BlueCross BlueShield Arizona

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PHARMACY COVERAGE GUIDELINE

REZDIFFRA™ (resmetirom) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for REZDIFFRA (resmetirom)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a physician specializing in the patient's diagnosis or in consultation with a Hepatologist or Gastroenterologist

Indication
- Noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (Stage F2 to F3) [**Note**: NASH is now called MASH (see Definitions section)]

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Age Requirement

- 18 years or older

Baseline Clinical Evaluation

- **ONE** of the following criteria that is consistent with NASH (or MASH) liver fibrosis:
  - Liver biopsy that is consistent with NASH (or MASH) liver fibrosis obtained less than 3 years prior showing Stage 2 or 3 fibrosis based on existing pathology, in an individual with no significant change in body weight of more than 5 percent or use of a medication that might affect nonalcoholic fatty liver disease score (NAS) or fibrosis stage
  - Noninvasive imaging test with **ONE** or more of the following:
    1. Vibration controlled transient elastography (VCTE)
    2. Magnetic resonance elastography (MRE)
    3. Point shear wave using elastography using acoustic radiation force impulse (ARFI)
    4. Two dimensional shear wave elastography
  - Serum/Serologic test with **ONE** or more of the following:
    1. Aspartate aminotransferase to platelet ratio (APRI)
    2. Enhanced Liver Fibrosis (ELF) test plus FIB 4 index
    3. FIB 4 index (platelet count, ALT, AST, age)
    4. Gamma glutamyl transpeptidase to platelet ratio (GPR)
    5. Hepascore
    6. FibroTest/FibroSure
- **THREE** of the following metabolic risk factors:
  - Large waist circumference defined as men 94 cm (37 inches) or women greater than80 cm (32 inches) **OR** BMI equal to or greater than 30 kg/m^2
  - Triglycerides equal to or greater than 150 mg/dL (1.7 mmol/L) **OR** on specific treatment
  - HDL cholesterol less than 40 mg/dL (1.03 mmol/L) in males or less than 50 mg/dL (1.29 mmol/L) in females **OR** on specific treatment
  - Blood pressure greater than or equal to 140/90 mmHg on two separate occasions or on treatment
  - Diagnosis of type 2 diabetes
- Evidence of liver steatosis (greater than 5 percent by imaging or histology) and one risk factor for cardiometabolic dysfunction (e.g., dyslipidemia, obesity, pre or established type 2 diabetes mellitus, hypertension)
- Evidence of liver inflammation and hepatocellular injury such as lobar inflammation and ballooning injury to hepatocytes
- No other causes of steatotic liver disease
- No or minimal alcohol consumption (less than 20 g daily for females, less than 30 g daily for males)
- Will be used in combination with diet and exercise aiming for a weight loss goal of at least 7 to 10 percent

Alternative Therapies

- Failure (trial for at least three months duration), contraindication, intolerance to **Wegovy (semaglutide) 2.4 mg** injection weekly dosing

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be

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reported to the United States Food and Drug Administration (FDA) (see Definitions section)

Safety
- There is **NONE** of the following:
  - Use with strong CYP2C8 inhibitors (e.g., gemfibrozil, etc.)
  - Use with OATP1B1 and OATP1B3 inhibitors (e.g., cyclosporine)
  - Stage 4 fibrosis
  - Decompensated cirrhosis (Child Pugh Class B or C)
  - Severe renal impairment (estimated glomerular filtration rate less than 30 mL/min/1.73 m²)

Documentation Requirements
- Completed request form including:
  - Chart notes
  - Lab results
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration
- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):
Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualifications
- Continues to be seen by a physician specializing in the patient's diagnosis or in consultation with a Hepatologist or Gastroenterologist

Clinical Response
- **ONE** of the following:
  - Resolution of steatohepatitis with at least 2 point reduction in NAFLD activity score (i.e., NAS) without worsening fibrosis demonstrated by **BOTH** of the following:
    1. Absence of ballooning (score = 0) and absence or mild lobal inflammation (score = 0 to 1)
    2. No worsening of fibrosis as seen by any progression greater than or equal to 1 stage
  - At least one stage improvement in fibrosis without worsening NAS
  - Stabilization of fibrosis by blood tests (LFTs) and non invasive assessments

