Resmetirom (REZDIFFRA) Tablets in Metabolic Dysfunction-associated Steatohepatitis National Drug Monograph April 2024

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: ApoB, apolipoprotein B; ARD, absolute risk difference; ASCVD, atherosclerotic cardiovascular disease; CAP, controlled attenuation parameter; CFB, change from baseline; CKD, chronic kidney disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HOMA-IR, homeostasis model assessment-estimated insulin resistance, calculated (fasting glucose (mg/dL) x fasting insulin (µU/mL) / 405 (fasting glucose [mmol/L] x fasting insulin [µU/L / 22.5); LDL-C, low-density lipoprotein cholesterol; MELD, model for end-stage liver disease; MetSd, metabolic syndrome; MASH, metabolic dysfunction-associated steatohepatitis (formerly known as NASH); MRI-PDFF, magnetic resonance imaging-derived proton density fat fraction; NASH, nonalcoholic steatohepatitis; NIT, noninvasive test; NSD, no statistically significant difference; PRO-C3, N-terminal type III collagen propeptide (biomarker of active fibrogenesis); RES, resmetirom; RR, relative risk; SGLT2i, sodium glucose cotransporter-2 inhibitor; SSD, statistically significant difference; TE, transient elastography; TG, triglyceride(s); THR, thyroid hormone receptor; WDAE, withdrawal due to adverse event; WMM, weight management medication(s); WNWF, with no worsening of fibrosis; WNWN, with no worsening of NAS score

FDA Approval Information

Description / Mechanism of Action

- Dysfunctional thyroid hormone receptor (THR)-β and intrahepatic hypothyroidism occur in metabolic dysfunction-associated steatohepatitis (MASH; formerly referred to as nonalcoholic steatohepatitis [NASH]).[1]
- Resmetirom is a liver-directed THR-β selective agonist that was designed to increase liver fat metabolism and reduce lipotoxicity-mediated hepatocyte injury, liver inflammation and fibrosis.[2,3]

Indication Under Review in This Document

- Treatment of adults with noncirrhotic NASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) in conjunction with diet and exercise.
- 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 in patients with decompensated cirrhosis.

PBM Note: The prescribing information makes no recommendation about the method of diagnosis (liver biopsy vs noninvasive tests).

Dosage Regimen and Dosage Form Under Review

Actual Body Weight	Recommended Dosage	Dosage With Concomitant Moderate CYP2C8 Inhibitors*
< 100 kg	80 mg orally once daily	60 mg orally once daily
≥ 100 kg	100 mg orally once daily	80 mg orally once daily

* Such as clopidogrel

- Tablets: 60 mg, 80 mg, and 100 mg

Efficacy Considerations

- No active-controlled trials have been performed.
- Two phase 3 placebo-controlled randomized clinical trials (RCTs) showed efficacy of resmetirom in NASH.
- Three phase 2 studies provided supportive evidence of efficacy[4,5] including improved quality of life.[6]
- Trials thus far have only assessed histologic endpoints. The FDA proposed (1) NASH resolution with no worsening of fibrosis and (2) improvement of fibrosis by ≥ 1 stage with no worsening of the NAFLD activity score (NAS) as the two histologic end points "reasonably likely to predict clinical benefit in a phase 3 trial involving adults with NASH and liver fibrosis."[7]
- The MAESTRO-NASH OUTCOMES trial is ongoing.
- Note: The term NASH is used instead of MASH when it was the term used in trials.

Phase 3 Randomized Clinical Trials

- Table 1 summarizes the methods of the phase 3 RCTs.

