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Drug Use Research & Management Program
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New Drug Evaluation: Rezdiffra (resmetirom), oral tablet

Date of Review: August 2024
Generic Name: Resmetirom

End Date of Literature Search: 05/08/2024
Brand Name (Manufacturer): Rezdiffra™ (Madrigal Pharmaceuticals)

Dossier Received: yes

Plain Language Summary:

- Nonalcoholic steatohepatitis (NASH) is a type of liver disease caused by build-up of fat which damages cells in the liver in people who do not have another known reason for liver disease, such as alcohol or hepatitis C. Over time, this can cause scarring or irreversible damage to the liver or death.
- Nonalcoholic steatohepatitis is more common in people with other health conditions like obesity, type 2 diabetes mellitus, high cholesterol, and high blood pressure. These other conditions are sometimes called metabolic syndrome.
- Medical and lifestyle therapy for all these conditions is an important part of treating nonalcoholic steatohepatitis.
- Resmetirom is the first medicine approved by the Food and Drug Administration (FDA) to treat nonalcoholic steatohepatitis. In people with nonalcoholic steatohepatitis who do not have irreversible severe scarring of the liver (e.g., cirrhosis), resmetirom reduced scarring (e.g., fibrosis) and other signs of liver disease in some patients who took this medicine for at least one year.
- The company that makes resmetirom is studying the medicine to see if it will reduce other serious effects of nonalcoholic steatohepatitis, such as death and liver failure.
- Diarrhea and nausea were the most common side effects from resmetirom.
- The Drug Use Research and Management group recommends providers explain why someone needs resmetirom before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. What are the benefits and harms of resmetirom in patients with nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis?
2. Are there specific subpopulations for which resmetirom is better tolerated or more effective?

Conclusions:

- Resmetirom is a new medication approved through the accelerated drug pathway indicated in conjunction with diet and exercise for the treatment of adults with NASH and moderate to advanced liver fibrosis (defined as fibrosis stage 2 or 3 [F2 to F3]).
- There is moderate-quality evidence from one good quality trial that:

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- Resmetirom increased NASH resolution at week 52 using nonalcoholic fatty liver disease (NAFLD) activity score (NAS) when compared to placebo (resmetirom 80 mg 25.9% vs. 9.7%, difference 16.4%, 95% CI 11.0 to 21.8%, p<0.001; resmetirom 100 mg 29.9% vs. 9.7%, difference 20.7%, 95% CI 15.3 to 26.2%, p<0.001).[1]
- Resmetirom improved fibrosis by at least one stage without worsening of NAS at week 52 compared to placebo (resmetirom 80 mg 24.2% vs. 14.2%, difference 10.2%, 95% CI 4.8 to 15.7%, p<0.001; resmetirom 100 mg 25.9% vs. 14.2%, difference 11.8%, 95% CI 6.4 to 17.2%, p<0.001).[1]
- This study enrolled adults with biopsy proven, non-cirrhotic NASH, and with hemoglobin A1C (HbA1C) <9% at start of treatment.

- The most common adverse event with resmetirom is diarrhea, which tends to resolve after a few weeks.
- Long term safety and clinical efficacy data beyond 1 year are insufficient. Studies evaluating clinical outcomes are in progress.
- There is limited data in non-White populations, patients with significantly uncontrolled (HbA1C ≥9%) type 2 diabetes (T2D), who have Stage 1 or 4 NASH, or liver fibrosis from other causes. T2D is the risk factor with the largest impact for development of nonalcoholic fatty liver disease (NAFLD), fibrosis progression, and hepatocellular carcinoma (HCC).[2]

Recommendations:

- Implement prior authorization (PA) to ensure safe and appropriate use.

Background:

Nonalcoholic fatty liver disease (NAFLD) is present when least 5% of hepatocytes display macrovesicular steatosis in the absence of ongoing or recent consumption of significant amounts of alcohol or other secondary causes of fatty liver disease.[2-4] Significant alcohol consumption is typically defined as greater than 21 drinks/week (or ≥30 g/day) in men and greater than 14 drinks/week (or ≥20 g/day) in women for 2 years preceding baseline liver histology.[2-4] NAFLD has a clinical range from hepatic steatosis to cirrhosis.[3] Nonalcoholic steatohepatitis (NASH) is a subcategory of NAFLD which includes inflammation and hepatocyte injury (e.g., hepatocyte ballooning), with or without evidence of liver fibrosis.[3] NAFLD is estimated to affect 25% of people worldwide, and 12-14% of those with NAFLD are estimated to have NASH. Prevalence continues to increase over time as risk factors for NASH and NAFLD become more comon.[3] Incidence of hepatic decompensation, HCC, and death due to NASH cirrhosis are anticipated to double or triple by 2030.[2] In the United States, it is the second most common cause of HCC for those on the transplant waiting list.[3] The term metabolic dysfunction-associated steatohepatitis (MASH) is sometimes used in place of NASH.[5]