Adherence
- Adherence to medication with diet and exercise aiming for weight loss of at least 7 to 10 percent

Brand Specific Criteria
- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety
- There is **NONE** of the following:

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- Use with strong CYP2C8 inhibitors (e.g., gemfibrozil, etc.)
- Use with OATP1B1 and OATP1B3 inhibitors (e.g., cyclosporine)
- Stage 4 fibrosis
- Decompensated cirrhosis (Child Pugh Class B or C)
- Severe renal impairment (estimated glomerular filtration rate less than 30 mL/min/1.73 m²)
- No significant drug related liver toxicity

Documentation Requirements

- Chart notes
- Lab results
- Supporting clinical documentation with evidence of improvement

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications

2. Off-Label Use of Cancer Medications

Description:

Rezdiffra (resmetirom) is a thyroid hormone receptor-beta (THR-beta) agonist indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH now known as MASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis). This indication is approved under accelerated approval based on improvement of MASH and fibrosis. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Use of Rezdiffra (resmetirom) in individuals with decompensated cirrhosis should be avoided.

In 2024, American Association for the Study of Liver Diseases nonalcoholic fatty liver disease (AASLD NAFLD) Practice Guidance recommended changes in nomenclature. Metabolic dysfunction-associated steatotic liver disease (MASLD previously NAFLD) is an all-encompassing term that includes all disease grades and stages and refers to a population in which ≥5% of hepatocytes display macrovesicular steatosis in the absence of a readily identified alternative cause of steatosis (e.g., medications, starvation, monogenic disorders) in individuals who drink little or no alcohol (defined as < 20 g/d for women and <30 g/d for men). The spectrum of disease includes nonalcoholic fatty liver (NAFL, now known as metabolic dysfunction–associated steatotic liver or MASL), characterized by macrovesicular hepatic steatosis that may be accompanied by mild inflammation, and metabolic dysfunction-associated steatohepatitis, MASH (previously NASH), which is characterized by the presence of inflammation and cellular injury (ballooning), with or without fibrosis, and finally cirrhosis, which is characterized by bands of fibrous septa leading to the formation of cirrhotic nodules.

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Experimental evidence suggests that MASH may be, in part, a condition of diminished liver thyroid hormone levels (a form of hepatic hypothyroidism). Resmetirom is a liver-directed, orally active agonist for thyroid hormone receptor (THR) that is more selective than triiodothyronine (T3) for THR-beta than THR-alpha receptors. Resmetirom demonstrates specific uptake into the liver. In MASH, selectivity for THR-beta may provide metabolic benefits of thyroid hormone that are mediated by the liver, including reduction of excess hepatic fat, atherogenic lipids (low-density lipoprotein–cholesterol [LDL-C], triglycerides), and lipoproteins (apolipoprotein B [ApoB], lipoprotein[a] [Lp(a)], Apo CIII), while avoiding unwanted systemic actions of excess thyroid hormone in heart and bone that are mediated through THR-alpha.

The pathogenesis of MASLD has not been fully determined. A widely backed theory implicates insulin resistance as the significant mechanism leading to hepatic steatosis, and possibly steatohepatitis. Insulin resistance has been seen in individuals with MASH who are not overweight and those who have a normal glucose tolerance. Others have proposed an additional oxidative injury, is required to establish the necroinflammatory component of steatohepatitis. Lipid peroxidation and free oxygen radical species can deplete antioxidant enzymes such as glutathione, vitamin E, beta-carotene, and vitamin C, thus making the liver susceptible to oxidative injury. Hepatic iron, gut hormones, antioxidant deficiencies, and intestinal bacteria have all been implicated in the pathogenesis of MASLD. Hepatic steatosis is an indicator of excessive accumulation of toxic lipids in the liver, including triglycerides, free fatty acids (FFA), ceramides, and free cholesterol.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Some causes of Steatotic Liver Disease (SLD): steatosis of any etiology

- Drug induced liver disease
- Monogenic liver disease
- Alcohol induced liver disease (ALD)
- Cryptogenic liver disease
- Metabolic dysfunction-associated liver disease (MASLD)

Steatotic (fatty) liver disease (SLD):

- A comprehensive term defined as hepatic steatosis of any etiology identified on radiologic imaging or by liver biopsy.