Table 1 Summary of Phase 3 RCTs of Resmetirom

Reference, Country	Study Design Interventions GRADE Quality	Major Entry Criteria	Selected Results
Harrison (2024),[7] 15 countries	MAESTRO-NASH: 52-week interim results of an ongoing 52-month (4.5-year) phase 3 MN DB PC RCT. Two pathologists read biopsies centrally. Multiplicity controlled. Clinical outcome primary endpoint will be assessed at Month 54. Resmetirom 100 mg QD Resmetirom 80 mg QD Placebo QD GRADE: • Low for NASH resolution WNWF (downgraded for indirectness to clinical outcomes and imprecision – suboptimal information size) • Low for fibrosis improvement WNWN (downgraded for imprecision – suboptimal information size – and indirectness to cirrhosis)	Adults with biopsy-confirmed NASH. **Prescreening Criteria**: No history of significant alcohol consumption† and have either (1) ≥ 3 of 5 metabolic risk factors (modified International Diabetes Foundation criteria*) and AST > 20 U/L; or (2) fibrosis stage F2 or F3 with NASH (NAS ≥ 4, all components) on historical liver biopsy < 2 yrs old. **Major Inclusion Criteria**: Adults with suspected or confirmed diagnosis of NASH suggested by the historical data, meeting criteria in this order: (a) First, prescreening metabolic risk factors and AST criteria as shown above; (b) Second, meet one of the following consistent with liver fibrosis: • PRO-C3 > 14 ng/mL or ELF ≥ 9; • VCTE FibroScan CAP of ≥ 280 dB/m and liver stiffness measurement (LSM) of ≥ 8.5 kPa; or • Historical liver biopsy obtained > 24 wks and < 2 yrs before randomization showing fibrosis stage F2 or F3 with no significant change in body weight > 5% or medication that might affect NAS or fibrosis stage. (c) Third, MRI-PDFF fat fraction ≥ 8% or, if MRI-PDFF not doable or available, FibroScan CAP ≥ 280 dB/m. (d) Fourth, baseline biopsy-proven NASH (obtained < 24 wks before randomization) with stage F1A, F1B, F2, or F3 fibrosis (only F2 and F3 were used for primary efficacy analyses) and	**Two Liver Biopsy Primary Endpoints** • **NASH resolution** with reduction in NAS by ≥ 2 points with no worsening of fibrosis (WNWF) at Wk 52 • **Fibrosis improvement** by ≥ 1 stage with no worsening of NASH (WNWN) at Wk 52 **Results at Wk 52** **Measure** / **RES100** N = 323 / **RES80** N = 322 / **PBO** N = 321 **NASH resolution WNWF, n (%)**: **97 (29.9)** / **83 (25.9)** / **31 (9.7)** RR (95% CI): 3.1 (2.1, 4.5) / 2.7 (1.8, 3.9) / — ARD (95% CI): 20.4 (14.4, 26.3) / 16.1 (10.4, 21.9) / — **Fibrosis improvement WNWN, n (%)**: **84 (25.9)** / **78 (24.2)** / **46 (14.2)** RR (95% CI): 1.8 (1.3, 2.5) / 1.7 (1.2, 2.4) / — ARD (95% CI): 11.7 (5.5, 17.8) / 9.9 (3.8, 15.9) / — **Fatal AE, n (%)**: **2 (0.6)** / **1 (0.3)** / **1 (0.3)** **SAEs, n (%)**: **41 (12.7)** / **35 (10.9)** / **37 (11.5)** **WDAEs, n (%)**: **22 (6.8)** / **6 (1.9)** / **7 (2.2)** **MACE, n (%)**: **1 (0.3)** / **1 (0.3)** / **1 (0.3)** Blue text = Intervention had notable increase in risk vs other treatment groups **Other** SSD between each RES group and PBO in CFB (reductions) in LDL-C at Wk 24. **NITs – findings suggested apparent improvements on RES in the following:** • MRI-PDFF at Wks 16 and 52 • FibroScan CAP at Wk 52 • VCTE or MRE liver stiffness

Reference, Country	Study Design Interventions GRADE Quality	Major Entry Criteria	Selected Results
		NAFLD activity score (NAS) of ≥ 4 (scale, 0–8) with subscores of ≥ 1 for steatosis, lobular inflammation, and hepatocellular ballooning. **Major Exclusion Criteria**: • Significant ingestion of alcohol for > 3 consecutive months within 1 yr prior to screening • Use of drugs associated with NAFLD • Active hyperthyroidism or untreated clinical hypothyroidism. • Bariatric surgery or intestinal bypass surgery within previous 5 yrs or planned during study. • Weight gain or loss ≥ 5% within 12 wks prior to randomization. • HgA1C > 9%. • Cirrhosis (fibrosis stage F4) • Hepatocellular carcinoma • MELD score ≥ 12 • Hepatic decompensation • Other causes of chronic liver disease • ALT > 250 U/L ***Modified IDF Criteria for Metabolic Risk Factors:** • Large waist (> 37 inches men; > 32 inches women); • TG > 150 mg/dL or taking medications to lower TG; • HDL-C < 40 mg/dL men; < 50 mg/dL women; • BP > 140/90 mmHg on 2 occasions or taking antihypertensives • T2D: Taking medications for T2D or HOMA-IR > 3.8	
Harrison (2023),[8] US	MAESTRO-NAFLD-1: 52-wk phase 3 DB PC safety study using NITS to	Adults with ≥ 3 risk factors for MetSd, and ONE of the following:	**Safety**

