Semaglutide (WEGOVY) in Metabolic Dysfunction–Associated Steatohepatitis
National Drug Mini-Monograph

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VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: BEL, best evidence level; BMI, body mass index; CLI, comprehensive lifestyle intervention; CRP, C-reactive protein; CVD, cardiovascular disease; DB, double-blind; ELF, enhanced liver fibrosis; F2/F3, liver fibrosis stage 2/3; FAST, FibroScan AST; GGT, γ-glutamyltransferase; GIP, glucose-dependent insulinotropic polypeptide; GLP1RA, glucagon-like peptide-1 receptor agonist; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HOMA-IR, homeostatis model assessment of insulin resistance; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction-associated steatohepatitis (formerly, NASH); MC, multicenter; MEN 2, Multiple Endocrine Neoplasia syndrome type 2; MN, multinational; MTC, medullary thyroid carcinoma; NAS, nonalcoholic fatty liver disease activity score (range 0–8; ≥5 indicates a diagnosis of definite NASH and ≤3 rules it out); NASH, nonalcoholic steatohepatitis (former term for MASH; NASH is used in this review when any source reference used the term NASH); NIT, noninvasive test; NMA, network meta-analysis; PC, placebo-controlled; PRO-C3, N-terminal propeptide of type III collagen; Q, GRADE quality of evidence; RCT, randomized clinical trial; SoE, strength of evidence; T2D, type 2 diabetes; VCTE, vibration-controlled transient elastography

FDA PRESCRIBING INFORMATION[1]	
Description / MOA	Glucagon-like peptide-1 receptor agonist (GLP1RA); the second agent approved for the treatment of noncirrhotic MASH, following resmetirom. Semaglutide was previously approved for use in combination with a reduced calorie diet and increased physical activity for • reducing the risk of major adverse cardiovascular events (MACE) in adults with established CVD and either obesity or overweight; and • reducing excess body weight and maintaining weight reduction long term in patients ≥ 12 years of age with obesity or overweight in the presence of ≥ 1 weight-related comorbid condition.
Indication Under Review	Treatment of noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH; formerly, nonalcoholic steatohepatitis/NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) in adults.
Dosage Regimen	*Initial Dosage*: 0.25 mg SC once weekly for 4 weeks. *Escalation (once weekly SC)*: 0.5 mg on Weeks 5–8, 1 mg on Weeks 9–12, and 1.7 mg on Weeks 13–16. *Maintenance (once weekly SC)*: 2.4 mg from Weeks 17 and on. If patients do not tolerate the maintenance dosage of 2.4 mg once weekly, the dosage can be decreased to 1.7 mg once weekly. Consider reescalation to 2.4 mg once weekly.
Dosage Forms Under Review	Injection: Single-dose pens in 5 strengths – 0.25 mg/0.5 mL, 0.5 mg/0.5 mL, 1 mg/0.5 mL, 1.7 mg/0.75 mL, and 2.4 mg/0.75 mL
Pretreatment Procedures	□ Glucose – Check baseline glucose in patients with type 2 diabetes (T2D) because of the risk of hypoglycemia; consider dosage reduction of concomitant insulin or insulin secretagogues (e.g., sulfonylureas) to reduce risk.
Treatment Monitoring	□ Glucose – In patients with T2D □ Renal function – In patients with adverse reactions (e.g., vomiting, diarrhea) that could lead to volume depletion □ Diabetic retinopathy complications – In patients with history of diabetic retinopathy □ Heart rate increase □ Depression or suicidal thoughts

EFFICACY CONSIDERATIONS

The ESSENCE Trial

Semaglutide 2.4 mg in Participants With Metabolic Dysfunction-Associated Steatohepatitis: Baseline Characteristics and Design of the Phase 3 ESSENCE Trial[2]

Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis[3]

Design

Ongoing 240-week, two-part, multinational, DB PC RCT

Pre-qualification Period. To increase the likelihood of patients having F2/F3 fibrosis and therefore decrease the likelihood of failing biopsy screening, one or more of the following criteria had to be met:

- a historical liver biopsy within 180 days prior to the first screening visit that could be centrally assessed;
- a history of any of the following NIT results: enhanced liver fibrosis (ELF) ≥ 9.8, liver stiffness ≥ 9.1 kPa (assessed using vibration-controlled transient elastography [VCTE]/FibroScan), magnetic resonance elastography ≥ 3.2 kPa, FibroScan-aspartate transaminase(FAST) score ≥ 0.67; biopsy consistent with MASH with stage 2 or 3 fibrosis; or a fibrosis- 4 (FIB- 4) score ≥ 1.3.

