

New Drug Evaluation: Rezdifra (resmetirom), oral tablet

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Generic Name: Resmetirom

End Date of Literature Search: initial 05/08/2024, repeat 6/27/24

Brand Name (Manufacturer): Rezdifra™ (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 current standards of care for diagnosis and treatment of nonalcoholic steatohepatitis (NASH)?
2. What are the benefits and harms of resmetirom in patients with nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis?
3. Are there specific subpopulations for which resmetirom is better tolerated or more effective?

Conclusions:

- NASH is a subcategory of nonalcoholic fatty liver disease (NAFLD). Liver biopsy is required for definitive diagnosis, though fibrosis staging and ongoing management can be assessed with sequential screening using noninvasive biochemical tests and imaging techniques such as fibrosis-4 index (FIB-4), elastography, and enhanced liver fibrosis (ELF) test.^{1,2}

- Development of NAFLD and NASH are highly associated with specific metabolic comorbidities. These include obesity, insulin resistance, type 2 diabetes mellitus (T2D), high blood pressure, and atherogenic dyslipidemia.² T2D and obesity are the risk factors with the largest impact for development of nonalcoholic fatty liver disease (NAFLD), fibrosis progression, and hepatocellular carcinoma (HCC).¹⁻³ Guideline directed pharmacotherapeutic and lifestyle management of these comorbidities are essential in management of patients with NASH.^{1,2}
- Pharmacotherapeutic treatment of overweight and obesity with certain glucagon-like peptide-1 receptor agonists (GLP-1 RAs), semaglutide and liraglutide, is guideline recommended and compendia supported.^{1,2,4,5}
- 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 or F3]).
- There is moderate-quality evidence from one good quality trial that:
 - Resmetirom increased NASH resolution at week 52 using 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).⁶
 - 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).⁶
 - 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.

Recommendations:

- Implement prior authorization (PA) for resmetirom to ensure safe and appropriate use.
- Consider adding coverage of specific GLP-1 RAs with compendia-support for treatment of NASH in adult patients with overweight ($\geq 27 \text{ kg/m}^2$) or obesity (body mass index $\geq 30 \text{ kg/m}^2$).

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.^{2,3,7} Significant alcohol consumption is typically defined as greater than 21 drinks/week (or $\geq 30 \text{ g/day}$) in men and greater than 14 drinks/week (or $\geq 20 \text{ g/day}$) in women for 2 years preceding baseline liver histology.^{2,3,7} NAFLD has a clinical range from hepatic steatosis to cirrhosis.² 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.² 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 common.² Incidence of hepatic decompensation, HCC, and death due to NASH cirrhosis are anticipated to double or triple by 2030.³ In the United States, it is the second most common cause of HCC for those on the transplant waiting list.² The terms metabolic dysfunction-associated steatohepatitis (MASH) and metabolic dysfunction-associated steatotic liver disease (MASLD) were introduced in place of NASH and NAFLD in June 2023.^{1,8} A new category, MetALD (MASLD with moderate alcohol consumption [20-50 g/day in women and 30-60 g/day in men]) was also introduced.¹ MASLD diagnosis requires at least one cardiometabolic risk factor in an individual with documented steatosis. Large cohorts have shown nearly complete concordance with 99.8% of those with MASLD meeting NAFLD criteria, and 94.7% of those with NAFLD meeting MASLD criteria.¹ Recent European guidelines use the terms interchangeably.¹

Major risk factors for NAFLD are obesity, insulin resistance, type 2 diabetes mellitus (T2D), high blood pressure, and atherogenic dyslipidemia. T2D and obesity are the leading risk factors for NAFLD development, progression, and HCC.¹⁻³ Women with polycystic ovary syndrome (PCOS) have increased insulin resistance, and thus, are at increased risk of both T2D and NAFLD.² 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%).⁷ Higher rates of NAFLD are also seen in those with hypothyroidism, hypogonadism, and growth hormone deficiency.³ NAFLD in individuals who do not have overweight or obesity is estimated at 4.1% in the US and 19% in Asia.³

The role of ethnicity is unclear in the development of hepatic fibrosis. In people of Hispanic ancestry (with or without diabetes), prevalence of steatohepatitis is about 20% higher than the general population, though this seems to be driven by higher rates of obesity.²

Multiple guidelines with varying methodologic quality have been published related to NAFLD. Details of the guideline methods are listed in **Appendix 2**. Guidelines from the American Association of Clinical Endocrinology (AACE) and European Association for the Study of the Liver (EASL)/European Association for the Study of Diabetes/European Association for the Study of Obesity include evidence grades and recommendation levels and are referenced preferentially over ungraded guidelines in this document.

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.^{1,3} Screening involves both establishing a diagnosis by ruling out other causes of liver disease, as well as determining clinically significant levels of fibrosis. 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.^{1,2} 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.² 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.^{1,2} The VCTE is the best validated imaging modality to identify advanced disease.² A magnetic resonance elastography (MRE) is more accurate, though availability is limited in the United States, and it does not replace biopsy for diagnosis of NASH.² A liver ultrasound is not recommended for routine diagnosis.² Patients with intermediate to high fibrosis risk are generally referred to a hepatologist for further workup and possible liver biopsy.²

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.^{2,7} No non-invasive methods can assess relevant microscopic features of NAFLD such as ballooning or lobular inflammation (Level of evidence 2, strong consensus; EASL).¹ Liver biopsy is not required for management of most cases with NAFLD, but is still required for definitive diagnosis of steatohepatitis and to rule out other causes of liver disease (Level of Evidence 1; strong consensus, EASL).¹ Biopsy is generally not appropriate for monitoring disease evolution or response to therapy due to invasiveness and procedure-related limitations (Level of Evidence 5, strong consensus, EASL), other than for individual cases or in clinical trials (Level of Evidence 1, open recommendation, strong consensus, EASL).¹

Noninvasive tests for treatment response, including alanine aminotransferase (ALT), FIB-4, ELF, and liver stiffness tests are associated with histologic response; however, validation and minimum clinically important difference (MCID) are still needed, and the most appropriate test may depend on the type of intervention and patient-related factors (Level of Evidence 2, strong consensus; EASL).^{1,3} Sequential assessment with non-invasive tools may assist in ruling out fibrosis progression (Level of Evidence 3, weak recommendation, strong consensus; EASL) and may predict overall and liver-related disease complications and mortality

(Level of Evidence 2, weak recommendation, strong consensus, EASL).¹ The most recent guidelines from EASL suggest diagnostic test thresholds and ability to predict liver-related outcomes when using specific biochemical and imaging techniques.¹