Reference, Country	Study Design Interventions GRADE Quality	Major Entry Criteria	Selected Results
	identify patients and measure treatment response. Randomization stratified by T2D status and ASCVD status OL Resmetirom 100 mg DB Resmetirom 100 mg DB Resmetirom 80 mg) DB Placebo GRADE: Low (Downgraded for indirectness to clinical efficacy outcome and imprecision – suboptimal information size – for both VCTE efficacy and safety)	(1) presumed NAFLD – liver fibrosis by FibroScan (kPa ≥ 5.5 to < 8.5; CAP ≥ 280 dB/m OR MRE ≥ 2.0 to < 4.0), liver fat ≥ 8% by MRI-PDFF (w/in previous 8 wks) and consistent with fibrosis stage ≥ 1 to < 4; if no MRI-PDFF, then FibroScan CAP ≥ 300 dB/m or CAP ≥ 280 with steatosis ≥ 1 on historic liver biopsy; OR (2) liver biopsy w/in previous 2 yrs showing NASH/NAFLD with steatosis and one of (a) NAS ≥ 4, steatosis ≥ 1, with fibrosis stage F0 OR with F1A/1C and PRO-C3 < 14; (b) NAS < 4, steatosis ≥ 1, with fibrosis stage ≤ 3; or (c) NAS ≥ 4, steatosis ≥ 1, fibrosis stage ≤ 3 without ballooning. **Major Exclusions**: Cirrhosis (F4) from DB arms; h/o significant alcohol consumption for ≥ 3 mos within 1 yr of screening; h/o bariatric surgery or intestinal bypass surgery in previous 5 yrs; ≥ 5% weight gain or loss within 12 wks; HbA1c > 9.0%; dx of hepatocellular carcinoma; MELD score ≥ 12; hepatic decompensation or impairment; ALT > 250 IU; pioglitazone ≥ 15 mg/d; drugs historically associated with NAFLD; active hyperthyroidism; untreated clinical hypothyroidism. Allowed Background Medications: Thyroxine ≤ 75 µg/d in DB arms and any dose in OL arms. Stable doses of pioglitazone < 15 mg/d, GLP-1RAs, and vitamin E > 400 IU/d.	**Measure** / **OL RES100 N =171** / **DB RES100 N =325** / **DB RES80 N =327** / **DB PBO N =320** **SAEs, n (%)** / **7 (4.1)** / **24 (7.4)** / **19 (5.8)** / **20 (6.3)** RR (95% CI) / 0.6 (0.28, 1.52) / 1.2 (0.67, 2.10) / 0.9 (0.51, 1.71) / REF ARD (95% CI) / 2.2 (–1.8, 6.1) / 1.1 (–2.8, 5.0) / 0.4 (–3.2, 4.1) / REF **WDAEs, n (%)** / **2 (1.2)** / **10 (3.1)** / **8 (2.4)** / **4 (1.3)** RR (95% CI) / 0.9 (0.17, 5.01) / 2.5 (0.78, 7.77) / 2.0 (0.60, 6.44) / REF ARD (95% CI) / 0.08 (–1.9, 2.1) / 1.8 (–0.4, 4.1) / 1.2 (–0.9, 3.3) / REF **FibroScan VCTE at Wk 52** **Measure** / **OL RES100 N =50** / **DB RES100 N =102** / **DB RES80 N =83** / **DB PBO N =107** **Improved by ≥ 2 kPa, n (%)** / **28 (55)** / **44 (43)** / **27 (32)** / **27 (25)** RR (95% CI) / 2.2 (1.45, 3.34) / 1.7 (1.15, 2.54) / 1.3 (0.82, 2.02) / REF ARD (95% CI) / 30.8 (14.7, 46.8) / 17.9 (5.2, 30.6) / 7.3 (5.7, 20.3) / REF **Improved by ≥ 30%, n (%)** / **22 (43)** / **37 (36)** / **22 (26)** / **22 (21)** RR (95% CI) / 2.1 (1.32, 3.48) / 1.8 (1.12, 2.77) / 1.3 (0.77, 2.16) / REF ARD (95% CI) / 23.4 (7.7, 39.2) / 15.7 (3.6, 27.8) / 5.9 (–6.3, 18.1) / REF **Other** SSD between RES (each dose) and PBO in %CFB in MRI-PDFF and CFB in FibroScan CAP, LDL-C, apoB, and TGs.

† Significant alcohol was defined as ≥ 2 alcoholic drinks per day for men and 1.5 per day for women. One alcoholic drink = 12 oz (355 mL) of 5% alcohol by volume beer, 5 oz (148 mL) of 12% wine, or 1.5 oz (44.4 mL) of 40% distilled spirits. ≥ 30 g/d (men) or ≥ 20 g/d (women).

