.g., hepatotoxicity) necessitating discontinuation of therapy – laboratory and/or medical documentation must be provided
3. The medication is prescribed by a gastroenterologist or hepatologist
4. The dose does not exceed 80 mg once daily for a weight less than 100 kg or 100 mg once daily for a weight equal to or greater than 100 kg

**Approval duration**: 1 year

## DOSAGE/ADMINISTRATION:

**THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.**

**FDA-approved**

- Resmetirom (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).
- The recommended dosage of Resmetirom (Rezdiffra) is based on actual body weight. For patients weighing less than 100 kg, the recommended dosage is 80 mg orally once daily, and for patients weighing greater than or equal to 100 kg, the recommended dosage is 100 mg orally once daily.
- Resmetirom (Rezdiffra) can be administer with or without food.

**Dose Adjustments**

- Resmetirom (Rezdiffra) increases plasma concentrations of some statin therapies (e.g., atorvastatin, pravastatin, rosuvastatin and simvastatin) requiring the following statin dosage adjustments:
    - Rosuvastatin and simvastatin: Limit daily statin dosage to 20 mg
    - Pravastatin and atorvastatin: Limit daily statin dosage to 40 mg
- Resmetirom (Rezdiffra) is a weak CYP2C8 inhibitor and may increase exposure of certain CYP2C8 substrates; therefore, monitor patients more frequently for substrate-related adverse reactions if co-administration is necessary.
- Concomitant use of resmetirom (Rezdiffra) with strong CYP2C8 inhibitors (e.g., gemfibrozil) and organic anion-transporting polypeptides [OATP1B1 or OATP1B3 inhibitors (e.g., cyclosporine)] is not recommended.
- Resmetirom (Rezdiffra) use should be avoided in patients with moderate to severe hepatic impairment (i.e., Child-Pugh Class B or C) and those with decompensated cirrhosis. No dosage adjustment are recommended for patients with mild hepatic impairment (i.e., Child-Pugh Class A) or renal impairment.

**Drug Availability**

- Resmetirom (Rezdiffra) tablets are packaged in white high-density polyethylene bottles closed with a child-resistant closure containing an induction seal. Below are the available strengths:
    - 60 mg tablets: white oval-shaped film-coated tablets, debossed “P60” on one side and plain on the other side (NDC 82576-060-30 for 30 count bottle)
    - 80 mg tablets: yellow, oval-shaped, film-coated tablets, debossed with “P80” on one side and plain on the other side (NDC 82576-080-30 for 30 count bottle and NDC 82576-080-90 for 90 count bottle)
    - 100 mg tablets: beige to pink, oval-shaped, film-coated tablets, debossed with “P100” on one side and plain on the other side (NDC 82576-100-30 for 30 count bottle)

## PRECAUTIONS:

**Boxed Warning**

- None

**Contraindications**

- None

**Precautions/Warnings**

- **Hepatotoxicity:** Hepatotoxicity has been observed with use of resmetirom (Rezdiffra). One patient had normal alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TB) levels at baseline, who received resmetirom (Rezdiffra) 80 mg daily, developed substantial elevations of liver biochemistries that resolved when treatment was interrupted. After reinitiating resmetirom (Rezdiffra), the patient had elevations of ALT, AST, and TB. Peak values observed were 58 x upper limit of normal (ULN) for ALT, 66 x ULN for AST, 15 x ULN for TB, with no elevation of alkaline phosphatase (ALP). Elevations in liver enzymes were accompanied by elevations in immunoglobulin G levels, suggesting drug-induced autoimmune-like hepatitis (DI-ALH). The liver tests returned to baseline following hospitalization and discontinuation of resmetirom (Rezdiffra) without any therapeutic intervention. Monitor patients during treatment with resmetirom (Rezdiffra) for elevations in liver tests and for the development of liver-related adverse reactions. Monitor for symptoms and signs of hepatotoxicity (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, and/or eosinophilia [>5%]). If hepatotoxicity is suspected, discontinue resmetirom (Rezdiffra) and continue to monitor the patient. If laboratory values return to baseline, weigh the potential risks against the benefits of restarting resmetirom (Rezdiffra). If laboratory values do not return to baseline, consider DI-ALH or autoimmune liver disease in the evaluation of elevations in liver tests.
- **Gallbladder-Related Adverse Reactions:** In clinical trials, cholelithiasis, acute cholecystitis, and obstructive pancreatitis (gallstone) were observed more often in resmetirom-treated patients than in placebo-treated patients. If cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated. If an acute gallbladder event is suspected, interrupt resmetirom (Rezdiffra) treatment until the event is resolved.
- **Drug Interaction with Certain Statins:** An increase in exposure of atorvastatin, pravastatin, rosuvastatin and simvastatin was observed when concomitantly administered with resmetirom (Rezdiffra), which may increase the risk of adverse reactions related to these drugs. Dosage adjustment for certain statins is recommended and monitor for statin-related adverse reactions including but not limited to elevation of liver tests, myopathy, and rhabdomyolysis**.**

## BILLING/CODING INFORMATION:

### HCPCS Coding

| | |
|---|---|
| J8499 | Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified |

### ICD-10 Diagnosis Codes That Support Medical Necessity

| | |
|---|---|
| K75.81 | Nonalcoholic steatohepatitis (NASH) |

## REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

## PROGRAM EXCEPTIONS:

**Federal Employee Program (FEP):** Follow FEP guidelines.

**State Account Organization (SAO):** Follow SAO guidelines.

**Medicare Part D:** Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

**Medicare Advantage:** No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

## DEFINITIONS:

**NAFLD Activity Score (NAS) Scale**

| Item | Definition | Score |
|---|---|---|
| Steatosis | < 5% | 0 |
| | 5 – 33% | 1 |
| | > 33 – 66% | 2 |
| | > 66% | 3 |
| Lobular inflammation | No foci | 0 |
| | < 2 foci/ x 200 field | 1 |
| | 2 – 4 foci/ x 200 field | 2 |
| | > 4 foci/ x 200 field | 3 |
| Ballooning degeneration | None | 0 |
| | Few balloon cells | 1 |
| | Many cells/prominent ballooning | 2 |

## RELATED GUIDELINES:

None

## OTHER:

None

## REFERENCES:


1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2024. URL www.clinicalpharmacilogy-ip.com Accessed 4/29/25.
2. DynaMed [database online]. Ipswich, MA: EBSCO Information Services.; 2024. URL http://www.dynamed.com. Accessed 4/25/24.

3. Micromedex Healthcare Series [Internet Database]. Greenwood Village, CO: Thomson Healthcare. Updated periodically. Accessed 4/29/25.
4. Rezdiffra (resmetirom) [package insert]. Madrigal Pharmaceuticals, Inc., West Conshohocken (PA): March 2024.

## COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 07/09/25.

## GUIDELINE UPDATE INFORMATION:

| | |
|---|---|
| 06/15/24 | New Medical Coverage Guideline – Resmetirom (Rezdiffra) tablets in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH)/noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis. |
| 09/15/24 | Review and revision to guideline consisting of revising the position statement to require documentation of the FIB-4 score, allow for non-invasive liver tests as an alternative to liver biopsy, and extension of the initial approval duration to 1 year. |
| 06/15/25 | Review and revision to guideline consisting of revising the position statement to clarify treatment of present metabolic risk factors and updating references. |
| 08/15/25 | Review and revision to guideline consisting of revising the position statement to remove the FIB-4 score requirement. |