Major risk factors for NAFLD are obesity, insulin resistance, type 2 diabetes mellitus (T2D), high blood pressure, and atherogenic dyslipidemia. T2D is the leading risk factor for NAFLD development, progression, and HCC.[2,3] Women with polycystic ovary syndrome (PCOS) have increased insulin resistance, and thus, are at increased risk of both T2D and NAFLD.[3] Comorbid NAFLD has been documented in a significant proportion of people with metabolic syndrome (54%), T2D (53%), high body mass index (BMI) (46%), high triglycerides (46%), low high density lipoprotein (HDL) cholesterol (36%), and wide waist circumference (36%).[4] Higher rates of NAFLD are also seen in those with hypothyroidism, hypogonadism, and growth hormone deficiency.[2] NAFLD in individuals who do not have overweight or obesity is estimated at 4.1% in the US and 19% in Asia.[2]

The role of ethnicity is unclear in the development of hepatic fibrosis. People of Hispanic ancestry (with or without diabetes) have steatohepatitis at a rate about 20% higher than the general population, though this seems to be driven by higher rates of obesity.[3]

NASH is associated with various stages of fibrosis: Stage 0 (no fibrosis); Stage 1 (mild; perisinusoidal or periportal), Stage 2 (moderate; perisinusoidal and portal/periportal), Stage 3 (severe; bridging fibrosis), and Stage 4 (cirrhosis).[3] The NAFLD activity score (NAS) is an unweighted composite 0 to 8 point score determined by the summation three components: steatosis grade, lobular inflammation, and ballooning scores.[3] Steatosis grade is scored on an ordinal scale as 0 (none) to 3 (severe) based on percentage of parenchymal involvement of steatosis.[3] Lobular inflammation is scored as 0 to 3 by assessment of inflammatory foci per 200x field, while ballooning is scored as 0 to 2 based on no, few, or many ballooned cells.[3] The FDA has published guidance for industry in the development of research studies for NASH.[6] The NAS, in conjunction with fibrosis staging, is considered critical inclusion criteria for clinical trials.[6] Data from longitudinal cohort studies paired with biopsies indicates that progression of fibrosis by one stage in those with NASH takes an average of 7 years. Patients with cirrhosis require additional monitoring for other complications including HCC, and approximately 3-20% develop clinical decompensation each year.[2]

Routine population screening for NASH is not currently recommended, but those with known hepatic steatosis or clinically suspected NAFLD based on risk factors (e.g., obesity or metabolic syndrome) should undergo initial assessment using liver fibrosis prediction calculations.[2] The preferred initial test is the fibrosis-4 index (FIB-4), which is validated to predict changes over time in hepatic fibrosis and has good specificity and negative predictive value to rule out advanced fibrosis.[3] FIB-4 calculates the risk of hepatic cirrhosis using age, plasma aminotransferases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) and platelet count to assess the need for further testing and biopsy.[3] Those with an intermediate score (≥1.3-2.67) or high score (>2.67) should receive further workup with a liver stiffness measurement (LSM), generally done using vibration-controlled transient elastography (VCTE) or an enhanced liver fibrosis (ELF) test (a proprietary blood test) when VCTE is unavailable.[3] A liver ultrasound is not recommended for routine diagnosis.[3] Patients with intermediate to high fibrosis risk are generally referred to a hepatologist for further workup and possible liver biopsy.[3] The gold standard for diagnosis of NASH is liver biopsy, but it should not be used as the screening method to diagnose NAFLD prior to less invasive screening tests.[3] The VCTE is the best validated imaging modality to identify advanced disease.[3] A magnetic resonance elastography (MRE) is a more accurate, though availability is limited in the United States.[3]