Once diagnosis is confirmed, NASH is categorized by fibrosis severity (**Table 1**).² 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.² Steatosis grade is scored on an ordinal scale as 0 (none) to 3 (severe) based on percentage of parenchymal involvement of steatosis.² 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.² The FDA has published guidance for industry in the development of research studies for NASH.⁹ The NAS, in conjunction with fibrosis staging, is considered critical inclusion criteria for clinical trials.⁹ However, improved mortality from treatment induced histological changes has not been demonstrated, and long-term follow up studies are needed to demonstrate that stopping disease progression and/or decreasing steatosis, resolution of steatohepatitis, or improvement of fibrosis results in reduced risk of clinical outcomes (Level of Evidence 3, strong consensus, EASL).¹ 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, and 14 years for those with NAFLD without NASH.³ Patients with cirrhosis require additional monitoring for other complications including HCC, and approximately 3-20% develop clinical decompensation each year.³

Table 1. Stages of NASH Fibrosis^{2,10}

Fibrosis Stages	Description
No Fibrosis (F0)	None
Stage 1, Mild (F1) <ul style="list-style-type: none">• F1A• F1B• F1C	Perisinusoidal OR periportal fibrosis <ul style="list-style-type: none">• Mild perisinusoidal fibrosis• Moderate perisinusoidal fibrosis• Only portal/periportal fibrosis
Stage 2 Moderate (F2)	Perisinusoidal AND portal/periportal fibrosis
Stage 3, Severe (F3)	Bridging fibrosis
Stage 4, Cirrhosis (F4)	Cirrhosis

The AACE guidelines recommend cardiometabolic risk factor management with guideline-directed therapy for persons with NAFLD and comorbidities including T2D, dyslipidemia, obesity, metabolic syndrome, prediabetes, hypertension, and cardiovascular disease (Grade A; High/Intermediate Strength of Evidence; Best Level of Evidence [BEL] 1; AACE).²

Pioglitazone and GLP-1 RAs are recommended for people with T2D and biopsy-proven NASH (Grade A; High Strength of Evidence; BEL 1; AACE) and should be considered when there is increased risk of NASH based on non-invasive tests (Grade A; High Strength of Evidence; BEL 1; AACE).^{2,3} However, pioglitazone has notable side effects, including weight gain and potential risk for worsening heart failure.^{2,3} Pioglitazone use in non-cirrhotic NASH has not demonstrated histologic efficacy on steatohepatitis and liver fibrosis in large Phase III trials to be recommended as a NASH-targeted therapy (Level of Evidence 2, weak recommendation, consensus, EASL), though multiple smaller studies of varying quality of evidence have shown improvement in fibrosis.^{1,7} In people with T2D and NAFLD, treatment with pioglitazone, GLP-1 Ras, and sodium-glucose cotransporter-2 (SGLT2) inhibitors can be considered for cardiometabolic benefit, though there is not evidence of benefit for treatment of steatohepatitis with SGLT2 inhibitors (Grade A; High Strength of Evidence; BEL 1; AACE).² Vitamin E can

also be considered for those with NASH without comorbid T2D or advanced fibrosis (Grade B; High Strength of Evidence; BEL 1; downgraded due to risk/benefit; AACE),^{2,11} though not all organizations recommend vitamin E due to lack of robust demonstration of histological efficacy on steatohepatitis and liver fibrosis in large phase III trials and potential long term risks (Level of Evidence 2, weak recommendation, strong consensus, EASL), while multiple smaller studies of varying evidence quality have shown histologic and fibrosis improvement.^{1,7}

In adults with NAFLD and overweight, weight loss of at least 5% reduces liver fat and has cardiometabolic benefits, 7-10% reduces liver inflammation, and 10% or more improves fibrosis and may reverse steatohepatitis (Level of Evidence 2, strong recommendation, strong consensus, EASL).^{1,2} Lifestyle interventions (diet and exercise) are recommended for all adults with NAFLD (Grade A, intermediate Strength of evidence, BEL 1, AACE).² In those with NAFLD and overweight, lifestyle changes with goal weight loss of at least 5%, but ideally more than 10%, are recommended (Grade B; Intermediate/High Strength of Evidence; BEL 1; AACE. Level of Evidence 2, strong recommendation, strong consensus, EASL).^{1,2} AACE downgraded recommendations for lifestyle changes because of small sample sizes, large heterogeneity of interventions, short duration, and few studies with liver biopsy. When not effectively achieved by lifestyle interventions, pharmacotherapeutic augmentation of lifestyle interventions for weight loss are recommended for those with NAFLD or NASH and obesity (Grade B; Intermediate Strength of Evidence; BEL 1; downgraded due to small sample sizes and short trial duration; AACE) or BMI 27 kg/m² or higher with semaglutide 2.4 mg/week or liraglutide 3 mg/day (Grade B; High/Intermediate Strength of Evidence; BEL 1; downgraded due to different formulations and doses used in the semaglutide and liraglutide NASH trials; AACE).² Hepatic histologic benefit could be expected if substantial weight loss is induced by GLP-1 RAs, but has not yet been extensively documented (Level of Evidence 2, strong consensus, EASL), though GLP-1 RAs are safe for use in NASH (including compensated cirrhosis) and are recommended for use with indications of T2D and obesity due to cardiometabolic benefits (Level of Evidence 2, strong recommendation, strong consensus, EASL).¹ Obesity pharmacotherapy (with preference to semaglutide 2.4 mg/week [best evidence] or liraglutide 3 mg/day) as adjunctive therapy to lifestyle modification for individuals with obesity and NAFLD or NASH to promote cardiometabolic health and treat or prevent T2D, CVD, and other end-stage manifestations of obesity must be considered (Grade A; High/Intermediate Strength of Evidence; BEL 1, AACE).²

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.¹¹ Bariatric surgery is also an option to treat NAFLD and improve cardiometabolic health.^{1,2}

As the rate of obesity and T2D increases, the prevalence of NASH in children 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 (Grade B; Intermediate Strength of Evidence; BEL 1; downgraded due to limited number of randomized controlled trials and small sample sizes; AACE). GLP-1 RAs for pediatrics with T2D and obesity can be considered (Grade D; Expert Opinion, BEL 4; AACE).²

Drugs when prescribed for weight loss are currently excluded from the Oregon Medicaid state plan. The P&T committee has recommended that the Oregon Health Authority (OHA) identify a funding plan before covering drugs when prescribed for weight management. However, when drugs are prescribed for indications other than weight loss, they are required to be covered on the Oregon Medicaid plan when there is sufficient evidence for efficacy and safety. Utilization can be limited to medically appropriate use for FDA-approved or compendia-supported indications. Semaglutide and liraglutide have a compendia-support for use to treat NASH in adults with overweight or obesity.^{4,5} An update to the Medicaid state plan is not required for coverage of compendia-supported indications.