Safety Considerations

Safety Profile from US Prescribing Information

Boxed Warnings	None
Contraindications	None
Other Warnings / Precautions	Hepatotoxicity (monitor during treatment) Gallbladder-related adverse reactions
Common Adverse Events (≥ 5%)	Diarrhea, nausea, pruritus, vomiting, constipation, abdominal pain, dizziness
Drug Interactions	Strong CYP2C8 inhibitors such as gemfibrozil (not recommended) Moderate CYP2C8 inhibitors such as clopidogrel (reduce resmetirom dose: 60 mg daily if < 100kg and 80 mg daily if ≥ 100 kg) OATP1B1 and OATP1B3 inhibitors such as cyclosporine (not recommended) Atorvastatin, pravastatin, rosuvastatin, simvastatin (reduce statin dose as recommended) CYP2C8 substrates (monitor for substrate adverse effects)
Specific Populations	Moderate to severe (Child-Pugh Class B or C) hepatic impairment – avoid use

Network Meta-analyses

- One network meta-analysis included a phase 2 resmetirom trial[5] (Table 7).

Table 2 Summary of Network Meta-analyses Comparing 25 MASH Therapies Including Resmetirom by Liver Histology

Ranked Best	Ranked Worst	RES Better Than	RES Similar to	RES Worse Than
NASH resolution WNWF				
Liraglutide 1.8 mg QD	RES 80 mg QD	None	Liraglutide 1.8 mg QD Pioglitazone 45 mg QD Vitamin E 800 IU QD + Pioglitazone 45 mg QD Pioglitazone 30 mg QD Vitamin E 800 IU QD	None
Fibrosis Improvement WNWN				
Vitamin E 800 IU QD	RES 80 mg QD	None	Vitamin E 800 IU QD Vit E 800 IU QD + Pioglitazone 45 mg QD	None

Only FDA-approved drugs are shown.

Evidence Gaps

- Clinical outcomes such as progression to cirrhosis, hepatic decompensation, hepatocellular carcinoma, liver transplantation, and all-cause mortality
- Long-term (> 5 years) safety and efficacy data

Other Considerations

Table 3 Onset of Benefit and Adequate Therapeutic Trial

Trial	Outcome Measure	Onset of Significant Treatment Benefit (Wks)	Duration of an Adequate Therapeutic Trial (Wks)
MAESTRO-NASH	NASH resolution WNWF	No data before Wk 52	52 wks based on assessment time point in trial
	Fibrosis improvement WNWN		
MAESTRO-NAFLD-1	CFB in ALT	—	36

Other Therapeutic Options

Table 4 Summary of Placebo-controlled Clinical Trials Evaluating Potential Treatments for MASH Using Histologic Outcome Measures

INTERVENTION	NASH-RELATED FDA INDICATION(S)	STUDY POPULATION	N	STUDY DURATION (WKS)	NASH RESOLUTION WNWF	FIBROSIS IMPROVEMENT WNWN	WEIGHT CHANGE	CV BENEFIT	SAFETY AND OTHER CONSIDERATIONS
Resmetirom 80 mg (< 100 kg) or 100 mg (≥ 100 kg) QD	Noncirrhotic NASH with F2–3 fibrosis in conjunction with diet and exercise	Presumed NAFLD or biopsy-confirmed NASH with F1–3 fibrosis[7]	966	52 (interim results)	Yes	Yes	–0.4%	?	Hepatotoxicity, gallbladder, GI, drug interactions, avoid in Child-Pugh Class B or C hepatic impairment Similar rates of MACE and other CV events between resmetirom groups and placebo.
Semaglutide 0.4 mg SC QD (study dose)	Off-label dose T2D MACE risk reduction	NASH with F1–3 fibrosis[9] ± T2D, BMI > 25 kg/m^2	320	72	Yes	No	–13%	Yes	Thyroid C-cell tumors, contraindicated if personal or family history of medullary thyroid carcinoma (MTC) or has Multiple Endocrine Neoplasia syndrome type 2 (MEN 2); GI, gallstones, pancreatitis
Semaglutide 2.4 mg SC QWk	Obesity	NASH cirrhosis[10]	71	48	No	No	–9%		
Liraglutide 1.8 mg QD	T2D Obesity	NASH ± Child-Pugh A cirrhosis[11]	52	48	Nonsignificant improvement (RR 4.3; 95% CI 1.0, 17.7)	—	–6%	Yes	Thyroid C-cell tumors, contraindicated if personal or family history of MTC or has MEN 2; GI, gallstones, pancreatitis
Vitamin E (RRR-alpha-tocopherol) 800 IU QD or 400 mg BID	—	Noncirrhotic NASH without T2D (PIVENS trial)[12, 13]	247	96	Not evaluated Nonsignificantly higher rate of NASH resolution (regardless of changes in fibrosis).	Not evaluated No improvement in fibrosis.	~+0.2 kg	No	Contraindicated in cirrhosis and hypersensitivity to polysorbate 80 (aka Tweens) for applicable products. Hemorrhagic stroke, potential risk of prostate cancer, potential vitamin K deficiency. Inconsistent association with all-cause mortality. Low utilization in NAFLD / NASH in VHA.
Vitamin E 400 IU BID	—	NASH with T2D (proof-of-concept VA trial)[14]	105	72	Yes	Not evaluated	+0.5 kg		
Vitamin E 400 IU BID + Pioglitazone 45 mg QD	—			72	Yes	Not evaluated	+5.7 kg	?	Peripheral edema, weight gain, hypoglycemia. Also see vitamin E and pioglitazone monotherapies.
Pioglitazone 30–45 mg QD	T2D	NASH with prediabetes or T2D (includes VA patients)[15]	101	72	Not evaluated Resolved NASH (regardless of changes in fibrosis)	Not evaluated NSD in rate of fibrosis improvement	+2.5 kg	Yes	Contraindicated in cirrhosis, heart failure, and history of bladder cancer. Weight gain (counteracts weight loss goal), peripheral edema, bone loss / fractures, bladder cancer. Low utilization in NAFLD / NASH in VHA.
Pioglitazone 30 mg QD	T2D	Noncirrhotic NASH without T2D (PIVENS trial)[12]	247	96	Not evaluated Resolved NASH (regardless of changes in fibrosis)	Not evaluated No improvement in fibrosis scores.	+4.7 kg		
Pioglitazone 30 mg QD	T2D	NASH without T2D[16]		48	Not evaluated Reduced hepatocyte injury.	Not evaluated Reduced fibrosis.	+2.8 kg		