14-week Screening Period. Included an in-trial liver biopsy if there was no historical liver biopsy within the previous 180 days.

240-week Treatment Period. Part 1 (0–72 weeks) and Part 2 (0–240 weeks).

Primary Efficacy Endpoint(s)

Resolution of steatohepatitis with no worsening of liver fibrosis, and improvement in liver fibrosis with no worsening of steatohepatitis. To establish efficacy, semaglutide had to be statistically superior to placebo in at least one of the two primary histological liver endpoints.

Population

Major Inclusion Criteria. Adults ≥ 18 years of age; biopsy-documented steatohepatitis and liver fibrosis of stage 2 (F2) or 3 (F3), NAS score of ≥ 4 with a score of ≥ 1 in steatosis, lobular inflammation and hepatocyte ballooning.

Major Exclusion Criteria. Chronic liver disease other than MASLD; average alcohol consumption of > 30 g/d for men and > 20 g/d for women as per the alcohol use disorders identification test (AUDIT); presence or a history of ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis or liver transplantation; MELD score > 12; AST/ALT > 5 x ULN; eGFR < 30 mL/min/1.73 m^2; HgA1c > 9.5%; history of acute pancreatitis; MASH medication not at stable doses for the previous 90 days; use of GLP-1RA in previous 90 days; glucose-lowering, lipid-lowering, or weight-lowering medication (other than a GLP-1RA) not at stable doses for the previous 90 days.

Baseline Characteristics (N = 800). Mean age 56 years; mean BMI 34.6 kg/m^2; 67.5% White; 42.9% male; 55.9% T2D; 31.2% stage 2 and 68.8% stage 3 liver fibrosis; 35.0% from North America. No US VHA investigators/patients.

Interventions

Semaglutide 2.4 mg or placebo SC once weekly (following a 16-week dose escalation phase that was part of the treatment period).

Co-therapies

Guidance-consistent standard care for MASH and co-existing conditions; lifestyle counseling.

Assessments of lifestyle interventions included weight loss attempts, monthly record of average minutes of exercise per week; and whether a diet was being followed to lose weight.

Results

72-week (Part 1) Interim Efficacy

Endpoint	Semaglutide	Placebo	RR (95% CI)	ARD (95% CI)	Q
Resolution of steatohepatitis with no worsening of liver fibrosis	336/534 (62.9)	91/266 (34.3)	1.8 (1.54, 2.20)	28.7 (21.1, 36.2)	M[α]
Reduction in liver fibrosis with no worsening of steatohepatitis	197/534 (36.8)	60/266 (22.4)	1.6 (1.28, 2.10)	14.4 (7.5, 21.3)	L[α]
Both resolution of steatohepatitis and reduction in fibrosis	175/534 (32.7)	43/266 (16.1)	2.0 (1.50, 2.73)	16.6 (10.7, 22.6)	L[α β]

Values for the interventions are shown as n/N (%).

[α] Downgraded for indirectness (reduction in steatohepatitis and fibrosis are surrogates for liver-related complications such as cirrhosis, hepatic decompensation, or liver transplantation)

[β] Downgraded for imprecision (optimal information size not met/wide confidence interval)

Other Apparent Improvements with Semaglutide vs Placebo

- Noninvasive tests: ELF score, liver stiffness on VCTE; FAST score; PRO-C3 level; and GGT level
- Reduction in steatosis, ballooning, and total NAS
- Mean percentage change from baseline in body weight: –10.5% vs –2.0% (ARD –8.5%; 95% CI –9.6, –7.4).
- Cardiometabolic effects: Glycemia, insulin resistance (HOMA-IR); high-sensitivity CRP (measure of systemic low-grade inflammation); and lipids.

Subgroup Analyses

- Semaglutide was superior to placebo in subgroup analyses by age, sex, baseline fibrosis stage, type 2 diabetes status, and in baseline BMI categories representing overweight or obese: ≥ 27 to < 30 kg/m^2, ≥ 30 to < 35 kg/m^2, and ≥ 35 kg/m^2.