A phase 3 study of semaglutide for treatment of NASH is in process.³ Phase 2 results of placebo-controlled studies of liraglutide, semaglutide, and tirzepatide in NASH/MASH utilizing histologic endpoints are published and summarized briefly in **Appendix 3**. Additional studies of liraglutide with other comparisons (ex., metformin, lifestyle) and semaglutide with non-histological endpoints have also been published.¹²⁻¹⁴

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).¹⁵ It was FDA approved in March 2024 through the accelerated approval pathway based on histologic improvement of NAFLD activity scores and fibrosis staging.¹⁵ 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.¹⁵ 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.¹⁵

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).⁶ All patients received nutrition and exercise counseling at each visit and exercise and nutrition focused newsletters throughout the study.⁶ 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.⁶ 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.⁶ A smaller exploratory subpopulation (N=84) including only patients with stage F1A and F1C were also randomized.⁶ 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.⁶ 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.⁶

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%).⁶ Patients were primarily White (89.3%), had a BMI of more than 35 kg/m², 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%).⁶ Most patients were stage F3 (61.9%) or F2 (33%).⁶ 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.⁹ 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).⁶ 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 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).⁶ Adherence was reported at >80% for 92% of participants.⁶ There was no effect on body weight or heart rate found with resmetirom treatment.⁶

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.² 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.

Recent guidelines state resmetirom should be considered as a MASH-targeted therapy in line with local approval labeling for non-cirrhotic adults with significant liver fibrosis (Stage \geq 2) (Level of Evidence 2, strong evidence, consensus, EASL).¹

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 4**), 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).¹⁶

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.⁶ 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%).⁶ Grade 3 (serious) or higher adverse events occurred in similar rates in each group and was highest in the placebo group (**Table 2**).⁶ 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.⁶ 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.¹⁵ There are no human data available for use in pregnancy and an adverse event reporting line is available from the manufacturer to report pregnancies.¹⁵ Maternal NASH with liver fibrosis is associated with increased risk of gestational diabetes, hypertensive complications, preterm birth, and postpartum hemorrhage.¹⁵

Table 2. Adverse Events affecting > 10% of patients in any group⁶

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)
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.¹⁷ Additional open-label arms with at risk populations (e.g. moderate renal impairment) await publication.¹⁷ 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%).¹⁷ 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.¹⁷ Additional details available in **Table 4**.

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

Comparative Endpoints^{9,18}

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 3. Pharmacology and Pharmacokinetic Properties.¹⁵

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
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 4. 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 ⁶ 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	<u>Demographics:</u> 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 <u>Key Inclusion Criteria:</u> - ≥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	<u>ITT:</u> 1. 322 2. 323 3. 321 <u>PBAP:</u> 1. 316 2. 321 3. 318 <u>Attrition:</u> 1. 56 (17.4%) 2. 71 (22.0%) 3. 39 (12.1%)	<u>Primary Endpoint (PBAP):</u> 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 <u>Key Secondary Endpoint (ITT):</u> LDL cholesterol week 24 (LSM % change ± SD) 1. -13.6 ± 1.7 2. -16.3 ± 1.7 3. -0.1 ± 1.7	16.4/7 10.2/10 11.8/9	<u>Outcomes (ITT):</u> 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%)		Risk of Bias (low/high/unclear): <u>Selection Bias:</u> (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. <u>Performance Bias:</u> (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. <u>Detection Bias:</u> (Low) Pathologists blinded and suspected liver-related events and major atherosclerotic cardiac events adjudicated by blinded committee. <u>Attrition Bias:</u> (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. <u>Reporting Bias:</u> (Low) Protocol published with prespecified outcomes. <u>Other Bias:</u> (Unclear) Sponsor designed. Sponsor/contract research organization performed site monitoring, data collection, and data analysis. Data interpretation and publication manuscript done by sponsor employees. Applicability:

		<p>inflammation, hepatocellular ballooning]) -Stable weight; GLP-1 RA doses stable from 6 months before biopsy -GFR \geq45 by MDRD-6</p> <p><u>Key Exclusion Criteria:</u> -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)</p>		<p>1 vs. 3: Difference -13.7% 95% CI -17.5 to -10.0) P<0.001</p> <p>2 vs. 3: Difference -16.4% 95% CI -20.1 to -12.6 P<0.001</p>	<p>NA</p> <p>NA</p>	<p>2. 1 (0.3%) 3. 1 (0.3%)</p>	<p><u>Patient:</u> 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. <u>Intervention:</u> Dose regimen based on prior studies. <u>Comparator:</u> 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. <u>Outcomes:</u> Surrogate outcomes used, clinical outcomes awaited with ongoing studies. <u>Setting:</u> 245 sites in 15 countries</p>
<p>2. MAESTRO-NAFLD-1^{16,17}</p> <p>Phase 3, DB/OL, PC</p> <p>Safety study</p> <p>52 week treatment period and 4 week follow up period</p>	<p>1. DB Resmetirom 80 mg orally once daily</p> <p>2. DB Resmetirom 100 mg orally once daily</p> <p>3. DB Placebo orally once daily</p> <p>4. OL Resmetirom 100 mg orally once daily</p>	<p><u>Demographics:</u> -Mean age 56 years -Female 57% -White 88% -Hispanic 34% -Mean BMI 35.2-36.1kg/m² -T2D 49% -Dyslipidemia 88% -Hypertension 75% -GLP-1 RAs 6.0-11.7% -SGLT2 inhibitor 4.7-10.5%</p> <p><u>Key Inclusion Criteria:</u> -\geq18 years -\geq3 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 \geq5.5 kPa & FibroScan CAP \geq280 dB/m \geq8% hepatic fat -standard care dyslipidemia therapy for \geq30 days -GFR \geq45 (DB arms) or \geq30 and <45 (OL arm) by MDRD-6</p>	<p><u>ITT:</u> 1. 327 2. 325 3. 320 4. 171</p> <p><u>Safety:</u> 1. 327 2. 324 3. 318 4. 171</p> <p><u>Attrition:</u> 1. 83/327 (25.4%) 2. 69/324 (21.3%) 3. 67/318 (21.1%) 4. 19/171 (11.1%)</p>	<p><u>Primary Endpoint:</u> NA</p> <p>Primary endpoints were safety related.</p>	<p>NA</p>	<p><u>Primary Safety Endpoints:</u></p> <p>TEAE week 52</p> <p>1. 88.4% 2. 86.1 % 3. 81.8% 4. 86.5%</p> <p>Severe TEAE (Grade 3 or higher):</p> <p>1. 7.6% 2. 9.0% 3. 9.1% 4. 7.0%</p> <p>Discontinuation due to adverse reaction:</p> <p>1. 9 (2.8%) 2. 10 (3.1%) 3. 4 (1.3%) 4. 2 (1.2%)</p>	<p>NA</p> <p>Risk of Bias (low/high/unclear): <u>Selection Bias:</u> (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. <u>Performance Bias:</u> (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. <u>Detection Bias:</u> (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. <u>Attrition Bias:</u> (High) Missing data related to Covid-19 clinical closures and drug shortages 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.</p>

