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Policy Number: C28242-A

Rezdiffra (resmetirom)

PRODUCTS AFFECTED

Rezdiffra (resmetirom)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Noncirrhotic nonalcoholic steatohepatitis (NASH), Metabolic dysfunction-associated steatohepatitis (MASH)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. NONCIRRHOTIC NONALCOHOLIC STEATOHEPATITIS (NASH)/METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH):
   1. Documented diagnosis of Noncirrhotic nonalcoholic steatohepatitis (NASH) or Metabolic dysfunction-associated steatohepatitis (MASH)
      AND

2. Documentation diagnosis was confirmed by ONE of the following [DOCUMENTATION REQUIRED]:
   (a) Liver biopsy
   OR
   (b) Imaging (FibroScan, magnetic resonance elastography [MRE]), biomarker testing (FIB-4, NFS, ELF), or relevant scoring tool (FAST, MAST, MEFIB) [See Appendix]
   AND
3. Documentation member has moderate to advanced liver fibrosis stage F2 or F3
   NOTE: Resmetirom is not indicated for stage 4, severe, cirrhotic liver fibrosis
   AND
4. Prescriber attests or clinical reviewer has found that member is receiving standard of care for metabolic risk factors as applicable (e.g., hypertension, type 2 diabetes, dyslipidemia)
   AND
5. Appropriate lifestyle modifications have been implemented, including adherence to healthy diet to promote weight loss, regular physical activity, and avoidance of alcohol that will continue during treatment, supported by documentation of counseling in chart notes
   AND
6. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal (e.g., steatosis, fibrosis, etc.) [DOCUMENTATION REQUIRED]
   AND
7. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Rezdiffra (resmetirom) include: Avoid use in patients with moderate to severe hepatic impairment (Child-Pugh Class B or C), avoid use in patients with decompensated cirrhosis.]

CONTINUATION OF THERAPY:

A. NONCIRRHOTIC NONALCOHOLIC STEATOHEPATITIS (NASH)/METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH):
   1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
      AND
   2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
      AND
   3. Documentation member has NOT progressed to liver fibrosis stage 4 (F4)
      AND
   4. Documentation of positive clinical response as demonstrated by low disease activity, stabilization, and/or improvements in the condition's signs and symptoms (e.g., improved steatosis, improved fibrosis, improvement in fibrosis score, lack of disease progression, etc.) [DOCUMENTATION REQUIRED]
      AND
   5. Appropriate lifestyle modifications have been implemented, including adherence to healthy diet to promote weight loss, regular physical activity, and avoidance of alcohol that will continue during treatment, supported by documentation of counseling in chart notes

DURATION OF APPROVAL:

Initial authorization: 6 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a board-certified gastroenterologist or hepatologist [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
<100kg: 80 mg once daily
≥100kg: 100 mg once daily

Maximum Quantity Limits – 1 tablet daily

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Hepatotropics – Thyroid Hormone Receptor-Beta Agonists

FDA-APPROVED USES:
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). 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 trials.
Limitations of Use: Avoid use of Rezdiffra in patients with decompensated cirrhosis.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease 2023
https://journals.lww.com/hep/Fulltext/2023/05000/AASLD_Practice_Guidance_on_the_clinical_assessment.31.aspx
Table 5 Parameters for the noninvasive assessment of NAFLD according to clinical context of use