NOTES: A post hoc analysis of a 26-week phase 2 PC RCT in patients with T2D showed that tirzepatide, relative to placebo, produced significantly greater reductions in K-18 (10 mg) and Pro-C3 (15 mg) biomarkers for NASH.[17] Two RCTs evaluating the SGLT2i empagliflozin (10 mg QD) in patients with T2D and NAFLD did not evaluate NASH resolution WNWF and fibrosis improvement WNWN.[18, 19]

Table 5 Treatment Options for MASH: Place in Therapy

Drug	Formulary	MASH-related CFU Place in Therapy	FDA Place in Therapy in MASH	2023 AASLD NAFLD Guideline Place in Therapy in MASH[20]	2022 AACE/AASLD NAFLD Practice Guideline[21]
Resmetirom	TBD	• **MASH**: TBD	With diet and exercise for treatment of NASH with stages F2–F3 fibrosis	Approved in 2024	Approved in 2024
Semaglutide (OZEMPIC) SC Injection 0.5 mg, 1 mg, 2 mg	PA-F	• **T2D w/ASCVD ± CKD**: With metformin • **T2D w/o ASCVD or CKD**: After ≥ 2 oral medications (including metformin) or basal insulin	Off label	Semaglutide can be considered for its approved indications (T2D, obesity) in patients with NASH, as it confers a CV benefit and improves NASH.	For Obesity and NAFLD/NASH: Clinicians must consider WMM (with preference to semaglutide 2.4 mg/week [best evidence] or liraglutide 3 mg/day) as adjunctive therapy to lifestyle modification. [High / intermediate strength of evidence; Best Evidence Level: 1]
Semaglutide (RYBELSUS) Tablets 7 mg, 14 mg	NonF	• No CFU	Off label	See OZEMPIC Note: The PIONEER 6 trial showed that oral semaglutide had a nonsignificant reduction in MACE; however, it was not designed to prove CV benefit[22]	See OZEMPIC
Semaglutide (WEGOVY) SC Injection 2.4 mg	NonF	• **Chronic Weight Management (O/O)**: BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 + weight-related comorbidity + trial of CLI + one of (1) ≥ 1 WMM, (2) BMI ≥ 40 or BMI 35 to < 40 with significant or difficult to manage weight-related condition or is unable to achieve weight loss goals required for surgery; or (3) T2D treated with OZEMPIC AND requires additional weight loss to achieve ≥ 5% reduction from initial body weight.	Off label	See OZEMPIC	See OZEMPIC
Liraglutide (SAXENDA 3 mg, VICTOZA 1.2 mg, 1.8 mg) SC Injection	NonF	• **Chronic Weight Management (O/O)**: BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 + weight-related comorbidity + trial of CLI + one of (1) ≥ 1 WMM, (2) Prediabetes (3) T2D AND eligible for or treated with but is unable to use OZEMPIC for T2D	Off label	No recommendation.	See OZEMPIC

