PDL DRUG REVIEW

Proprietary Name: Wegovy®
Common Name: semaglutide injection
PDL Category: Endocrine and Metabolic Agents

Pharmacology/Usage: Semaglutide, the active ingredient of Wegovy®, is a human glucagon-like peptide-1 (GLP-1) receptor agonist (or GLP-1 analog). Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. Note that GLP-1 is a physiological regulator of appetite and caloric intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation. Animal studies demonstrate that semaglutide distributed to and activated neurons in brain regions involved in regulation of food intake. The exact mechanism of cardiovascular risk reduction has not been established.

Indication: In combination with a reduced calorie diet and increased physical activity:

- To reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight.
- To reduce excess body weight and maintain weight reduction long term in:
    - Adults and pediatric patients aged 12 years and older with obesity.
    - Adults with overweight in the presence of at least one weight-related comorbid condition.

Limitations of use include that Wegovy® contains semaglutide. The co-administration with other semaglutide-containing products or with any other GLP-1 receptor agonist is not recommended.

There is no pregnancy category for this medication; however, the risk summary indicates that based on animal reproduction studies, there may be potential risks to the fetus from exposure to semaglutide during pregnancy. In addition, weight loss offers no benefit to a pregnant patient and may cause fetal harm. When pregnancy is recognized, advise the pregnant patient of the risk to a fetus and discontinue Wegovy®. In addition, because of the potential for fetal harm, discontinue Wegovy® in patients at least 2 months before they plan to become pregnant to account for the long half-life of semaglutide. The safety and efficacy of use have not been established in the pediatric population for the cardiovascular risk reduction indication. The safety and efficacy of use for weight reduction have not been established in pediatric patients less than 12 years of age.

Dosage Form: Solution available in pre-filled, disposable, single-dose pens for Injection:

- 0.25mg/0.5ml.
- 0.5mg/0.5ml.
- 1mg/0.5ml.
- 1.7mg/0.75ml.
- 2.4mg/0.75ml.

Recommended Dosage: In patients with type 2 DM, monitor blood glucose prior to starting Wegovy® and during Wegovy® treatment. Prior to the start of treatment, train patients on proper injection technique. Inject subcutaneously (SC) in the abdomen, thigh, or upper arm. The time of day and the injection site can be changed without dose adjustment.

Administer Wegovy® in combination with a reduced-calorie diet and increased physical activity. Administer it once weekly, on the same day each week, at any time of day, with or without meals.

For the recommended dosage in adults, start Wegovy® with a dosage of 0.25mg injected SC once weekly. Then follow the dose escalation schedule presented in the table below (which was adapted from the prescribing information) to minimize gastrointestinal adverse reactions. If patients do not tolerate a dose during dosage escalation, consider delaying dosage escalation for 4 weeks.

Treatment- adults	Weeks	Once weekly SC dosage
Initiation	1 through 4	0.25mg
Escalation	5 through 8	0.5mg
	9 through 12	1mg
	13 through 16	1.7mg
Maintenance	17 & onward	1.7mg or 2.4mg

The maintenance dosage in adults is either 2.4mg (recommended) or 1.7mg once weekly. Consider treatment response and tolerability when selecting the maintenance dosage.

For the recommended dosage in pediatric patients aged 12 years and older, start Wegovy® per the dosage escalation schedule presented in the table below (which was adapted from the prescribing information) to minimize gastrointestinal adverse reactions. If patients do not tolerate a dose during dosage escalation, consider delaying dosage escalation for 4 weeks. The 0.25mg, 0.5mg, and 1mg once-weekly dosages are initiation and escalation dosages and are not approved as maintenance dosages.

Treatment- pediatric	Weeks	Once weekly SC dosage
Initiation	1 through 4	0.25mg[1]
Escalation	5 through 8	0.5mg[1]
	9 through 12	1mg[1]
	13 through 16	1.7mg
Maintenance	17 & onward	2.4mg

[1] Not approved as maintenance dosages.