Modality type	Cut point: Likely	Cut point: Unlikely	Strengths/limitations, references/caveats
Identification of hepatic steatosis			
Imaging			
Ultrasound	"Detected"	NA	Semiquantitative assessment: mild/moderate/severe; low sensitivity with less severe steatosis[322]; steatosis can have similar echo characteristics as advanced fibrosis
FibroScan: CAP	≥ 288 dB/min		Limited accuracy for quantification[323]
MRI-PDFF	≥ 5%	< 5%	Most sensitive across spectrum of steatosis; accurate to assess dynamic change[324]
Identification of "at-risk" NASH			
FAST	≥ 0.67	< 0.35	≤ 0.35 (sensitivity 90%), ≥ 0.67 (specificity 90%); in validation cohorts, the PPV of FAST ranged between 0.33 and 0.81[28,325]
MAST	≥ 0.242	≤ 0.165	0.242 (specificity 90%),[326] 0.165 (sensitivity 90%)[326]
MEFIB	FIB-4 ≥ 1.6 plus MRE ≥ 3.3 kPa	FIB-4 <1.6 plus MRE <3.3 kPa	Sequential approach identifies patients with at least stage 2 fibrosis with > 90% PPV[327]
cT1	≥ 875 ms	< 825 ms	Requires further validation[328]
Detection of advanced fibrosis			
Serum			
FIB-4	≥ 2.67	< 1.3	No added cost[117,329,330]; not accurate in age <35 y and lower rule-out threshold among high-risk individuals who have high pretest probability
NFS	≥ 0.672	< −1.44	No added cost; not accurate in age <35 y, people with obesity and/or type 2 diabetes[117,329,330]
ELF	≥ 9.8	< 7.7	Blood test sent to a reference laboratory[331]; cost
FIBROSpect II	≥ 17	< 17	Blood test sent to a reference laboratory[332]; cost
Imaging			
VCTE	≥ 12 kPa	< 8 kPa	Point of care[4]
ARFI	≥ 1.34	< 1.3	Cut points not well validated[333]
SWE	≥ 12 kPa	< 8 kPa	Cut points not well validated[488]
MRE	≥ 3.63 kPa	< 2.55 kPa	MRE LSM ≥ 3.63 kPa (associated with advanced fibrosis, AUROC of 0.93)[334]
Diagnosis of cirrhosis (rule-in or rule-out)	Rule-in	Rule-out	
CPR			
FIB-4	≥ 3.48	< 1.67	90% specificity cut point for ruling-in and 90% sensitivity for ruling out cirrhosis, respectively[4,335]
ELF	≥ 11.3	< 7.7	ELF ≥ 11.3 is associated with increased risk of hepatic decompensation among patients with cirrhosis[331]
Imaging			
VCTE	≥ 20 kPa	< 8 kPa	LSM by VCTE ≥ 20 kPa is associated with cirrhosis, but for ruling out, cirrhosis optimal cut point is <8 kPa[4]
MRE	≥ 5 kPa	< 3 kPa	LSM by MRE ≥ 5 kPa has a very good (approaches 95%) specificity for diagnosis of cirrhosis and is also associated with increased risk of incident hepatic decompensation[334,336]

Please note that "at-risk" NASH is defined as NAS with stage ≥ 2 fibrosis

Abbreviations: AUROC, area under the receiver operating characteristic curve; CAP, controlled attenuation parameter; CPR, clinical prediction rule; cT1, corrected T1; ELF, Enhanced Liver Fibrosis; FAST, FibroScan assessed liver stiffness measurement in kPa, CAP, and serum aspartate aminotransferase; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement; MAST: score from MRI-PDFF, MRE, and serum aspartate aminotransferase; MEFIB, FIB-4 ≥1.6 plus MRE ≥3.3 kPa; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging–proton density fat fraction; NFS, NAFLD Fibrosis Score; PPV, positive predictive value; SWE, shear wave elastography; VCTE, vibration-controlled elastography.

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), formerly nonalcoholic fatty liver disease (NAFLD), is a term that includes all disease grades and stages when ≥ 5% of hepatocytes display macrovesicular steatosis in the absence of a readily identified alternative cause (e.g., medications, starvation, lysosomal acid lipase deficiency, Wilson disease, inborn errors of metabolism) 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, characterized by macrovesicular hepatic steatosis that may be accompanied by mild inflammation, and metabolic dysfunction associated steatohepatitis (MASH), formerly nonalcoholic steatohepatitis (NASH), which is additionally 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, in which the earlier features of MASH/NASH may no longer be fully appreciated on a liver biopsy.

The clinical trials conducted for Resmetirom and the FDA label use the NAFLD and NASH nomenclature as well as the current Hepatology guidelines. The nomenclature was updated in 2023. The classification of steatotic liver disease (SLD) is new and broken up by metabolic, steatotic, steatohepatitis, and overlap with alcohol induced liver disease.

NAFLD, including NASH, is associated with multiple comorbid conditions that include metabolic syndrome (obesity, type 2 diabetes mellitus, hypertension, dyslipidemia) and hypothyroidism and is associated with increased cardiovascular risk. Patients with advanced NASH fibrosis have increased morbidity and mortality from both cardiovascular disease and from progression of their liver disease, including progression to cirrhosis, liver failure, and hepatocellular carcinoma. Diagnosis often requires a liver biopsy.