Treatment recommendations focus on risk factor management with guideline directed therapy for comorbidities such as T2D and dyslipidemia.[3] Lifestyle interventions (diet and exercise) are recommended for all adults with NAFLD.[3] Weight loss of greater than 5% has cardiometabolic benefits and reduces liver fat. Weight loss of 10% or more of body weight may reverse steatohepatitis and liver fibrosis.[3] Pioglitazone and GLP-1 RAs are recommended for people with T2D and biopsy-proven NASH and should be considered when there is increased risk of NASH based on non-invasive tests.[2,3] However, pioglitazone has notable side effects, including weight gain and potential risk for worsening heart failure.[2,3] In people with T2D and NAFLD, treatment with pioglitazone, GLP-1 RAs and SGLT2 inhibitors can be considered for cardiometabolic benefit.[3] Vitamin E may also be considered for those with NASH without comorbid T2D or cirrhosis.[3,7] Pharmacotherapeutic augmentation of lifestyle interventions for weight loss are recommended for those with NAFLD or NASH and obesity or BMI 27 kg/m^2 or higher with semaglutide 2.4 mg/week or liraglutide 3 mg/day.[3] The role of GLP-1 RAs and SGLT2 inhibitors in those without overweight or T2D (e.g., lean NAFLD) is undefined and requires additional data.[7] Bariatric surgery is also an option to treat NAFLD. A phase 3 study of semaglutide for treatment of NASH is underway.[2]

As the rate of obesity and T2D increases, children who develop NASH becomes more common. Diagnosis in children differs from adults as predictive calculations and the proprietary blood tests have only been validated in adults. They require further validation for children and may be inaccurate in this population. Serum ALT is usually recommended as an initial screening test with treatment focused on lifestyle changes. Guidelines recommend consideration of GLP-1 RAs for pediatrics with T2D and obesity based on expert opinion.

Noninvasive tests for treatment response, including ALT, FIB-4, ELF, and liver stiffness tests are associated with histologic response; however, validation and MCID are still needed.[2]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Resmetirom is a partial agonist of the thyroid hormone receptor-beta (THR-β) indicated in conjunction with diet and exercise for the treatment of adults with NASH who have moderate to advanced liver fibrosis (F2 to F3).[8] It was FDA approved in March 2024 through the accelerated approval pathway based on histologic improvement of NAFLD activity scores and fibrosis staging.[8] Continued approval is contingent upon verification and description of clinical benefit (e.g., death from any cause, liver transplantation, hepatic decompensation events) in confirmatory trials.[8] This oral agent is dosed by actual body weight at 80 mg daily for those under 100 kg and 100 mg daily for people weighing 100 kg or more. Dosage adjustments are required for certain concomitant medications.[8]

Evidence for efficacy, safety, and FDA approval of resmetirom is from an ongoing phase 3 trial called MAESTRO-NASH. Enrolled adults had at least 3 of 5 metabolic risk factors (large waist or BMI, dyslipidemia with increased triglycerides, dyslipidemia with reduced HDL, hypertension, or T2D), biopsy confirmed NASH, and a NAS total score of 4 or more with presence of histological steatosis, lobular inflammation, and ballooning (with a score of at least 1 for each component).[1] All patients received nutrition and exercise counseling at each visit and exercise and nutrition focused newsletters throughout the study.[1] Weight was required to be stable for 3 months prior to enrollment, those taking GLP-1 RAs were required to have a stable dose for 6 months, and patients with an HbA1C of more than 9% were excluded.[1] The intention-to-treat primary population (N=966) consisted of all randomized patients with F1B, F2, and F3 fibrosis stage, and the primary biopsy analysis population (N=955) which was used to evaluate the primary endpoints included patients whose week 52 biopsies were not delayed secondary to the coronavirus 2019 pandemic.[1] A smaller exploratory subpopulation (N=84) including only patients with stage F1A and F1C were also randomized.[1] Patients were randomized with stratification by presence or absence of T2D and fibrosis stage to receive resmetirom 80 mg daily, resmetirom 100 mg daily, or placebo.[1] There were no comparisons between the two different resmetirom dosage groups. Randomization was not stratified by weight, but an analysis by weight (greater than or less than 100 kg) and resmetirom dose was performed *post hoc*. Biopsy was performed at baseline and at week 52 to determine NAFLD activity score and fibrosis stage.[1]

Baseline characteristics were mostly similar, though fewer participants in the placebo group were of Hispanic or Latino ethnicity (resmetirom 80 mg 22%, resmetirom 100 mg 25.1%, placebo 16.2%) and fewer had an NAS of 5 or greater (resmetirom 80 mg 82.6%, resmetirom 100 mg 89.2%, placebo 78.8%).[1] Patients were primarily White (89.3%), had a BMI of more than 35 kg/m^2, had T2D (67% with baseline HbA1C ~6.6%), hypertension (78.1%), and dyslipidemia (71.3%), and did not have a history of atherosclerotic cardiovascular disease (ASCVD) (5.9%).[1] Most patients were stage F3 (61.9%) or F2 (33%).[1] For patients with T2D, only 21% were on a GLP-1 RA, 20% on an SGLT2 inhibitor, and 18.2% on insulin. For those with dyslipidemia, 68.7% were taking a statin.