	• In the subgroup with baseline BMI of < 27 kg/m^2 (i.e., non-overweight/obese patients), the estimated difference in responder proportions favored semaglutide but the 95% CI crossed the value zero: 4.47 (–15.85, 24.79).
Other Relevant Trials	Semaglutide 2.4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial[4] A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis[5] Improved health-related quality of life with semaglutide in people with non-alcoholic steatohepatitis: A randomised trial[6] Randomised clinical trial: semaglutide versus placebo reduced liver steatosis but not liver stiffness in subjects with non-alcoholic fatty liver disease assessed by magnetic resonance imaging[7]

SAFETY CONSIDERATIONS

Boxed Warnings	Thyroid C-cell tumors
Contraindications	Personal or family history of medullary thyroid carcinoma (MTC) Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
Other Warnings	Acute pancreatitis Acute gallbladder disease Hypoglycemia in patients on insulin or an insulin secretagogue Acute kidney injury Severe gastrointestinal adverse reactions Hypersensitivity reactions Diabetic retinopathy complications in patients with type 2 diabetes (T2D) Increased heart rate Suicidal behavior and ideation Pulmonary aspiration during general anesthesia or deep sedation
Top 5 AEs	Nausea, diarrhea, vomiting, constipation, abdominal pain
Drug Interactions	*Insulin or an Insulin Secretagogue (e.g., sulfonylurea)*. When initiating semaglutide, consider decreasing the dose of insulin or insulin secretagogue to decrease the risk of hypoglycemia. *Delayed Gastric Emptying*. May affect absorption of concomitantly used oral medications
Pregnancy	*Females Who Are Pregnant*. May cause fetal harm. Avoid in pregnancy. *Females and Males of Reproductive Potential.* Discontinue semaglutide at least 2 months before a planned pregnancy.
Lactation	Semaglutide is likely to be present in human milk. Weigh risks vs benefits.
ESSENCE Safety Results	**Selected Adverse Events During 72 Weeks of Therapy**

Adverse Event	Semaglutide	Placebo
Any AE	690/800 (86.2)	315/395 (79.7)
Fatal AE	3/800 (0.4)	6/395 (1.5)
Serious AE	107/800 (13.4)	53/395 (13.4)
GI disorder	20/800 (2.5)	6/395 (1.5)
Discontinuation due to AE	21/800 (2.6)	13/395 (3.3)
Gallbladder-related disorder	20/800 (2.5)	6/395 (1.5)
Acute pancreatitis	3/800 (0.4)	2/395 (0.5)
Malignant neoplasm	13/800 (1.6)	9/395 (2.3)
Hypoglycemia with T2DM	33/446 (7.4)	12/222 (5.4)
Hypoglycemia without T2DM	1/354 (0.3)	1/173 (0.6)

Values expressed as n/N (%)

INDIRECT RELATIVE EFFICACY–SAFETY FROM NETWORK META-ANALYSES

No NMAs that include the ESSENCE trial were found.

OTHER CONSIDERATIONS	
FDA Review	FDA Multidisciplinary Review and Gastrointestinal Advisory Committee Materials on semaglutide/Wegovy in MASH were not available.
ICER Review	Not available
NICE Review	In development
Comprehensive Lifestyle Intervention (CLI)	*Operational Definition*. See NCP-MOVE-CLI-Definition.pdf . *Adequate Trial of CLI*. The VA/DoD Clinical Practice Guideline for the Management of Adult Overweight and Obesity (July 2020) states (on page 28 of 147) "Achieving 5–10% weight loss after six months is a reasonable initial treatment goal that can produce clinically significant benefits, especially for patients with obesity-associated conditions." Furthermore, "Patients who are meeting short- and intermediate-term goals should continue current treatment until long-term weight loss goals are achieved. When patients are not meeting short- and intermediate-term goals, the treatment plan should be modified to address identified barriers to health behavior change. If, despite increased attention to these barriers, the patient continues to struggle, consideration should be given to increasing the intensity of treatment. This can be achieved by increasing the intensity or frequency of the CLI, adding a recommended pharmacotherapeutic agent for weight loss, and consultation with, or referral to, a bariatric surgical team." Also see PBM Sharepoint (https://dvagov.sharepoint.com/sites/VHAPBM/Formulary/SitePages/Home.aspx) > Clinical Guidance > Clinical Recommendations > Weight Management Medications Clinical Recommendations, Appendix A: Participation in a Comprehensive Lifestyle Intervention.
Evidence Gaps	• Effects of semaglutide on final clinical outcomes of MASH (e.g., liver transplantation, liver-related death) and longer-term risk-benefit profile. • Effects of semaglutide in non-obese (BMI ≥ 25 to < 27 kg/m^2) or lean (BMI < 25 kg/m^2) patients with MASH. The ESSENCE trial did not have a BMI requirement for study entry or exclude lean MASH; however, only 6.6% of patients were in the BMI < 25 kg/m^2 category at baseline. • Efficacy and safety of semaglutide in patients with MASH and early liver cirrhosis • Effects of semaglutide in patients with MASH diagnosed by NITs vs liver biopsy • Safety of semaglutide in patients with cirrhosis related to MASH