Drug	Formulary	MASH-related CFU Place in Therapy	FDA Place in Therapy in MASH	2023 AASLD NAFLD Guideline Place in Therapy in MASH[20]	2022 AACE/AASLD NAFLD Practice Guideline[21]
Tirzepatide (MOUNJARO) SC Injection 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15mg	NonF	• **T2D**: After ≥ 1 mg of semaglutide injection + ≥ 2 glucose lowering drugs; also after empagliflozin if patient has ASCVD or CKD.	Off label	No recommendation	No recommendation
Tirzepatide (ZEPBOUND) SC Injection 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg	NonF	• **Chronic Weight Management (O/O)**: BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 + weight-related comorbidity + trial of CLI + one of (1) ≥ 1 WMM, (2) BMI ≥ 40 or BMI 35 to < 40 with significant or difficult to manage weight-related condition or is unable to achieve weight loss goals required for surgery	Off label	No recommendation	No recommendation
Vitamin E (RRR alpha-tocopherol)	Yes*	• None	NA	Can be considered in select patients; some patients without diabetes showed improvement in NASH.	Can be considered for treatment of NASH in patients without T2D but cannot be recommended in T2D or advanced fibrosis because of insufficient evidence. [Grade B; high strength of evidence; Best Evidence Level 1; downgraded because of risk/benefit.]
Pioglitazone	Yes	• None	Off label	Can be considered in patients with T2D for improvement in NASH	Recommended for patients with T2D and biopsy-confirmed NASH. [Grade A; high strength of evidence; Best Evidence Level 1]

CLI, comprehensive lifestyle intervention; CPU, clinical practice update; O/O, obesity or overweight; T2D, type 2 diabetes mellitus; WMM, weight management medication

* Readily available as a racemic mixture of alpha tocopherols. The pure RRR alpha-tocopherol used in studies is not routinely stocked in VHA and may need to be purchased from a source other than the pharmacy prime vendor.

Projected Place in Therapy

- **Epidemiology and Prevalence of MASH in Veterans**. About 30% of the US population has metabolic dysfunction-associated steatotic liver disease (MASLD; aka nonalcoholic fatty liver disease [NAFLD]). An estimated 1.5% to 2.8% have the more severe metabolic dysfunction-associated steatohepatitis (MASH; aka nonalcoholic steatohepatitis [NASH]).[23] In VA (January 2023–January 2024) an estimated 153,000 patients had MAFLD and 30,000 patients had MASH.
- **Potential Place in Therapy Based on the Evidence**. Resmetirom is the only approved liver-directed therapy for noncirrhotic MASH with F2–3 fibrosis. Low-quality evidence from a placebo-controlled trial supports the use of resmetirom in patients with biopsy-confirmed MASH to improve rates of MASH resolution and fibrosis improvement. These histologic improvements occurred without weight reduction or improvement in T2D control. Further studies are needed to determine whether the histologic improvements lead to clinically meaningful reductions in MASH-associated cirrhosis, liver decompensation, hepatocellular carcinoma, liver transplantation, and mortality. There is no evidence to support off-label use for MASH cirrhosis.

Table 6 Summary of Resmetirom Treatment Effects

Benefits	Harms
• In the placebo group, 90% failed to resolve NASH, with resmetirom 80mg resulting in a small to moderate reduction of 161 fewer failures in 1,000 patients (95% CI 219 fewer to 104 fewer failures). • In the placebo group, 86% failed to improve at least 1 stage of fibrosis, with resmetirom 80 mg resulting in small to moderate reduction of 99 fewer failures in 1,000 (95% CI 159 fewer to 38 fewer). • There is currently no evidence that resmetirom will prevent the development of clinically relevant cirrhosis or need for liver transplantation.	• Most adverse events were mild or moderate in intensity. • The top three common adverse reactions (≥ 10 per 100 patient-years [PY]) were diarrhea, nausea, and pruritus. • The median time to onset of diarrhea was 6–17 days, and median duration of diarrhea was 20 days. • Gallbladder-related adverse reactions occurred in < 1 per 100 PY in all treatment groups (resmetirom 80 and 100 mg and placebo). • Hepatotoxicity occurred in 1 patient (0.05%) on resmetirom 80 mg out of a combined safety population of 2019 patients.

- **Potential Place in Therapy in VHA**. Resmetirom may be used in patients who have a diagnosis of MASH with F2–F3 fibrosis with NAS ≥ 4 based on liver biopsy. Patients should participate for at least 6 months and continue participation in a CLI. Resmetirom is not indicated for MASH with cirrhosis. If liver function worsens, discontinue resmetirom.