There were two primary endpoints: NASH resolution and fibrosis improvement. These surrogate endpoints align with FDA industry guidance.[6] NASH resolution at week 52 was defined as achievement of hepatocellular ballooning score of 0, lobular inflammation score of 0 to 1, and reduction of NAS by 2 or more points with no worsening of fibrosis (change from F1B to F2 was not considered worsening). There was a statistically significant difference in NASH resolution with both dosage strengths when compared to placebo (resmetirom 80 mg 25.9% vs. 9.7%, difference 16.4%, 95% CI 11.0 to 21.8%, p<0.001; resmetirom 100 mg 29.9% vs. 9.7%, difference 20.7%, 95% CI 15.3 to 26.2%, p<0.001).[1] The second primary endpoint was defined as improvement in fibrosis by at least one stage without worsening of NAS. A change from F1B to F2 was not considered improvement and a change from F2 to F1B was not considered worsening. There was a

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statistically significant response with both dosage strengths when compared to placebo (resmetirom 80 mg 24.2% vs. 14.2%, difference 10.2%, 95% CI 4.8 to 15.7%, p<0.001; resmetirom 100 mg 25.9% vs. 14.2%, difference 11.8%, 95% CI 6.4 to 17.2%, p<0.001).[1] Adherence was reported at >80% for 92% of participants.[1] There was no effect on body weight or heart rate found with resmetirom treatment.[1]

This trial is limited by some baseline imbalances in NAS severity between placebo and resmetirom groups. Attrition was higher in resmetirom groups. Outcomes measured show histologic improvement while awaiting clinical outcomes data. No comparison to other potential treatments, including aggressive weight management, which has been shown to reverse steatohepatitis and liver fibrosis.[3] Durability of response and long-term safety are unknown. Inclusion criteria limit data to a population with relatively well controlled T2D, it is unknown if the response would be similar in poorly controlled T2D. The primarily White study population is not representative of disease or of those affected most by metabolic risk factors in the United States.

Ongoing studies include continuation of blinded MAESTRO-NASH for up to 54 months (4.5 years), an extension study of the safety study MAESTRO-NAFLD (**Table 3**), and MAESTRO-NASH-OUTCOMES which is an event driven study of patients with NASH cirrhosis to evaluate long-term outcomes (e.g., all-cause mortality, liver transplant and liver-related events, HCC, and confirmed model for end-stage liver disease [MELD] increase).[9]

Clinical Safety:

Over 91% in every group reported an adverse events, most were mild to moderate severity; diarrhea (resmetirom 80 mg 27.0%, resmetirom 100 mg 33.4%, placebo 15.6%) and nausea (resmetirom 80 mg 22.0%, resmetirom 100 mg 18.9%, placebo 12.5%) were the most common adverse events occurring more frequently than placebo.[1] Diarrhea duration was a median of 15 to 20 days. Discontinuation due to adverse events by week 52 occurred most frequently in the resmetirom 100 mg group (6.8%) compared to resmetirom (1.8%) or placebo (2.2%).[1] Grade 3 (serious) or higher adverse events occurred in similar rates in each group and was highest in the placebo group (**Table 1**).[1] One major adverse cardiac event (MACE) was listed for each study group. Two fatal adverse events occurred in the resmetirom 100 mg group and one in each of the resmetirom 80 mg and placebo groups.[1] Long-term safety remains unknown.

There are no contraindications, but label warnings and precautions include risk of hepatotoxicity, gallbladder-related adverse reactions, and drug interactions with most commonly used statins, which may increase risk of statin related adverse reactions such as myopathy and rhabdomyolysis and require statin dosage adjustment.[8] There are no human data available for use in pregnancy and an adverse event reporting line is available from the manufacturer to report pregnancies.[8] Maternal NASH with liver fibrosis is associated with increased risk of gestational diabetes, hypertensive complications, preterm birth, and postpartum hemorrhage.[8]

Table 1. Adverse Events affecting > 10% of patients in any group[1]

Adverse event	Resmetirom 80mg N=322 N (%)	Resmetirom 100 mg N=323 N (%)	Placebo N=321 N (%)
Diarrhea	87 (27.0)	108 (33.4)	50 (15.6)
Covid-19	69 (21.4)	54 (16.7)	66 (20.6)
Nausea	71 (22.0)	61 (18.9)	40 (12.5)
Arthralgia	48 (14.9)	35 (10.8)	40 (12.5)
Back Pain	35 (10.9)	27 (8.4)	39 (11.8)

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Urinary tract infection	33 (10.2)	27 (8.4)	27 (8.4)
Fatigue	33 (10.2)	26 (8.0)	28 (8.7)
Pruritus	26 (8.1)	37 (11.5)	22 (6.9)
Vomiting	28 (8.7)	35 (10.8)	17 (5.3)