		<p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> -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 					<p>Other Bias: (Unclear) Sponsor funded and designed study. Site monitoring, data collection and data analysis performed by sponsor and contract research organizations</p> <p>Applicability:</p> <p>Patient: Underrepresentation of non-White populations heavily affected by metabolic diseases, limited generalizability to Medicaid population.</p> <p>Intervention: Dose regimen based on prior studies.</p> <p>Comparator: Placebo appropriate for disease with limited treatment options.</p> <p>Outcomes: 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.</p> <p>Setting: 80 sites in Unites States</p>
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Abbreviations : 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

Appendix 2: Guidelines, Practice Guidance, and Expert Reviews for NAFLD/MASLD

Organization	Guideline	Year	Methodological Notes and Limitations
<ul style="list-style-type: none"> • American Association of Clinical Endocrinology (AACE) • Co-sponsored by American Association for the Study of Liver Diseases (AASLD) 	Diagnosis and Management of NAFLD in Primary Care and Endocrinology Clinic Settings ²	2022	<ul style="list-style-type: none"> • No outside funding received for development of guideline • AACE subcommittee reviewed all disclosures against list of affected companies to reach consensus for task force nonconflicted majority, conflicted minority with management strategy, and those who were disqualified. One co-chair reported conflicts of interest and the other reported having none. • Literature search performed by AACE staff and search methods (e.g., inclusion dates, etc) reported. Search terms not reported. • Recommendations include strength of evidence grade and best evidence level. Evidence levels and quality grading of articles assigned by AACE staff.
<ul style="list-style-type: none"> • European Association for the Study of the Liver (EASL) • European Association for the Study of Diabetes (EASD) • European Association for the Study of Obesity (EASO) 	Management of MASLD ¹	2024	<ul style="list-style-type: none"> • Guideline methods utilize Delphi process¹⁹ • Methodologist involvement and systematic review were optional based on the EASL guideline process; for this guideline, once the final population, intervention, comparison, outcome (PICO) questions had been determined, a systematic review of the literature was conducted on the most important scientific databases (PubMed, Scopus, Embase, Google Scholar) by performing a free-text search. Search terms not reported. • The EASL Ethics Committee must approve any financial conflicts of interest declared by the panel chair and members prior to acceptance to the panel.¹⁹ • Multiple conflicts of interest present for chair, assistant chair, and most panel members. Details of mitigation strategy used when voting on areas with reported conflicts not reported. • Recommendations include level of evidence and recommendation grade.
<ul style="list-style-type: none"> • American Association for the Study of Liver Diseases (AASLD) 	Practice Guidance on the Clinical assessment and management of NAFLD ³	2023	<ul style="list-style-type: none"> • Update of AASLD practice guidance from 2018 • Most authors report conflicts of interest. <ul style="list-style-type: none"> ○ Committees may mitigate using a variety of methods (e.g., disclosure, recusal, divestiture, or AASLD-independent review) Specific method not reported. ○ When assigning writing group the Ethics Committee reviews disclosures for compliance with AASLD Code for the Assessment

			<p>and Management of Conflict of Interest. This Code requires that Practice Guidelines and Metrics committee chairs may not have “Direct Financial Relationships with Companies” during term of service. A minority of guidance writing group members are permitted to have Direct Financial Relationships with Companies up to \$10,000 per company per year.²⁰</p> <ul style="list-style-type: none"> • Guidance funded by American Association for the Study of Liver Diseases. • Methodologist and supporting team conduct literature search. Search terms not reported. <ul style="list-style-type: none"> ○ AASLD guidance statements are put forward to help clinicians understand and implement the most recent evidence based on comprehensive review and analysis of the literature. AASLD has published guidances on aspects of a topic that lacked sufficient data to perform systematic reviews. These differ from guidelines which use clinically relevant questions, which are then answered by systematic reviews of the literature, and followed by data-supported recommendations. The guidelines are developed by a multidisciplinary panel of experts who rate the quality (level) of the evidence and the strength of each recommendation using the Grading of Recommendations Assessment, Development, and Evaluation system.²¹ • Recommendations not graded. Each section written by a lead author and assisted by a secondary author.²²
<ul style="list-style-type: none"> • America Gastroenterological Association (AGA) 	Clinical Practice Update on Lifestyle Modification Using Diet and Exercise to Achieve Weight Loss in the Management of NAFLD: Expert Review ²³	2021	<ul style="list-style-type: none"> • Expert review by 3 authors. All report conflicts of interest. • Search methods not described. • Recommendations not graded and presented as “Best Practice Advice”.
<ul style="list-style-type: none"> • America Gastroenterological Association (AGA) 	Clinical Practice Update on Diagnosis and Management of NAFLD in Lean Individuals: Expert Review ¹¹	2022	<ul style="list-style-type: none"> • Expert review by 3 authors. All report conflicts of interest. • Guidance funded from National Institutes of Health (NIH) grant. • Search methods not described. • Recommendations not graded and presented as “Best Practice Advice”.
<ul style="list-style-type: none"> • National Institute for Health and Care Excellence 	NAFLD Assessment and Management ⁷	2016	<ul style="list-style-type: none"> • Drug Use Research and Management (DURM) high quality trusted source

Appendix 3. Efficacy Summary of Phase 2 Studies of Interest for Glucagon-like peptide-1 receptor agonists (GLP1-RA) and dual GLP-1 RA/glucose-dependent insulinotropic polypeptides (GIP) agonists.