The maintenance dosage of Wegovy® in pediatric patients aged 12 years and older is 2.4mg once weekly. If patients do not tolerate the 2.4mg once-weekly maintenance dosage, the maintenance dosage may be reduced to 1.7mg once weekly. Discontinue Wegovy® if the patient cannot tolerate the 1.7mg once-weekly dosage.

If one dose is missed and the next scheduled dose is more than 2 days away (48 hours), administer Wegovy® as soon as possible. If one dose is missed and the next scheduled dose is less than 2 days away (48 hours), do not administer the dose. Resume dosing on the regularly scheduled day of the week. If 2 or more consecutive doses are missed, resume dosing as scheduled or, if needed, restart Wegovy® and follow the dose escalation schedule, which may reduce the occurrence of GI symptoms associated with restarting treatment.

Dose adjustments are not recommended for patients with hepatic impairment or for patients with renal impairment.

Drug Interactions: Wegovy® lowers blood glucose and cause hypoglycemia. This risk of hypoglycemia is increased when Wegovy® is used in combination with insulin or insulin secretagogues (e.g., sulfonylureas). The addition of Wegovy® in patients treated with insulin has not been evaluated. When starting Wegovy®, consider reducing the dose of concomitantly administered insulin secretagogue or insulin to reduce the risk of hypoglycemia.

Wegovy® causes a delay of gastric emptying and thus has the potential to impact the absorption of concomitantly administered oral medications. In clinical trials with semaglutide 1mg, semaglutide did not affect the absorption of orally administered medications. Nevertheless, monitor the effects of oral medications concomitantly administered with Wegovy®.

Box Warning: Wegovy® has a box warning regarding the risk of thyroid C-cell tumors.

- In rodents, semaglutide causes dose-dependent and treatment duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is not known whether Wegovy® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined.
- Wegovy® is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Wegovy® and inform them of symptoms of thyroid tumors. Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Wegovy®

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Wegovy® 2.4mg) minus reported % incidence for placebo in Wegovy®-treated adults with obesity or overweight. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included nausea (28%), diarrhea (14%), vomiting (18%), abdominal pain (10%), headache (4%), fatigue (6%), dyspepsia (6%), dizziness (4%), abdominal distension (2%), eructation (6%), hypoglycemia in Type 2 DM (4%), flatulence (2%), gastroenteritis (2%), gastroesophageal reflux disease (2%), gastritis (3%), gastroenteritis viral (1%), hair loss (2%), and dysesthesia (1%).

Listed % incidence for adverse drug reactions= reported % incidence for drug (Wegovy® 2.4mg) minus reported % incidence for placebo in Wegovy®-treated pediatric patients aged 12 years and older with obesity. Please note that an incidence of 0% means the incidence was the same as or less than placebo. The most frequently reported adverse events included nausea (24%), vomiting (26%), diarrhea (3%), headache (1%), abdominal pain (9%), nasopharyngitis (2%), dizziness (5%), gastroenteritis (4%), constipation (4%), gastroesophageal reflux disease (2%), sinusitis (2%), urinary tract infection (2%), ligament sprain (2%), anxiety (2%), hair loss (4%), cholelithiasis (4%), eructation (4%), influenza (3%), rash (3%), and urticaria (3%).

Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists, including semaglutide. After starting treatment, observe patients for signs and symptoms of acute pancreatitis. If acute pancreatitis is suspected, discontinue treatment; if acute pancreatitis is confirmed, Wegovy® should not be restarted. There is limited experience from clinical trials with Wegovy® in patients with a history of pancreatitis. It is not known if patients with a history of pancreatitis are at higher risk for development of pancreatitis on Wegovy®.