THERAPEUTIC ALTERNATIVES AND THEIR PLACE IN THERAPY

DRUG	VANF	CFU	FDA	AACE/AASLD GUIDELINE[8]/AASLD SEMAGLUTIDE PRACTICE GUIDANCE[9]	EASL-EASD-EASO GUIDELINES[10]
Semaglutide inj, soln	PA-F	OZEMPIC for T2D.	For (1) improvement of glycemic control in adults with T2DM as an adjunct to diet and exercise; (2) reduction in the risk of MACE in adults with T2DM and established CVD; (3) reduction in the risk of sustained eGFR declined, ESKD, and CV death in adults with T2DM and CKD.	GLP1RAs are recommended for persons with T2DM and biopsy-proven NASH. (Grade A; high SoE; BEL 1) Must consider treating diabetes with pioglitazone and/or GLP1RAs when there is an elevated probability of having NASH based on elevated plasma aminotransferase levels and NITs.	At the time of publication of the guidelines, there were no data on histologic improvement in large, well-designed, phase 3 trials with GLP1RAs, and therefore they could not be recommended as MASH-targeted therapies. (LoE 5, strong recommendation, strong consensus) GLP1RAs are safe to use in MASH including compensated cirrhosis and should be used for their respective indications (i.e., T2DM and obesity), as they improve cardiometabolic outcomes.
	NonF	WEGOVY for weight management, with CLI.	In combination with a reduced calorie diet and increased physical activity, for (1) reduction in risk of MACE in adults with established CVD and either obesity or overweight; or (2) reduction in excess body weight and maintenance of weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition.	Give preference to semaglutide 2.4 mg/week for chronic WM in individuals with a BMI ≥ 27 kg/m^2 and NAFLD or NASH (Grade B; high/intermediate SoE; BEL 1). Consider obesity pharmacotherapy (with preference to semaglutide 2.4 mg/week [best evidence] or liraglutide 3 mg/day) as adjuncts to lifestyle modification for individuals with obesity and NAFLD or NASH to promote cardiometabolic health and treat or prevent T2DM, CVD, and other end-stage manifestations of obesity. (Grade A; high/intermediate SoE; BEL 1) **Semaglutide Update**: "Candidates should have MASH with stage 2–3 fibrosis, identified using noninvasive tests (NITs) such as VCTE (8–15 kPa), MRE (3.1–4.4 kPa), or ELF (9.2–10.5), rather than liver biopsy, which is impractical and unnecessary for most patients. In those with VCTE (15-20 kPa), MRE (4.4-5 kPa), or ELF (10.5-11.3), an individualized decision to treat should be based on exclusion of cirrhosis with another confirmatory NIT, or cross-sectional imaging excluding nodular-appearing liver contour and signs of portal hypertension, or a platelet count of <150,000/mm^3. While semaglutide is not approved to treat patients with MASH cirrhosis (VCTE>20 kPa, MRE>5.0 kPa, ELF>11.3 and/or evidence of portal hypertension), those with compensated cirrhosis who are receiving semaglutide for another FDA-approved indication should be monitored carefully." "Lifestyle modification remains the cornerstone of MASLD/MASH management alongside semaglutide. Combination use with resmetirom at the dose of 2.4 mg/week has not been studied. While no NITs reliably predict histologic response at the individual patient level, reductions from baseline to 72 weeks of treatment suggest significant improvement in MASH resolution (ALT >17 U/L or ≥20%; CAP ≥30%) and fibrosis improvement (VCTE LSM ≥30%; MRE LSM ≥20%; ELF≥0.5). Non-response may be suspected if ALT or NITs worsen. Benefit is uncertain if sub-optimal response and may require an individualized approach and further follow-up."	