- Steatotic liver disease (SLD) is further classified as:
  - **Metabolic dysfunction-associated steatotic liver disease (MASLD)** – Individuals with MASLD have fatty liver (>5% hepatic steatosis) with at least **one** risk factor for cardiometabolic dysfunction (such as dyslipidemia or obesity), no other causes of SLD, and minimal or no alcohol consumption (i.e., <20 g daily for females and <30 g daily for males). This category was previously known as nonalcoholic fatty liver disease (NAFLD).

  - **MASLD with metabolic dysfunction-associated steatohepatitis (MASH)** – Individuals with MASH have histologic evidence of inflammation and hepatocellular injury, such as ballooning of hepatocytes, with or without fibrosis. This category was previously known as nonalcoholic steatohepatitis (NASH).

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- **MASH cirrhosis** – Individuals with MASH cirrhosis have cirrhosis with current or previous histologic evidence of MASH or history of MASLD.

- **Metabolic dysfunction- and alcohol-associated liver disease (MetALD)** – Individuals with liver steatosis, have at least one metabolic risk factor, and a history of moderate (but not heavy) alcohol use. This category recognizes that SLD can involve a combination of metabolic dysfunction and alcohol.

Cirrhosis:
- A late stage of liver fibrosis that in advanced stages is considered to be irreversible
- Cirrhosis often has multiple signs and symptoms including fatigue, loss of appetite, jaundice, abdominal distension, bleeding and bruising, and many others

Compensated Cirrhosis:
- Cirrhosis without evidence of decompensation
- Some individuals with compensated cirrhosis may be asymptomatic

Decompensated Cirrhosis:
- Cirrhosis with signs and symptoms such as confusion (hepatic encephalopathy), fluid in the abdomen (ascites), yellowing of the skin and mucous membranes (jaundice), or kidney failure

Examples of Noninvasive Imaging:
- Vibration-controlled Transient elastography (VCTE)
- Magnetic resonance elastography (MRE)
- Acoustic radiation force impulse (ARFI)
- Two-dimensional shear wave elastography (2D-SWE)
- FibroScan

Examples of Fibrosis Assessment by Serologic Testing:
- Aspartate aminotransferase to platelet ratio (APRI)
- Enhanced Liver Fibrosis (ELF) score (3 elements involved in matrix turnover: hyaluronic acid, tissue inhibitor of metalloproteinase-1, and N-terminal procollagen III peptide)
- FIB-4 index (platelet count, ALT, AST, age)
- FibroSpect
- FibroTest/FibroSure
- Hepascore

FIB-4 calculator:
https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis#why-use

Clinical Research Network System (CRN) Non-alcoholic Fatty Liver Disease (NAFLD/MASLD) Activity Score – NAS		
Histological feature	Score	Category definition
Steatosis	0	<5%
	1	5–33%

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	2	34–66%
	3	>66%
Hepatocyte ballooning	0	None
	1	Few or borderline ballooning
	2	Many or predominant ballooning
Lobular Inflammation	0	None
	1	1–2 foci per ×200 field
	2	2–4 foci per ×200 field
	3	>4 foci per ×200 field
NAS is sum of steatosis and lobar inflammation and ballooning: ranges 0-8 A score of ≥4 from above with steatosis and hepatocyte ballooning is generally considered diagnostic of NASH, but patients can still have NASH with lower NAS scores if steatosis and hepatocyte ballooning are present. NAFLD (without NASH) is defined as any steatosis and any ballooning OR lobular inflammation. NASH is defined as any steatosis and any ballooning AND lobular inflammation.		
Fibrosis	0	No Fibrosis
	1A	Mild zone 3 perisinusoidal fibrosis
	1B	Moderate zone 3 perisinusoidal fibrosis
	1C	Periportal/portal fibrosis
	2	Perisinusoidal & periportal/portal fibrosis
	3	Bridging fibrosis
	4	Cirrhosis
The regions surrounding the hepatic arteries and portal veins are known as periportal (zone 1), while those adjacent to the central vein are called the pericentral areas of the lobule (zone 3), with the cells in between these regions, referred to as mid-lobular hepatocytes (zone 2).		