Evidence suggests that NASH may be, in part, a condition of diminished liver thyroid hormone levels or hepatic hypothyroidism, and that the incidence of clinical and subclinical hypothyroidism is higher in patients with NAFLD/NASH relative to age matched controls. Resmetirom is a liver-directed, orally active agonist of thyroid hormone receptor (THR) that is 28-fold more selective than triiodothyronine (T3) for THR-β versus THR-α. It is highly protein bound (>99%), has poor tissue penetration outside the liver, and demonstrates specific uptake into the liver. In NASH, selectivity for THR-β may provide metabolic benefits of thyroid hormone that are mediated by the liver, including reduction of excess hepatic fat, atherogenic lipids, and lipoproteins, while avoiding unwanted systemic actions of excess thyroid hormone in heart and bone that are largely mediated through THR-α.

The efficacy of Rezdiffra was evaluated based on an efficacy analysis at Month 12 in Trial 1 (NCT03900429), a 54-month, randomized, double-blind, placebo-controlled trial. Enrolled patients had metabolic risk factors and a baseline or recent liver biopsy showing NASH with fibrosis stage 2 or 3 and a NAFLD Activity Score (NAS) of at least 4. Efficacy determination was based on the effect of Rezdiffra on resolution of steatohepatitis without worsening of fibrosis and one stage improvement in fibrosis without worsening of steatohepatitis, on post-baseline liver biopsies collected at 12 months. The month 12 analysis included 888 F2 and F3 (at eligibility) patients randomized 1:1:1 to receive placebo (n = 294), Rezdiffra 80 mg once daily (n = 298), or Rezdiffra 100 mg once daily (n = 296), in addition to lifestyle counseling on nutrition and exercise. Patients were on stable doses of medications for diabetes, dyslipidemia, and hypertension. Month 12 histopathology results compared Rezdiffra with placebo on the percentage of patients with resolution of steatohepatitis and no worsening of liver fibrosis and the percentage of patients

with at least one stage improvement in liver fibrosis and no worsening of steatohepatitis. Two pathologists, Pathologist A and Pathologist B, independently read the liver biopsies for each patient. Both the 80 mg once daily and the 100 mg once daily dosages of Rezdiffra demonstrated improvement on these histopathology endpoints at Month 12 compared to placebo. Results for the steatohepatitis resolution endpoint based on Pathologist A's readings were 13%, 27%, 36%, for placebo, Rezdiffra 80 mg, Rezdiffra 100 mg, respectively. For the same endpoint, results based on Pathologist B's readings were 9%, 26%, 24%, for placebo, Rezdiffra 80 mg, Rezdiffra 100 mg, respectively. Results for the fibrosis endpoint based on Pathologist A's readings were 15%, 23%, 28%, for placebo, Rezdiffra 80 mg, Rezdiffra 100 mg, respectively. For the same endpoint, results based on Pathologist B's readings were 13%, 23%, 24%, for placebo, Rezdiffra 80 mg, Rezdiffra 100 mg, respectively. In a statistical analysis incorporating both pathologists' independent readings, Rezdiffra achieved statistical significance on both histopathology endpoints for both doses.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Rezdiffra (resmetirom) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Rezdiffra (resmetirom) include: Avoid use in patients with decompensated cirrhosis, avoid use in patients with moderate to severe hepatic impairment (Child-Pugh Class B or C).

OTHER SPECIAL CONSIDERATIONS:
None

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Rezdiffra TABS 60MG
Rezdiffra TABS 80MG
Rezdiffra TABS 100MG

REFERENCES

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3. Kanwal, F., Shubrook, J. H., Adams, L. A., Pfotenhauer, K., Wai-Sun Wong, V., Wright, E., … Cusi, K. (2021). Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology, 161(5), 1657–1669. https://doi.org/10.1053/j.gastro.2021.07.049Cusi, K., Isaacs, S., Barb, D., Basu, R., Caprio, S., Garvey, W. T., … Younossi, Z. (2022). American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings. Endocrine Practice, 28(5), 528–562. https://doi.org/10.1016/j.eprac.2022.03.010
4. American Association for the Study of Liver Diseases. (n.d.). New MASLD Nomenclature | AASLD. Retrieved from www.aasld.org website: https://www.aasld.org/new-masld-nomenclature [Accessed 13 June 2024]
5. Chen, V. L., Morgan, T. R., Rotman, Y., Patton, H. M., Cusi, K., Kanwal, F., & Kim, W. R. (2024). Resmetirom therapy for metabolic dysfunction-associated steatotic liver disease: October 2024 updates to AASLD Practice Guidance. Hepatology, 81(1). https://doi.org/10.1097/hep.0000000000001112

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: References	Q1 2025
NEW CRITERIA CREATION	Q3 2024