DRUG	VANF	CFU	FDA	AACE/AASLD GUIDELINE[8]/AASLD SEMAGLUTIDE PRACTICE GUIDANCE[9]	EASL-EASD-EASO GUIDELINES[10]
Liraglutide inj, soln	NonF	VICTOZA	For T2DM as an adjunct to diet and exercise to improve glycemic control and reduce risk of MACE in patients with T2DM and established CVD	Same as for semaglutide (but semaglutide has the best evidence)	
	NonF	SAXENDA for weight management, with CLI	For chronic weight management as an adjunct to a reduced-calorie diet and increased physical activity in adults with initial BMI of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of ≥ 1 weight-related comorbid condition. Off-label for MASH. A phase 2 PC RCT (LEAN) showed efficacy in resolution of MASH without worsening of fibrosis.[11] Needs additional evaluation in more extensive clinical trials.		
Terzepatide (GIP/GLP1RA)		MOUNJARO for weight management, with CLI	Off label for MASH. A phase 2 PC RCT (SYNERGY-NASH) showed efficacy in resolution of MASH without worsening of fibrosis.[12] Needs additional evaluation in more extensive clinical trials.	Not mentioned	
Resmetirom tab	NonF	For liver-biopsy–confirmed F2/F3 MASH with NAS ≥4 in the past 36 months, after participation for ≥ 6 months in a CLI	For treatment of noncirrhotic NASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis), in conjunction with diet and exercise. Approved under accelerated approval based on improvement of NASH and fibrosis. Continued approval for this indication is contingent upon verification and description of clinical benefit in confirmatory trials.	Not mentioned	Should be considered for patients with noncirrhotic MASH ≥F2 (LoE 2, strong recommendation, consensus). May be considered for patients with noncirrhotic MASLD with either (1) advanced fibrosis; (2) at-risk steatohepatitis with significant fibrosis (by liver biopsy, when available, or by NITs validated for that purpose); or (3) risk of adverse liver-related outcomes (e.g., by elastography- or biomarker-defined thresholds) (LoE 3, open recommendation, consensus). No data is available on durability of histologic benefits, individual response predictors, final liver-related clinical outcomes, and long-term safety.
Pioglitazone tab	VANF	None	Off label for MASH. Labeled for treatment of T2DM as an adjunct to diet and exercise to improve glycemic control.	Recommended for persons with T2DM and biopsy-proven NASH. (Grade A; high SoE; BEL 1)	Is safe to use in noncirrhotic MASH but lacks robust evidence of histologic efficacy in large phase 3 trials and therefore cannot be recommended as MASH-targeted therapy. (LoE 2, weak recommendation, consensus)
Vitamin E/Vitamin E Mixed cap	VANF	None	Not FDA-approved.	Can be considered for treatment of NASH in persons without T2DM, but there is not enough evidence at this time to recommend for persons with T2D or advanced fibrosis. (Grade B; high SoE; BEL 1)	Cannot be recommended as a MASH-targeted therapy (lack of robust demonstration of histologic efficacy on steatohepatitis and liver fibrosis derived from large phase 3 trials and a potential for long-term risks). (LoE 3, open recommendation)

POTENTIAL PLACE IN THERAPY OF SEMAGLUTIDE IN MASH	
Evidence Summary	• ESSENCE was a landmark trial which showed that semaglutide (2.4 mg SC once weekly) produced moderate improvements in surrogate histologic liver endpoints (steatohepatitis and fibrosis) in patients with noncirrhotic F2/F3 MASH. The effects of semaglutide on final liver-related clinical outcomes are uncertain at the time of this review. • The known effects of semaglutide on cardiometabolic parameters are potential advantages over resmetirom, which improves steatohepatitis and liver fibrosis but has no effects on glycemic control, weight, or risk of MACE. Semaglutide, with its weight loss effects, may be preferred over pioglitazone, which tends to cause weight gain and counteract weight loss treatment goals. Evidence for tirzepatide and liraglutide in F2–F3 MASH is promising but inconclusive. • No new safety issues with semaglutide were identified in the ESSENCE study patients with MASH. • At the time this review was prepared, semaglutide had the lowest cost for maintenance therapy for MASH, followed by pioglitazone, then resmetirom.
1L Therapy in Combination with CLI	• Semaglutide may be used for improvement of steatohepatitis and fibrosis in overweight or obese patients who have noncirrhotic, moderate to advanced MASH (consistent with fibrosis stage 2 or 3) determined by noninvasive tests or liver biopsy, and lean patients who have biopsy-confirmed MASH with stage 2 or 3 liver fibrosis. • Semaglutide should be used in patients who have a documented plan on addressing and monitoring appropriate lifestyle interventions.

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