Study	Intervention and Comparison	Population	Outcome	Notes
<p>LEAN²⁴</p> <p>Phase 2, MC, DB, RCT</p> <p>2016</p>	<p>1. Liraglutide 1.8 mg SC daily</p> <p>2. Placebo SC daily</p> <p>Liraglutide started at 0.6 mg and increased by 0.6 mg every 7 days until reaching target dose.</p> <p>Randomized 1:1</p>	<p>Randomized N=52 Primary outcome with paired biopsy N=45</p> <p>Inclusion: -18-70 years -BMI ≥ 25 kg/m² "definite" NASH on biopsy (steatosis >5%, hepatocyte ballooning, and lobular inflammation with or without T2D</p> <p>Exclusion: - other chronic liver disease -cirrhosis (Child-Pugh B/C) -Uncontrolled T2D (HbA1C $\geq 9.0\%$) -history of pancreatitis</p>	<p>Improvement of liver histology at week 48</p> <p>1. 39% 2. 9%</p> <p>RR 4.3 (95% CI 1.04 -17.74) P=0.019</p>	<ul style="list-style-type: none"> Conducted in United Kingdom Endpoint defined as disappearance of steatohepatitis (hepatocyte ballooning) and no worsening in fibrosis by Kleiner Fibrosis classification Sensitivity analysis defining those with missing biopsies as non-responders yielded similar primary endpoint results Most adverse events were mild to moderate and diarrhea, constipation, and loss of appetite were most common.
<p>NN9931-4493²⁵</p> <p>Phase 2, MC, DB, RCT</p>	<p>1. Semaglutide 2.4 mg SC weekly</p> <p>2. Placebo SC weekly</p> <p>Semaglutide started at 0.24 mg and increased every 4 weeks to 0.5 mg, 1.0 mg, 1.7 mg, and then target dose of 2.4 mg.</p> <p>Randomized 2:1</p>	<p>Randomized N=71 Primary outcome with paired biopsy N=63</p> <p>Inclusion: -18-75 years -BMI ≥ 27 kg/m² with or without T2D -Biopsy confirmed NASH-related cirrhosis (Fibrosis Stage 4) -NAS of 3 or higher with both lobular inflammation and hepatocyte ballooning</p> <p>Exclusion: -hepatic decompensation or liver transplantation -hepatocellular carcinoma -Gastroesophageal varices -pioglitazone, high dose vitamin E, or recent use of other GLP- RA</p>	<p>Improvement of liver fibrosis without worsening of NASH at week 48</p> <p>1. 11% 2. 29%</p> <p>OR 0.28 (95% CI 0.06 to 1.24) P=0.087 Not significant</p> <p>Secondary endpoint Resolution of NASH</p> <p>1. 34% 2. 21%</p> <p>OR 1.97 (95% CI 0.56 to 7.91) P=0.29 Not significant</p>	<ul style="list-style-type: none"> Conducted in United States and Europe All patients given standard of care dietary and lifestyle advice based on local standards. Single pathologist used for histology assessment Primary endpoint defined as improvement of liver fibrosis by one stage without worsening of NASH by one grade or more of either lobular inflammation, hepatocyte ballooning, or steatosis. Primary endpoint changed from MRE results to liver biopsy after study protocol completed but before data unblinding. Higher attrition (and lack of paired biopsy) in treatment group (9/47) vs placebo group (1/24); missing outcomes imputed as non-responders Most adverse events were mild to moderate and nausea, vomiting, and diarrhea were most common.

				<ul style="list-style-type: none"> Ten hepatic events occurred in 6 patients. Nine of these were in 5 patients who received semaglutide. All events were nonserious and mild or moderate in severity. More patients on semaglutide (17%) had severe adverse events compared to placebo (4%).
<p>NN9931-4296²⁶</p> <p>Phase 2, MC, DB, RCT</p>	<p>1. Semaglutide 0.1 mg SC daily</p> <p>2. Semaglutide 0.2 mg SC daily</p> <p>3. Semaglutide 0.4 mg SC daily</p> <p>4. Placebo SC daily (treatments blinded within dose levels)</p> <p>Semaglutide started at 0.05 mg and increased to 0.1 mg at 4 weeks, then by 0.1 mg every 4 weeks to target dose. Dose adjustment not permitted after achieving target dose.</p> <p>3:3:3:1:1:1 ratio</p>	<p>Randomized N=320 Paired biopsy available N=277</p> <p>Inclusion: -18-75 years -biopsy-confirmed NASH stage F1, F2, or F3 - BMI >25 kg/m² with or without T2D -NAS of 4 or higher with 1 or higher on each of 3 subcomponents</p> <p>Exclusion: -Excessive alcohol -other chronic liver disease -Uncontrolled T2D (HbA1C >10%)</p>	<p>NASH resolution with no worsening fibrosis in patients with F2 or F3 fibrosis at week 72</p> <p>1. 40% OR 3.36 (95% CI 1.29 to 8.86)</p> <p>2. 36% OR 2.71 (95% CI 1.06 to 7.56)</p> <p>3. 59% OR 6.87 (95% CI 2.60 to 17.63)</p> <p>4. 17%</p> <p>Improvement of at least one fibrosis stage without worsening NASH in patients with F2 or F3 fibrosis at week 72</p> <p>1. 49% OR 1.96 (95% CI 0.86 to 4.51)</p> <p>2. 32% OR 1.00 (95% CI 0.43 to 2.32)</p> <p>3. 43% OR 1.42 (95% CI 0.62 to 3.28)</p> <p>4. 33%</p> <p>Worsening of fibrosis (all randomized patients) at week 72</p> <p>1. 10%</p> <p>2. 8%</p> <p>3. 5%</p> <p>4. 19%</p>	<ul style="list-style-type: none"> Conducted in 16 countries Inclusion of Stage F1 added and exclusion of HbA1C >9.5% edited to 10% via amendment after trial was started. Goal sample size reduced after trial start based on emerging placebo response data from other trials. Primary endpoint defined as no more than mild residual inflammatory cells (score 0 or 1) and no hepatocyte ballooning (score 0) and not worsening liver fibrosis (increase of one or more stage) Confirmatory secondary endpoint defined as improvement of at least one fibrosis stage and no worsening NASH (increase of ≥1 point for either lobular inflammation score or the hepatocyte ballooning score) Primary end point and confirmatory secondary endpoint only included for patients with F2 (22% of study population) and F3 (49% of study population) fibrosis. 89% completed treatment and 94% completed trial; those without week 72 biopsy imputed as non-responders Lack of dose response noted in primary and confirmatory secondary endpoint. Most common side effects were nausea, constipation, decreased appetite, vomiting, and abdominal pain. Serious adverse events were more common in patients on semaglutide groups (19%) compared to placebo (10%).

SYNERGY-NASH ²⁷ Phase 2, MC, DB, RCT 024	<ol style="list-style-type: none"> 1. Tirzepatide 5 mg SC weekly 2. Tirzepatide 10 mg SC weekly 3. Tirzepatide 15 mg SC weekly 4. Placebo SC weekly <p>Tirzepatide started at 2.5 mg and increased by 2.5 mg every 4 weeks to goal.</p> <p>Randomized 1:1:1:1</p>	Randomized N=190 Week 52 biopsy results N=157 Inclusion: -18-80 years -BMI 27-50 kg/m ² with or without T2D -Biopsy confirmed MASH Stage 2 or 3 -NAS of 4 or higher with 1 or higher on each of 3 subcomponents Exclusion: -Excessive alcohol -other chronic liver disease -cirrhosis or hepatic decompensation -Uncontrolled T2D (HbA1C >9.5%)	Resolution of MASH without worsening of fibrosis (defined as no increase in the fibrosis stage) at week 52 <ol style="list-style-type: none"> 1. 44% Difference 34% (95% CI 17-50) 2. 56% Difference 46% (95% CI 29-62) 3. 62% Difference 53% (95% CI 36-69) 4. 10% <p>P<0.001 for all comparisons</p> Improvement of at least 1 fibrosis stage without worsening MASH <ol style="list-style-type: none"> 1. 55% Difference 25% (95% CI 5-46) 2. 51% Difference 22% (95% CI 1-42) 3. 51% Difference 21% (95% CI 1-42) 4. 30% 	<ul style="list-style-type: none"> • Missing biopsies imputed under assumption they follow the pattern of results seen in the placebo group • Included dose escalation, 96% of 10 mg and 85% of 15 mg group reached target dose. Dose reduced after target in 20% (10 mg) and 7% (15 mg). • End point defined as no increase in the fibrosis stage at week 52. MASH resolution was defined as no steatotic liver disease (steatosis score of 0) or simple steatosis (a steatosis score of 1, 2, or 3) without steatohepatitis and an inflammation score of 0 or 1 and a ballooning score of 0. • Tirzepatide groups lost 10.7-15.6% body weight vs. average of 0.8% weight loss in the placebo group. • Most adverse events were mild to moderate and nausea, diarrhea, decreased appetite and constipation were most common. • More adverse events were reported in tirzepatide groups (92-94%) than placebo (83%). Serious adverse events occurred at the same rate (6%).
Abbreviations: BMI = body mass index; DB = double-blind; F(#) = fibrosis stage; HbA1c = hemoglobin A1c; MASH = metabolic dysfunction-associated steatohepatitis; MC = multi-center; NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis; OR = odds ratio; RCT = randomized controlled-trial; RR = relative risk; SC = subcutaneous; T2D = type 2 diabetes mellitus.				