Additional safety data is available from a 52-week, double-blind (DB)/open-label (OL), placebo controlled, phase 3 safety trial (MAESTRO-NAFLD-1) in adults with NAFLD and presumed NASH.[10] Additional open-label arms with at risk populations (e.g. moderate renal impairment) await publication.[10] Diarrhea was the most common AE and was about twice as common compared to placebo (resmetirom 80 mg DB 23.5%, resmetirom 100 mg DB 31.2%, placebo 13.8%, resmetirom 100 mg OL 29.8%).[10] Onset usually occurred during first 12 weeks of therapy and resolved within a median of 15-26 days, though duration was less than a week for some patients and months in others.[10] Additional details available in **Table 3**.

Look-alike / Sound-alike Error Risk Potential: None

Comparative Endpoints[6,11]

Clinically Meaningful Endpoints:
1) All-cause mortality
2) Liver transplant
3) Hepatic decompensation events
4) Histological progression to cirrhosis
5) Increase of MELD score from below 12 to ≥15
6) Quality of Life
7) Serious adverse events
8) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) NASH resolution at week 52
2) Improvement in fibrosis score week 52

Table 2. Pharmacology and Pharmacokinetic Properties.[8]

Parameter	
Mechanism of Action	Partial agonist of the thyroid hormone receptor-beta (THR-β). THR-β is the major form of THR in the liver and stimulation of the THR-β in the liver reduces intrahepatic triglycerides, whereas actions of thyroid hormone outside the liver, including in heart and bone, are primarily mediated through THR-α.
Absorption	Median time to maximum plasma concentration (T_{max}) is ~ 4 hours after multiple daily doses of resmetirom 80 mg or 100 mg. No significant differences in pharmacokinetics after a high fat meal. Concomitant food decreased maximum concentration (C_{max}) by 33% and area under the curve (AUC) by 11%. T_{max} delayed by 2 hours compared to fasted state.
Distribution and Protein Binding	Volume of distribution 68 L 99% protein binding
Elimination	Steady state apparent clearance 17.5 L/h
Half-Life	4.5 hours

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Metabolism	CYP2C8 AUC increased 1.3x in mild, 2.7x in moderate, 19x in severe hepatic impairment (Child-Pugh A, B, and C)
Excretion	67% via feces, mostly as metabolites and 24% via urine

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. MAESTRO-NASH[1] NCT03900429 Phase 3, DB, PC RCT Week 52 results, ongoing with 54-month duration planned	1. Resmetirom 80 mg orally once daily 2. Resmetirom 100 mg orally once daily 3. Placebo orally once daily 1:1:1 randomization	Demographics: Age 56.7 years Male 43.9% White 89.3% Asian 2.9% Hispanic 21.1% BMI 35.6 kg/m^2 T2D 67.0% NAS ≥5 83.5% Fibrosis stage F1B 5.1% F2 33.0% F3 61.9% LDL 103-106.8 Key Inclusion Criteria: - ≥18 years - 3 of 5 metabolic risk factors of metabolic syndrome - VCTE showing CAP ≥280 dB/m AND liver-stiffness measurement ≥8.5 kPa withing 3 months of screening -(alternative to VCTE) Liver biopsy within 6 months of randomization -histologic evidence of NASH and a NAFLD activity score of 4 or more (≥1 for each component [steatosis, lobular inflammation, hepatocellular ballooning]) -Stable weight; GLP-1 RA doses stable from 6 months before biopsy	ITT: 1. 322 2. 323 3. 321 PBAP: 1. 316 2. 321 3. 318 Attrition: 1. 56 (17.4%) 2. 71 (22.0%) 3. 39 (12.1%)	Primary Endpoint (PBAP): NASH resolution at week 52 1. 25.9% 2. 29.9% 3. 9.7% 1 vs. 3 Difference 16.4% 95% CI 11.0 to 21.8 P<0.001 2 vs. 3 Difference 20.7% 95% CI 15.0 to 26.2 P<0.001 Improvement in fibrosis score week 52 1. 24.2% 2. 25.9% 3. 14.2% 1 vs. 3 Difference 10.2% 95% CI 4.8 to 15.7 P<0.001 2 vs. 3 Difference 11.8% 95% CI 6.4 to 17.2 P<0.001 Key Secondary Endpoint (ITT): LDL cholesterol week 24	16.4/7 20.7/5 10.2/10 11.8/9	Outcomes (ITT): Any AE # (%) 1. 296 (91.9%) 2. 296 (91.6%) 3. 298 (92.8%) AE attributed to resmetirom or placebo: 1. 124 (38.5%) 2. 134 (41.5%) 3. 88 (27.4%) AE leading to discontinuation by wk 52: 1. 6 (1.9%) 2. 22 (6.8%) 3. 7 (2.2%) Severe AE (Grade 3 or higher) 1. 43 (13.4%) 2. 47 (14.6%) 3. 52 (16.2%) Fatal AE 1. 1 (0.3%) 2. 2 (0.6%) 3. 1 (0.3%) MACE 1. 1 (0.3%) 2. 1 (0.3%) 3. 1 (0.3%)		**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Interactive web response system with stratification by T2D and fibrosis stage (F1, F2, F3). Minor baseline imbalances with lower percentage Hispanic patients and NAS ≥5 in placebo group. Other baseline risk factors generally balanced. Performance Bias: (Low) Patients and personnel blinding to treatment assignment and post-baseline tests that could unblind treatment group. Both pathologists reading biopsies received baseline and week 52 unpaired slides in 50-100 slide groups and were unaware of baseline characteristics and each other's assessment. Consensus review was done with both pathologists when there was disagreement. Potential unblinding by AE diarrhea/nausea. Detection Bias: (Low) Pathologists blinded and suspected liver-related events and major atherosclerotic cardiac events adjudicated by blinded committee. Attrition Bias: (Unclear) 11 of 966 in ITT had biopsy delayed due to covid 19, assumed missing at random and removed from PBAP. All other randomized patients with missing week 52 (or early termination) biopsy results counted as nonresponder with sensitivity analysis to assess non-responder imputations. Overall attrition higher in resmetirom groups. Reporting Bias: (Low) Protocol published with prespecified outcomes. Other Bias: (Unclear) Sponsor designed. Sponsor/contract research organization performed site monitoring, data collection, and data analysis. Data interpretation and publication manuscript done by sponsor employees.