Treatment with Wegovy® is associated with an increased occurrence of cholelithiasis and cholecystitis. Substantial or rapid weight loss can increase the risk of cholelithiasis; however, the incidence of acute gallbladder disease was greater in Wegovy®-treated patients than in placebo-treated patients, even after accounting for the degree of weight loss. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

Wegovy® lowers blood glucose and can cause hypoglycemia. Patients with diabetes mellitus taking Wegovy® in combination with insulin or an insulin secretagogue may have an increased risk of hypoglycemia. In patients with diabetes, monitor blood glucose prior to starting Wegovy® and during treatment. When starting Wegovy®, consider reducing the dose of concomitantly administered insulin or insulin secretagogue to reduce the risk of hypoglycemia.

There have been post marketing reports of acute kidney injury and worsening of chronic renal failure in patients treated with semaglutide. Monitor renal function when starting or escalating doses of Wegovy® in

patients reporting severe adverse gastrointestinal reactions. Monitor renal function in patients with renal impairment reporting any adverse reactions that could lead to volume depletion.

Serious hypersensitivity reactions have been reported with Wegovy®. If hypersensitivity reactions occur, discontinue use of Wegovy®, treat promptly per standard of care, and monitor until signs and symptoms resolve.

In a trial of adults with type 2 DM and BMI ≥27kg/m^2, diabetic retinopathy was reported by 4% of Wegovy®-treated patients and 2.7% of placebo-treated patients. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been studied. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

Treatment with Wegovy® was associated with increases in resting heart rate. Mean increases in resting heart rate of 1 to 4 beats per minute (bpm) were observed in Wegovy®-treated adult patients compared to placebo in clinical trials. Monitor heart rate at regular intervals consistent with usual clinical practice. If patients experience a sustained increase in resting heart rate, discontinue Wegovy®.

Suicidal behavior and ideation have been reported in clinical trials with other weight management products. Monitor patients treated with Wegovy® for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue Wegovy® in patients who experience suicidal thoughts or behaviors. Avoid Wegovy® in patients with a history of suicidal attempts or active suicidal ideation.

Contraindications: In the following conditions:

- A personal or family history of MTC or in patients with MEN 2.
- A prior serious hypersensitivity reaction to semaglutide or to any of the excipients of the product.

Manufacturer: Novo Nordisk

Analysis: As this review is to focus on the cardiovascular outcomes indication, this analysis section will only include the study for this specific indication. Study 1 was a multicenter, multinational, placebo-controlled, double-blind trial that assessed the effect of Wegovy® relative to placebo on major adverse cardiovascular events (MACE) when added to current standard of care, which included management of cardiovascular (CV) risk factor and individualized healthy lifestyle counseling (including diet and physical activity). In this trial, patients (N=17,604) were randomized to Wegovy® or placebo

All included patients were 45 years or older with an initial BMI of 27kg/m^2 or greater and established cardiovascular disease (prior MI, prior stroke, or peripheral arterial disease). Patients with a history of type 1 or type 2 diabetes were excluded. Concomitant CV therapies could be adjusted, at the discretion of the investigator, to ensure participants were treated per current standard of care for patients with established CVD. At baseline, the mean age was 62 years (range 45-93), while 72% were male, 84% were white, the mean baseline body weight was 97kg, and the mean BMI was 33kg/m^2. At baseline, prior MI was reported in 76% of randomized individuals, prior stroke in 23%, and peripheral arterial disease in 9%. In addition, heart failure was reported in 24% of patients. At baseline, CVD and risk factors were managed with lipid-lowering therapy (90%), platelet aggregation inhibitors (86%), angiotensin converting enzyme inhibitors or angiotensin II receptor blockers (74%), and beta blockers (70%). A total of 10% had moderate renal impairment and 0.4% had severe renal impairment.

The primary endpoint, MACE, was the time to first occurrence of a three-part composite outcome which included cardiovascular death, non-fatal MI, and non-fatal stroke. In total, 96.9% of patients completed the trial, and vital status was available for 99.4% of patients. The median follow-up duration was 41.8 months. A total of 31% of Wegovy®-treated patients and 27% of placebo-treated patients permanently discontinued study drug. For the primary analysis, a Cox proportional hazards model was used to test for superiority. Results suggested that Wegovy® significantly reduced the risk for first occurrence of MACE. The estimated hazard ratio (HR) was 0.80.