Appendix 4: Proposed Prior Authorization Criteria

Resmetirom (REZDIFFRA)

Goal(s):

- To ensure appropriate use of resmetirom in patients with nonalcoholic steatohepatitis (NASH)/metabolic dysfunction-associated steatohepatitis (MASH).

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. Is the request for continuation of therapy previously approved by the fee-for-service program?	Yes: Go to Renewal Criteria	No: Go to #4
4. Does the patient have a diagnosis of NASH (or MASH) as confirmed by liver biopsy (lifetime)?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness
5. Does the patient have fibrosis stage 2 or 3 as shown by appropriate diagnostic test within past 24 months? Note: appropriate tests may include biopsy, vibration controlled transient elastography (VCTE), magnetic resonance elastography (MRE), enhanced liver fibrosis test (ELF).	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness
6. Is the medication being ordered by, or in consultation with, a hepatologist or gastroenterologist?	Yes: Go to #7	No: Pass to RPh. Deny; medical appropriateness

Approval Criteria		
<p>7. Will the patient be engaged in a weight management lifestyle modification program in addition to pharmacotherapy?</p> <p>Note: Resmetirom is currently approved in conjunction with diet and exercise</p>	Yes: Go to #8	No: Pass to RPh. Deny; medical appropriateness
<p>8. Does the patient have comorbidities of:</p> <ul style="list-style-type: none"> • Hypertension OR • Dyslipidemia OR • Overweight with body mass index (BMI) ≥ 27 kg/m² or Obesity BMI ≥ 30 kg/m² 	Yes: Go to #9	No: Go to #10
<p>9. Is there documentation that the patient is prescribed or has a contraindication to guideline directed medication or lifestyle therapy for <u>each</u> diagnosed comorbidity?</p> <p>Example:</p> <ul style="list-style-type: none"> • Hypertension-blood pressure at goal range or receiving treatment with antihypertensives • Dyslipidemia-lipid panel at goal or receiving statin therapy • Overweight or obesity-lifestyle management <u>and treatment with glucagon-like peptide-1 receptor agonists (GLP-1 RA) with indication for overweight or obesity and compendia support for NASH</u> 	Yes: Go to #10	<p>No: Pass to RPh. Deny; medical appropriateness.</p> <p>Recommend optimize risk factor treatment.</p> <p><u>Recommend optimize risk factor treatment. Avoid simultaneous initiation of treatments with overlapping side effect profile (diarrhea, nausea) as resmetirom (e.g., GLP-1 RA)</u></p>
<p>10. Does the patient have comorbid type 2 diabetes mellitus?</p>	Yes: Go to #13	No: Go to #11
<p>11. Is there documentation that the patient has been screened for type 2 diabetes mellitus within past 12 months?</p>	Yes: Go to #12	No: Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
<p>12. Was the screening for type 2 diabetes mellitus negative?</p> <p>Note: screening options include hemoglobin A1c (HbA1c, goal <6.5%), fasting blood glucose (goal <126 mg/dL), or oral glucose tolerance test (goal <200 mg/dL)</p>	Yes: Approve for 12 months	No: Go to #13
<p>13. Is there documentation that the patient:</p> <ul style="list-style-type: none"> • 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) receptor agonist, and a sodium-glucose cotransporter-2 (SGLT2) inhibitor. 	Yes: Approve for 12 months	<p>No: Pass to RPh. Deny; medical appropriateness.</p> <p>Recommend optimize risk factor treatment. Avoid <i>simultaneous</i> initiation of treatments with overlapping side effect profile (diarrhea, nausea) as resmetirom (e.g., metformin or GLP-1 RA)</p>

Renewal Criteria		
<p>1. Does the provider attest that the patient remains on, and is adherent to, pharmacotherapeutic or lifestyle therapy for any current metabolic comorbidities?</p>	Yes: Go to #2	No: Pass to RPh. Deny; medical appropriateness
<p>2. Does the provider attest that the patient has been adherent to therapy with resmetirom OR is adherence apparent from medication claims history?</p>	Yes: Go to #3	<p>No: Pass to RPh. Approve once, for 3 months.</p> <p>Request documentation of adherence.</p>

Renewal Criteria		
<p>3. 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?</p> <p>Additional example tests: fibrosis-4 index (FIB-4), enhanced liver fibrosis test (ELF), vibration controlled transient elastography (VCTE), magnetic resonance elastography (MRE)</p>	<p>Yes: Go to #4</p>	<p>No: Pass to RPh. Approve once, for 3 months.</p> <p>Recommend biochemical monitoring.</p>
<p>4. If resmetirom initiation was more than 3 years ago, has the patient had noninvasive imaging (e.g., VCTE or MRE) or repeat liver biopsy to assess for progression of fibrosis in the past 3 years?</p> <p>If not applicable because resmetirom started less than 3 years ago skip to question #5</p>	<p>Yes: Go to #5</p>	<p>No: Pass to RPh. Approve once, for 3 months.</p> <p>Recommend noninvasive imaging or repeat biopsy.</p>
<p>5. Does the patient have evidence of stage F4 fibrosis (cirrhosis) OR has fibrosis stage worsened (e.g., stage F2 to F3) since starting resmetirom.</p>	<p>Yes: Pass to RPh. Deny; medical appropriateness</p>	<p>No: Go to #6</p>
<p>6. Is there documentation of a risk/benefit assessment for ongoing treatment with resmetirom with possible resolution of metabolic comorbidities?</p>	<p>Yes: Approve for 12 months</p>	<p>No: Pass to RPh. Approve once, for 3 months.</p> <p>Recommend provide additional documentation.</p>

P&T/DUR Review: [8/24 \(SF\)](#)
Implementation: [TBD](#)

Weight Management Drugs

Goal(s):

- To provide guidance for the use of weight management therapies to ensure they are used in the most appropriate patient populations in which evidence supports efficacy and safety.
- Allow case-by-case review for members covered under the EPSDT program. Recommend use of GLP-1 receptor agonists only for FDA-approved indications supported by the evidence.
- To provide guidance for the use of weight management drugs, like semaglutide (WEGOVY), to ensure coverage for the most appropriate patient populations in which evidence supports efficacy and safety for reduction in cardiovascular (CV) outcomes [and nonalcoholic steatohepatitis \(NASH, also called metabolic dysfunction-associated steatohepatitis \[MASH\]\)](#).