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		-GFR ≥45 by MDRD-6 Key Exclusion Criteria: -EtOH > 20g/d in women or > 30 g/d in men for 3 consecutive months within 1 year of screening -HbA1C > 9.0% -other chronic liver disease cause (not noncirrhotic NASH)		(LSM % change ± SD) 1. -13.6 ± 1.7 2. -16.3 ± 1.7 3. -0.1 ± 1.7 1 vs. 3 Difference -13.7% 95% CI -17.5 to -10.0) P<0.001 2 vs. 3 Difference -16.4% 95% CI -20.1 to -12.6 P<0.001	NA NA			**Applicability**: Patient: Underrepresentation of non-White populations heavily affected by metabolic diseases, limited generalizability to Medicaid population. Patients with significantly uncontrolled T2D excluded. Most applicable to patients with moderate to severe disease with multiple risk factors and high risk of disease progression. Intervention: Dose regimen based on prior studies. Comparator: Placebo appropriate for disease with limited treatment options. Unclear if patients were receiving maximally tolerated therapy for metabolic comorbidities in line with current standards of care. Outcomes: Surrogate outcomes used, clinical outcomes awaited with ongoing studies. Setting: 245 sites in 15 countries
2. MAESTRO-NAFLD-1[9,10] Phase 3, DB/OL, PC Safety study 52 week treatment period and 4 week follow up period	1. DB Resmetirom 80 mg orally once daily 2. DB Resmetirom 100 mg orally once daily 3. DB Placebo orally once daily 4. OL Resmetirom 100 mg orally once daily	Demographics: -Mean age 56 years -Female 57% -White 88% -Hispanic 34% -Mean BMI 35.2-36.1kg/m^2 -T2D 49% -Dyslipidemia 88% -Hypertension 75% -GLP-1 RAs 6.0-11.7% -SGLT2 inhibitor 4.7-10.5% Key Inclusion Criteria: -≥18 years -≥3 metabolic risk factors -At MAESTRO-NASH study sites: failed to screen for MAESTRO-NASH but confirmed NAFLD -At non-MAESTRO-NASH study sites: FibroScan VCTE/LSM ≥5.5 kPa & FibroScan CAP ≥280 dB/m	ITT: 1. 327 2. 325 3. 320 4. 171 Safety: 1. 327 2. 324 3. 318 4. 171 Attrition: 1. 83/327 (25.4%) 2. 69/324 (21.3%) 3. 67/318 (21.1%) 4. 19/171 (11.1%)	Primary Endpoint: NA Primary endpoints were safety related.	NA	Primary Safety Endpoints: TEAE week 52 1. 88.4% 2. 86.1 % 3. 81.8% 4. 86.5% Severe TEAE (Grade 3 or higher): 1. 7.6% 2. 9.0% 3. 9.1% 4. 7.0% Discontinuations due to adverse reaction: 1. 9 (2.8%) 2. 10 (3.1%) 3. 4 (1.3%) 4. 2 (1.2%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomization by interactive voice and web response system stratified by T2D and history of ASCVD. Some baseline differences between groups in gender and concomitant medication use. Performance Bias: (Low) Study personnel administering drug and performing assessments blinded to treatment. Missed study visits and drug kit delays due to Covid-19 in resulted in reduced exposure to drug, especially in DB arms (86-88% of DB patients and 19% of OL patients missed visits). Potential unblinding by AE diarrhea/nausea. Detection Bias: (Low) Study personnel administering drug and performing assessments blinded to treatment. Reporting of adverse events managed by pharmacovigilance team to maintain blind. Laboratory results were blinded if they could unblind personnel and were not required for patient management. Attrition Bias: (High) Missing data related to Covid-19 clinical closures and drug shortages