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References

1 Bohinc BN, Michelotti G, Xie G, et. al.: Repair-related activation of hedgehog signaling in stromal cells promotes intrahepatic hypothyroidism. Endocrinology 2014; 155: pp. 4591-4601.

2 REZDIFFRA (resmetirom) tablets [prescribing information online]. Bristol, TN: UPM Pharmaceuticals for Madrigal Pharmaceuticals, West Conshohocken PA. 3/2024. Available at: 217785s000lbl.pdf (fda.gov) . Accessed 3/14/2024.

3 Karim G, Bansal MB. Resmetirom: An Orally Administered, Smallmolecule, Liver-directed, β-selective THR Agonist for the Treatment of Non-alcoholic Fatty Liver Disease and Non-alcoholic Steatohepatitis. touchREV Endocrinol. 2023 May;19(1):60-70. doi: 10.17925/EE.2023.19.1.60. Epub 2023 May 1. PMID: 37313239; PMCID: PMC10258622.

4 Harrison SA, Bashir MR, Guy CD, Zhou R, Moylan CA, Frias JP, Alkhouri N, Bansal MB, Baum S, Neuschwander-Tetri BA, Taub R, Moussa SE. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2019 Nov 30;394(10213):2012-2024. doi: 10.1016/S0140-6736(19)32517-6. Epub 2019 Nov 11. PMID: 31727409.

5 Harrison SA, Bashir M, Moussa SE, McCarty K, Pablo Frias J, Taub R, Alkhouri N. Effects of Resmetirom on Noninvasive Endpoints in a 36-Week Phase 2 Active Treatment Extension Study in Patients With NASH. Hepatol Commun. 2021 Jan 4;5(4):573-588. doi: 10.1002/hep4.1657. PMID: 33860116; PMCID: PMC8034581.

6 Younossi ZM, Stepanova M, Taub RA, Barbone JM, Harrison SA. Hepatic Fat Reduction Due to Resmetirom in Patients With Nonalcoholic Steatohepatitis Is Associated With Improvement of Quality of Life. Clin Gastroenterol Hepatol. 2022 Jun;20(6):1354-1361.e7. doi: 10.1016/j.cgh.2021.07.039. Epub 2021 Jul 27. PMID: 34329774.

7 Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, Labriola D, Moussa SE, Neff GW, Rinella ME, Anstee QM, Abdelmalek MF, Younossi Z, Baum SJ, Francque S, Charlton MR, Newsome PN, Lanthier N, Schiefke I, Mangia A, Pericàs JM, Patil R, Sanyal AJ, Noureddin M, Bansal MB, Alkhouri N, Castera L, Rudraraju M, Ratziu V; MAESTRO-NASH Investigators. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. N Engl J Med. 2024 Feb 8;390(6):497-509. doi: 10.1056/NEJMoa2309000. PMID: 38324483.

8 Harrison SA, Taub R, Neff GW, Lucas KJ, Labriola D, Moussa SE, Alkhouri N, Bashir MR. Resmetirom for nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled phase 3 trial. Nat Med. 2023 Nov;29(11):2919-2928. doi: 10.1038/s41591-023-02603-1. Epub 2023 Oct 16. PMID: 37845512; PMCID: PMC10667098.

9 Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, Sanyal AJ, Sejling AS, Harrison SA; NN9931-4296 Investigators. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. N Engl J Med. 2021 Mar 25;384(12):1113-1124. doi: 10.1056/NEJMoa2028395. Epub 2020 Nov 13. PMID: 33185364.

10 Loomba R, Abdelmalek MF, Armstrong MJ, Jara M, Kjær MS, Krarup N, Lawitz E, Ratziu V, Sanyal AJ, Schattenberg JM, Newsome PN; NN9931-4492 investigators. Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. Lancet Gastroenterol Hepatol. 2023 Jun;8(6):511-522. doi: 10.1016/S2468-1253(23)00068-7. Epub 2023 Mar 16. PMID: 36934740; PMCID: PMC10792518.

11 Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, Hazlehurst JM, Guo K; LEAN trial team; Abouda G, Aldersley MA, Stocken D, Gough SC, Tomlinson JW, Brown RM, Hübscher SG, Newsome PN. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet. 2016 Feb 13;387(10019):679-690. doi: 10.1016/S0140-6736(15)00803-X. Epub 2015 Nov 20. PMID: 26608256.

12 Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, Neuschwander-Tetri BA, Lavine JE, Tonascia J, Unalp A, Van Natta M, Clark J, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR; NASH CRN. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010 May 6;362(18):1675-85. doi: 10.1056/NEJMoa0907929. Epub 2010 Apr 28. PMID: 20427778; PMCID: PMC2928471.