Metabolic dysfunction-associated steatohepatitis (MASH) grading and staging system	
Grade	**Description**
Mild (grade 1)	Steatosis (predominantly macrovesicular) involving up to 66% of biopsy; may see occasional ballooned zone 3 hepatocytes; scattered intra-acinar polymorphonuclear cells, intra-acinar lymphocytes; no or mild portal chronic inflammation
Moderate (grade 2)	Steatosis of any degree; ballooning of hepatocytes (predominantly zone3) obvious; intra-acinar polymorphonuclear cells noted, may be associated with zone 3 pericellular fibrosis; portal and intra-acinar chronic inflammation noted, mild to moderate

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Severe (grade 3)	Panacinar steatosis; ballooning and disarray obvious, predominantly inzone 3; intra-acinar inflammation noted as scattered polymorphonuclear cells, ballooned hepatocytes, mild chronic inflammation; portal chronic inflammation mild or moderate
Stage	**Description**
Fibrosis stage 0 (F0)	Absence of fibrosis
Fibrosis stage 1 (F1)	Zone 3 perisinusoidal fibrosis; focally or extensively present
Fibrosis stage 2 (F2)	Zone 3 perisinusoidal fibrosis with portal fibrosis
Fibrosis stage 3 (F3)	Zone 3 perisinusoidal fibrosis and portal fibrosis with bridging fibrosis
Fibrosis stage 4 (F4)	Cirrhosis

Alcohol consumption:
Significant alcohol consumption is defined as greater than or equal to approximately 2 alcoholic drinks per day for males, and approximately 1.5 alcoholic drinks per day for females. One alcoholic drink is equal to 12 ounces (355 mL) of 5% alcohol by volume (ABV) beer, 5 ounces (148 mL) of 12% ABV wine, or 1.5 ounces (44.4 mL) of 40% ABV distilled spirits.

A standard drink in the United States is any drink that contains 14 grams of pure alcohol (about 0.6 fluid ounces) One standard drink (or one alcoholic drink equivalent) is found in:

- 12 ounces of regular beer, which is usually about 5% alcohol
- 8-10 ounces of malt liquor or hard seltzer is about 7% alcohol
- 5 ounces of wine, which is typically about 12% alcohol
- 3-4 ounces of fortified wine (sherry or port) is about 17% alcohol
- 2-3 ounces of cordial, liqueur, or aperitif is about 24% alcohol
- 1.5 ounces of distilled spirits (brandy, cognac, gin, rum, tequila, whisky, vodka, etc.) is about 40% alcohol

Moderate amounts of alcohol are defined as 20 to 50 g daily (140 to 350 g per week) for females and 30 to 60 g daily (210 to 420 g per week) for males. This range of alcohol intake defines a spectrum between MASLD-predominant and alcohol-predominant disease. Patients with steatosis and heavy alcohol use (i.e., >50 g daily for females and >60 g daily for males) have alcohol-associated liver disease.

Resources:

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ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT03900429: A Phase 3, Multinational, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 (Resmetirom) in Patients With Non-Alcoholic Steatohepatitis (NASH) and Fibrosis to Resolve NASH and Reduce Progression to Cirrhosis and/or Hepatic Decompensation. Available from: http://clinicaltrials.gov. Last update posted February 20, 2024. Last verified February 2024. Accessed March 25, 2024. Re-evaluated March 04, 2026.

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