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		-≥8% hepatic fat -standard care dyslipidemia therapy for ≥30 days -GFR ≥45 (DB arms) or ≥30 and <45 (OL arm) by MDRD-6 <u>Key Exclusion Criteria</u>: -significant EtOH for ≥3 mo last year -history bariatric surgery or intestinal bypass in past 5y -≥ 5% weight loss in past 12wk -HbA1c >9% -HCC -MELD score ≥12 -ALT >250 unit/L -Pioglitazone >15 mg/d or < 15 mg/day and dose changed in past 12 wk -GLP-1 RA if dose changed in past 24 wk -Vitamin E if dose changed in past 12 wk						address with imputation where missing visit was imputed with previous visit data (if available) or next visit if previous was unavailable. If neither available then missing-at-random based multiple imputation used. <u>Reporting Bias</u>: (Unclear) Publications describe additional OL arms in study plan ([1]noncirrhotic NASH enrolled after randomization period 100 mg, [2]well-compensated NASH cirrhosis 80 mg starting dose, and [3] moderate renal impairment) to be reported separately. Full protocol not published. <u>Other Bias:</u> (Unclear) Sponsor funded and designed study. Site monitoring, data collection and data analysis performed by sponsor and contract research organizations **Applicability**: <u>Patient</u>: Underrepresentation of non-White populations heavily affected by metabolic diseases, limited generalizability to Medicaid population. <u>Intervention</u>: Dose regimen based on prior studies. <u>Comparator</u>: Placebo appropriate for disease with limited treatment options. <u>Outcomes</u>: Primary outcomes safety based. Clinical (non-surrogate) outcomes awaited with ongoing studies. Reduced exposure due to missing visits and drug delivery secondary to Covid-19 may have reduced magnitude of AEs experienced. <u>Setting</u>: 80 sites in Unites States

<u>Abbreviations</u> : AE = adverse event; ALT = alanine aminotransferase; ARR = absolute risk reduction; BMI = body mass index; CAP = controlled attenuation parameter; CI = confidence interval; EtOH = ethanol (alcohol); F[#] = fibrosis stage; GFR = glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonists; HCC = hepatocellular carcinoma; ITT = intention to treat; LSM = least squares mean; MACE = major adverse cardiovascular event; MDRD-6 = modification of diet in renal disease 6-variable formula; MELD = model for end-stage liver disease; mITT = modified intention to treat; mo = months; N = number of subjects; NA = not applicable; NAFLD = nonalcoholic fatty liver disease; NAS = NAFLD activity score; NASH = nonalcoholic steatohepatitis; NNH = number needed to harm; NNT = number needed to treat; PBAP = primary biopsy analysis population; PP = primary population; SD = standard deviation; TEAE = treatment emergent adverse events; T2D = type 2 diabetes mellitus; VCTE = vibration-controlled transient elastography or FibroScan; wk = week; y = year.

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use REZDIFFRA safely and effectively. See full prescribing information for REZDIFFRA.

REZDIFFRA (resmetirom) tablets, for oral use
Initial U.S. Approval: 2024

----------INDICATIONS AND USAGE----------

REZDIFFRA 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) 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. (1)

Limitations of Use

Avoid use of REZDIFFRA in patients with decompensated cirrhosis. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- The recommended dosage of REZDIFFRA is based on actual body weight. For patients weighing:
  - <100 kg, the recommended dosage is 80 mg orally once daily.
  - ≥100 kg, the recommended dosage is 100 mg orally once daily.

  Administer REZDIFFRA with or without food. (2.1)
- See full prescribing information for REZDIFFRA dosage modifications with concomitant use of moderate CYP2C8 inhibitors. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: 60 mg, 80 mg, and 100 mg (3)

----------CONTRAINDICATIONS----------

None.