13 Chalasani NP, Sanyal AJ, Kowdley KV, Robuck PR, Hoofnagle J, Kleiner DE, Unalp A, Tonascia J; NASH CRN Research Group. Pioglitazone versus vitamin E versus placebo for the treatment of non-diabetic patients with non-alcoholic steatohepatitis: PIVENS trial design. Contemp Clin Trials. 2009 Jan;30(1):88-96. doi: 10.1016/j.cct.2008.09.003. Epub 2008 Sep 10. PMID: 18804555; PMCID: PMC2929909.

[14] Bril F, Biernacki DM, Kalavalapalli S, Lomonaco R, Subbarayan SK, Lai J, Tio F, Suman A, Orsak BK, Hecht J, Cusi K. Role of Vitamin E for Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes: A Randomized Controlled Trial. Diabetes Care. 2019 Aug;42(8):1481-1488. doi: 10.2337/dc19-0167. Epub 2019 May 21. PMID: 31332029.

[15] Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, Tio F, Hardies J, Darland C, Musi N, Webb A, Portillo-Sanchez P. Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomized Trial. Ann Intern Med. 2016 Sep 6;165(5):305-15. doi: 10.7326/M15-1774. Epub 2016 Jun 21. PMID: 27322798.

[16] Aithal GP, Thomas JA, Kaye PV, Lawson A, Ryder SD, Spendlove I, Austin AS, Freeman JG, Morgan L, Webber J. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. Gastroenterology. 2008 Oct;135(4):1176-84. doi: 10.1053/j.gastro.2008.06.047. Epub 2008 Jun 25. PMID: 18718471.

[17] Hartman ML, Sanyal AJ, Loomba R, Wilson JM, Nikooienejad A, Bray R, Karanikas CA, Duffin KL, Robins DA, Haupt A. Effects of Novel Dual GIP and GLP-1 Receptor Agonist Tirzepatide on Biomarkers of Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes. Diabetes Care. 2020 Jun;43(6):1352-1355. doi: 10.2337/dc19-1892. Epub 2020 Apr 14. PMID: 32291277; PMCID: PMC7245348.

[18] Kuchay MS, Krishan S, Mishra SK, Farooqui KJ, Singh MK, Wasir JS, Bansal B, Kaur P, Jevalikar G, Gill HK, Choudhary NS, Mithal A. Effect of Empagliflozin on Liver Fat in Patients With Type 2 Diabetes and Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial (E-LIFT Trial). Diabetes Care. 2018 Aug;41(8):1801-1808. doi: 10.2337/dc18-0165. Epub 2018 Jun 12. PMID: 29895557.

[19] Pokharel A, Kc S, Thapa P, Karki N, Shrestha R, Jaishi B, Paudel MS. The Effect of Empagliflozin on Liver Fat in Type 2 Diabetes Mellitus Patients With Non-Alcoholic Fatty Liver Disease. Cureus. 2021 Jul 28;13(7):e16687. doi: 10.7759/cureus.16687. PMID: 34466320; PMCID: PMC8394637.

[20] Rinella, Mary E.1; Neuschwander-Tetri, Brent A.2; Siddiqui, Mohammad Shadab3; Abdelmalek, Manal F.4; Caldwell, Stephen5; Barb, Diana6; Kleiner, David E.7; Loomba, Rohit8. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 77(5):p 1797-1835, May 2023. | DOI: 10.1097/HEP.0000000000000323

[21] Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, Kashyap S, Mechanick JI, Mouzaki M, Nadolsky K, Rinella ME, Vos MB, Younossi Z. 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: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD). Endocr Pract. 2022 May;28(5):528-562. doi: 10.1016/j.eprac.2022.03.010. PMID: 35569886.

[22] Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, Jeppesen OK, Lingvay I, Mosenzon O, Pedersen SD, Tack CJ, Thomsen M, Vilsbøll T, Warren ML, Bain SC; PIONEER 6 Investigators. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2019 Aug 29;381(9):841-851. doi: 10.1056/NEJMoa1901118. Epub 2019 Jun 11. PMID: 31185157.

[23] Hamid O, Eltelbany A, Mohammed A, Alsabbagh Alchirazi K, Trakroo S, Asaad I. The epidemiology of non-alcoholic steatohepatitis (NASH) in the United States between 2010-2020: a population-based study. Ann Hepatol. 2022 Sep-Oct;27(5):100727. doi: 10.1016/j.aohep.2022.100727. Epub 2022 Jun 11. PMID: 35700934.