Length of Authorization:

- Up to 6 months
- Renewal up to 12 months

Requires PA:

- All drugs used for weight management.
- All doses of semaglutide (WEGOVY) require PA.
- Refer to the Glucagon-like Peptide-1 (GLP-1) Receptor Agonists and Glucose Dependent Insulinotropic Polypeptide (GIP) Receptor Agonist PA Criteria for approval of Semaglutide (OZEMPIC and RYBELSUS) for type 2 diabetes.

Note: Semaglutide is not currently covered for adults who do not have established cardiovascular disease or type 2 diabetes.

Table 1. Drugs FDA Approved for Weight Management

Drug	Adults	Pediatrics
Liraglutide (SAXENDA)	Yes	Yes – 12 years and older
Naltrexone/bupropion (CONTRAVE)	Yes	No
Phentermine/topiramate (QSYMIA)	Yes	Yes – 12 years and older
Semaglutide (WEGOVY)	Yes	Yes – 12 years and older
Tirzepatide (ZEPBOUND)	Yes	No
Setmelanotide (IMCIVREE)	Yes	Yes – 6 years and older
Orlistat (Xenical)	Yes	Yes – 12 years and older

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/

Table 2. BMI Cutoffs for Obesity by Sex and Age for Pediatric Patients Aged 12 Years and Older (CDC Criteria)

Age (years)	Body mass index (kg/m ²) at 95% percentile	
	Males	Females
12	24.2	25.2
12.5	24.7	25.7
13	25.1	26.3
13.5	25.6	26.8
14	26.0	27.2
14.5	26.4	27.7
15	26.8	28.1
15.5	27.2	28.5
16	27.5	28.9
16.5	27.9	29.3
17	28.2	29.6
17.5	28.6	30

Table 3. Evidence-Supported Indications

Drug	Indications
Liraglutide	<ul style="list-style-type: none"> Biopsy-confirmed non-alcoholic steatohepatitis (NASH) in adults 18 years and older
Semaglutide	<ul style="list-style-type: none"> Established cardiovascular disease (e.g., history of myocardial infarction, stroke, or symptomatic peripheral arterial disease) Biopsy-confirmed non-alcoholic steatohepatitis (NASH) in adults 18 years and older

Approval Criteria		
14. What diagnosis is being treated?	Record ICD10 code.	
15. Is this a request for continuation of therapy after an initial approval by FFS?	Yes: Go to renewal criteria	No: Go to #3

Approval Criteria		
<p><u>16.</u> Does the patient have a BMI corresponding to one of the following:</p> <p>1) ≥ 30 kg/m² or</p> <p>2) ≥ 27 kg/m² and comorbid conditions [e.g., diabetes mellitus, hypertension, dyslipidemia, fatty liver disease, or cardiovascular disease] or</p> <p>3) a BMI at the 95th percentile or greater for age and sex (Table 2 above)?</p>	<p>Yes: Go to #4</p> <p>Record baseline BMI</p>	<p>No: Deny; medical appropriateness</p>
<p><u>17.</u> Will the patient be engaged in a weight management lifestyle modification program in addition to pharmacotherapy?</p> <p>See clinical notes below</p>	<p>Yes: Go to #5</p>	<p>No: Deny; medical appropriateness. All drugs approved for weight loss are indicated as an adjunct to diet and exercise.</p>
<p>16-18. Is the requested medication for an FDA-approved age (Table 1) in a patient less than 21 years of age and 6 years of age or older?</p>	<p>Yes: Go to #36</p>	<p>No: Go to #112</p>
<p>17-19. Is the request for setmelanotide?</p>	<p>Yes: Go to #67</p>	<p>No: Go to #89</p>
<p>18-20. Does the patient have obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance OR does the patient have Bardet—Biedl syndrome (BBS)?</p>	<p>Yes: Go to #78</p>	<p>No: Deny; medical appropriateness.</p>
<p>19-21. Does the patient have a history of depression and/or suicidal ideation?</p>	<p>Yes: Deny; medical appropriateness.</p>	<p>No: Approve for up to 6 months.</p>

Approval Criteria		
<p>20. Does the patient have a BMI corresponding to 30 kg/m² or >27 kg/m² and comorbid conditions [e.g., diabetes mellitus, hypertension, dyslipidemia, or cardiovascular disease] for adults or a BMI at the 95th percentile or greater for age and sex (Table 2 above)?</p>	<p>Yes: Go to #9</p> <p>Record baseline BMI</p>	<p>No: Deny; medical appropriateness</p>
<p>26-22. Does the patient have comorbidities (e.g., hypertension, dyslipidemia, diabetes, fatty liver disease, depression, or sleep apnea)?</p>	<p>Yes: Go to #11 Approve for 6 months</p>	<p>No: Go to #10</p>
<p>27-23. Has the patient previously tried a weight loss treatment plan administered by a health care provider (e.g., diet and exercise program, nutritional counseling, and/or a calorie restricted diet) for a time period of at least 3 months within the previous 6 month timeframe*?</p> <p>* See Clinical Notes Below</p>	<p>Yes: Approve for 6 months. Go to #11</p>	<p>No: Deny; medical appropriateness. Lifestyle modifications are recommended by guidelines.</p>
<p>28. Will the patient be engaged in a weight management lifestyle modification program in addition to pharmacotherapy?</p>	<p>Yes: Approve for 6 months.</p>	<p>No: Deny; medical appropriateness. All drugs approved for weight loss are indicated as an adjunct to diet and exercise.</p>
<p>24. Is the request for a drug <u>FDA-approved or compendia supported for the requested condition as defined in Table 3?</u> Is the request for a weight management drug with an FDA-approved indication for secondary cardiovascular prevention?</p>	<p>Yes: Go to #1312</p>	<p>No: Pass to RPh. Deny; drugs are not covered by OHP for adults when indicated for weight loss.</p>