---------- WARNINGS AND PRECAUTIONS----------

- Hepatotoxicity: Monitor patients during treatment with REZDIFFRA for elevations in liver tests and for the development of liver-related adverse reactions. Discontinue REZDIFFRA and continue to monitor the patient if hepatotoxicity is suspected. (5.1)
- Gallbladder-Related Adverse Reactions: Cholelithiasis and cholecystitis were observed more often in REZDIFFRA-treated patients. If cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated. If an acute gallbladder event such as acute cholecystitis is suspected, interrupt REZDIFFRA treatment until the event is resolved. (5.2)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions with REZDIFFRA (reported in at least 5% of patients and higher compared to placebo) are: diarrhea, nausea, pruritus, vomiting, constipation, abdominal pain, and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Madrigal Pharmaceuticals, at 1-800-905-0324 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong or Moderate CYP2C8 Inhibitors: Concomitant use not recommended (strong inhibitor [e.g., gemfibrozil]); or reduce REZDIFFRA dosage (moderate inhibitor [e.g., clopidogrel]). (2.2, 7.1)
- OATP1B1 and OATP1B3 Inhibitors: Concomitant use with OATP inhibitors (e.g., cyclosporine) is not recommended. (7.1)
- Atorvastatin, Pravastatin, Rosuvastatin and Simvastatin: Limit the daily dosage of the statin as recommended. (5.3, 7.2)
- CYP2C8 Substrates: Monitor patients more frequently for substrate-related adverse reactions. (7.2)

---------- USE IN SPECIFIC POPULATIONS ----------

Hepatic Impairment: Avoid use of REZDIFFRA in patients with moderate to severe hepatic impairment (Child-Pugh Class B or C). (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2024

Resmetirom (REZDIFFRA)

Goal(s):
- To ensure appropriate use of resmetirom in patients with nonalcoholic steatohepatitis.

Length of Authorization:
- Up to 12 months

Requires PA:
- All pharmacy point-of-sale claims

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication and age? Note: resmetirom is currently approved for people 18 years and older	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Does the patient have fibrosis stage 2 or 3 as shown by liver biopsy within past 18 months?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the medication being ordered by, or in consultation with, a hepatologist or gastroenterologist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

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Approval Criteria		
5. Will the patient be engaged in a weight management lifestyle modification program in addition to pharmacotherapy? Note: Resmetirom is currently approved as an adjunct to diet and exercise.	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Does the patient have comorbidities of: • Hypertension OR • Dyslipidemia OR • Overweight or Obesity	**Yes:** Go to #7	**No:** Go to #8
7. Is there documentation that the patient is prescribed or has a contraindication to medication or lifestyle therapy for <u>each</u> diagnosed comorbidity?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness. Recommend optimize risk factor treatment.
8. Does the patient have comorbid Type 2 Diabetes Mellitus?	**Yes:** Go to #9	**No:** Approve for 12 months
9. Is there documentation that the patient: • Has a HbA1C <7% within past 6 months OR • Is prescribed or has a contraindication to metformin and a glucagon-like peptide 1 (GLP-1) agonist, and a sodium-glucose cotransporter-2 (SGLT2) inhibitor.	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Recommend optimize risk factor treatment. Avoid *simultaneous* initiation of treatments with overlapping side effect profile (diarrhea, nausea) as resmetirom (e.g., metformin or GLP-1 agonist)

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Renewal Criteria		
1. Does the provider attest that the patient has been adherent to therapy with resmetirom and any comorbid metabolic risk factors?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Has the patient had a complete metabolic panel, liver enzymes, or other appropriate biochemical or noninvasive imaging test within the past 12 months to assess for potential disease progression? Additional example tests: fibrosis-4 index (FIB-4), enhanced liver fibrosis test (ELF), vibration controlled transient elastography (VCTE), magnetic resonance elastography (MRE)	**Yes:** Go to #3	**No:** Pass to RPh. Approve once, for 3 months. Recommend biochemical monitoring.
3. If resmetirom initiation as more than 3 years ago, has the patient had noninvasive imaging or repeat liver biopsy to assess for progression of fibrosis in the past 3 years? If **not applicable** because resmetirom started less than 3 years ago skip to question #5	**Yes:** Go to #4	**No:** Pass to RPh. Approve once, for 3 months. Recommend noninvasive imaging or repeat biopsy.
4. Does the patient have evidence of stage F4 fibrosis (cirrhosis) OR has fibrosis stage worsened (e.g., stage F2 to F3) since starting resmetirom.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #5
5. Is there documentation of a risk/benefit assessment for ongoing treatment with possible resolution of comorbidities?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Approve once, for 3 months. Recommend provide additional documentation.

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Implementation: TBD

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