The treatment effect for the primary composite endpoint, its components, and other relevant endpoints in Study 1 are presented in the table below, which was adapted from the prescribing information.

	Patients with events, n (%)		
	Placebo (N=8,801)	Wegovy® (N=8,803)	HR
Primary Composite endpoint			
Composite of CV death, non-fatal MI, or non-fatal stroke	701 (8%)	569 (6.5%)	0.8; p<0.001
Key Secondary endpoints			
Cardiovascular death[1]	262 (3%)	223 (2.5%)	0.85
All-cause death[2]	458 (5.2%)	375 (4.3%)	0.81
Other Secondary endpoints			
Fatal or non-fatal MI[3]	334 (3.8%)	243 (2.8%)	0.72
Fatal or non-fatal stroke[3]	178 (2%)	160 (1.8%)	0.89

[1]CV death was the first confirmatory secondary endpoint in the testing hierarchy and superiority was not confirmed
[2]Confirmatory secondary endpoint. Not statistically significant based on the prespecified testing hierarchy.
[3] Not included in the prespecified testing hierarchy for controlling type-1 error.

The following table, also adapted from the prescribing information, includes the mean changes in anthropometry and cardiometabolic parameters at week 104 in Study 1.

	Placebo		Wegovy®		
	Baseline	Change from baseline	Baseline	Change from baseline	Difference from placebo
Body weight (kg)	96.8	-0.9	96.5	-9.4	-8.5
Waist circumference (cm)	111.4	-1.0	111.3	-7.6	-6.5
Systolic BP (mmHg)	131	-0.5	131	-3.8	-3.3
Diastolic BP (mmHg)	79	-0.5	79	-1.0	-0.5
Heart Rate	69	0.7	69	3.8	3.1
HbA1c (%)	5.8	0.00	5.8	-0.3	-0.3
	Baseline	% change from baseline	Baseline	% change from baseline	Relative difference from placebo (%)
Total Cholesterol (mg/dL)	156.0	-1.9	155.5	-4.6	-2.8
LDL Cholesterol (mg/dL)	78.5	-3.1	78.5	-5.3	-2.2
HDL Cholesterol (mg/dL)	44.2	0.6	44.1	4.9	4.2

	Placebo		Wegovy®		
	Baseline	Change from baseline	Baseline	Change from baseline	Difference from placebo
Triglycerides (mg/dL)	139.5	-3.2	138.6	-18.3	-15.6

The reduction of MACE with Wegovy® was not impacted by age, sex, race, ethnicity, BMI at baseline, or level of renal function impairment.

Place in Therapy: Wegovy® is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated in combination with a reduced calorie diet and increased physical activity to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight; and to reduce excess body weight and maintain weight reduction long term in adults and pediatric patients aged 12 years and older with obesity and in adults with overweight in the presence of at least one weight-related comorbid condition. A limitation of use includes that coadministration with other semaglutide-containing products or with any other GLP-1 receptor agonist is not recommended. Study 1 assessed the safety and efficacy of Wegovy® relative to placebo on MACE, when added to current standard of care. The primary endpoint, MACE, was the time to first occurrence of a three-part composite outcome which included cardiovascular death, non-fatal MI, and non-fatal stroke. Results suggested that Wegovy® significantly reduced the risk for first occurrence of MACE (HR 0.80). Wegovy® is the first weight management medication that is also FDA approved to lower the risk of MACE in adults with established cardiovascular disease and either obesity or overweight.

Summary

Wegovy® has been shown to improve MACE outcomes in overweight and obese patients with co-existing cardiovascular risk factors, when added on to background treatment/risk-reduction therapy and combined with diet and exercise. It is recommended Wegovy® remains non-preferred to assure appropriate clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions (covered diagnosis only)**

References

[1]Wegovy® [package insert]. Plainsboro, NJ: Novo Nordisk, Inc; 2024.