Approval Criteria		
32. Does the patient have established cardiovascular disease (e.g., history of myocardial infarction, stroke, or symptomatic peripheral arterial disease)?	Yes: Go to #13	No: Deny; drugs are not covered by OHP for adults when indicated for weight loss.
36. Is the request for continuation of therapy previously approved by FFS?	Yes: Go to Renewal Criteria	No: Go to #14
<u>25.</u> Has the patient previously tried a weight loss treatment plan administered by a health care provider (e.g., diet and exercise program, nutritional counseling, and/or a calorie restricted diet) for a time period of at least 3 months within the previous 6 month timeframe?	Yes: Go to <u>#15</u>	No: Deny; medical appropriateness
40-26. Is there documentation of a type 2 diabetes diagnosis?	Yes: Go to #15	No: Go to #14
<u>41-27.</u> Has the patient been screened for diabetes within the past year and do screening results indicate they do not have diabetes (e.g., HbA1c <6.5% or fasting blood glucose <126 mg/dl (7 mmol/L)?	Yes: Go to <u>#15</u>	No: Pass to RPh; Deny; medical appropriateness. Recommend <u>screening and if positive recommend</u> a GLP-1 RA indicated for glucose lowering (see GLP-1 RA/GIP RA PA criteria)
42. Does the patient have a BMI of 27 kg/m² or greater?	Yes: Go to #17 <u>Document current BMI</u>	No: Pass to RPh. Deny; medical appropriateness.
<u>28. Is the request for semaglutide?</u>	Yes: <u>Go to #16</u>	No: <u>Approve for up to 6 months</u>
<u>48-29.</u> Is the patient currently taking semaglutide (Ozempic) 2.0 mg weekly and is able to tolerate the medication and is still desiring additional weight loss?	Yes: Approve for up to 6 months	No: Go to <u>#17</u> <u>20</u>

Approval Criteria		
49-30. Will the patient try semaglutide (Ozempic) for at least 6 <u>4</u> months to ensure tolerability/compliance?	Yes: Approve Ozempic for up to 6 months	No: Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is this a request for continuation of therapy with a weight loss medication previously approved by FFS?	Yes: Go to #2	No: Go to Approval Criteria above
2. Is the person requesting the medication less than 21 years of age?	Yes: Go to #3	No: Go to #4
3. Has the patient lost at least 1% of BMI from baseline or maintained at least a 1% BMI weight loss?	Yes: Go to #7	No: Deny; medical appropriateness
4. Is the request for ongoing treatment for someone with established cardiovascular disease (e.g., history of myocardial infarction, stroke, or symptomatic peripheral arterial disease) <u>or NASH</u> ?	Yes: Go to #5	No: Pass to RPh. Deny; drugs are not covered by OHP for adults when indicated for weight loss.
5. Has the patient lost or maintained a BMI reduction of 5% or more?	Yes: Go to #6	No: Deny; medical appropriateness
6. Has the patient been adherent to therapy based on provider attestation?	Yes: Go to #7	No: Deny; medical appropriateness
7. Is the patient continuing with a weight loss treatment plan (e.g., diet and exercise program, nutritional counseling, and/or a calorie restricted diet)?	Yes: Approve for up to 12 months.	No: Deny; medical appropriateness. All drugs approved for weight loss are indicated as an adjunct to diet and exercise.

***Clinical Notes**

Adapted from the following guideline on the treatment of adolescents with obesity:

- American Academy of Pediatrics. *Pediatrics*. 2023;151(2): e2022060640. Available at: <https://publications.aap.org/pediatrics/article/151/2/e2022060640/190443/Clinical-Practice-Guideline-for-the-Evaluation-and?autologincheck=redirected>

Recommended Behavior Strategies

Strategy	Description
1. Reduction in sugar-sweetened beverages (SSBs)	Higher intake of sugar-sweetened beverages (carbonated beverages, sweetened beverages, soda, sports drinks, and fruit drinks) is associated with greater weight gain in adults and children. The American Heart Association (AHA) recommends not more than 25 g (6 tsp) each day of added sugar and not more than 1, 8-oz serving of SSB per week. The AAP discourages the consumption of sports drinks and energy drinks for children and adolescents. The AAP statement on fruit juice notes that it is a poor substitute for whole fruit because of its high sugar and calorie content and pediatricians should advocate for elimination of fruit juice in children with excessive weight gain.
2. Choose My Plate	MyPlate is the US Department of Agriculture’s (USDA) broad set of recommendations for healthy eating for Americans. These recommendations include multiple healthy diet goals: low in added sugar, low in concentrated fat, nutrient dense but not calorie dense, within an appropriate calorie range without defined calorie restriction, and with balanced protein and carbohydrate. The principles can be adapted to different food cultures. There is a surprising dearth of literature on the impact of these guidelines on health and BMI outcomes and on the most effective education practices. Available at: USDA choose my plate.gov
3. 60 minutes daily of moderate to vigorous physical activity	Aerobic exercise, especially for 60 min at a time, is associated with improved body weight in youth although its effect may be small and variable. It is also associated with better glucose metabolism profiles. High-intensity interval training in youth with obesity may improve body fat, weight, and cardiometabolic risk factors, although the effect is variable. The Physical Activity Guidelines for Americans recommends 60 min per day for children and adolescents.
4. Reduction in sedentary behavior	Reduction in sedentary behavior, generally defined as reduced screen time, has consistently shown improvement in BMI measures, although impact is small. Early studies focused on reduced television, a discrete activity that is simpler than current multifunctional electronic devices. The AAP recommends no media use under age 18 month, a 1-hour limit for ages 2–5 years, and a parent- monitored plan for media use in older children, with a goal of appropriate, not- excessive use but without a defined upper limit.

The activities most commonly associated with positive behavior change are: parental involvement in goal setting, problem solving, social support, demonstrating desired behaviors, and home environment modifications to support positive change.

Abbreviations: AAP – American Academy of Pediatrics; BMI = body mass index; oz = ounce; tsp = teaspoon; USDA = United States Department of Agriculture

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists and Glucose Dependent Insulinotropic Polypeptide (GIP) Receptor Agonist

Goal(s):

- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:

- Up to 12 months

Requires PA:

- All non-preferred GLP-1 receptor agonists and GLP-1 receptor + GIP receptor agonists. Preferred products do not require PA when prescribed as second-line therapy in conjunction with metformin.

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. Does the patient have a diagnosis of Type 2 diabetes mellitus?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness. For requests for non-alcoholic or metabolic dysfunction-associated steatohepatitis (NASH/MASH), see weight management PA criteria.

Approval Criteria

<p>3. Will the prescriber consider a change to a preferred product?</p> <p>Message:</p> <ul style="list-style-type: none"> Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee. 	<p>Yes: Inform prescriber of covered alternatives in class</p>	<p>No: Go to #4</p>
<p>4. Has the patient tried and failed to meet hemoglobin A1C goals with metformin or have contraindications to metformin?</p> <p>(document contraindication, if any)</p>	<p>Yes: Approve for up to 12 months</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p> <p>Recommend trial of metformin. See below for metformin titration schedule.</p>

Initiating Metformin

<p>1. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.</p>
<p>2. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).</p>
<p>3. If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.</p>
<p>4. The maximum effective dose can be up to 1,000 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.</p>

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T Review: 10/22 (KS), 8/20 (KS), 6/20), 3/19, 7/18, 9/17; 1/17; 11/16; 9/16; 9/15; 1/15; 9/14; 9/13; 4/12; 3/11
 Implementation: 1/1/23; 9/1/20; 5/1/19; 8/15/18; 4/1/17; 2/15; 1/14