GLP-1 AGONIST / WEIGHT LOSS

Semaglutide

Ozempic; Wegovy; GLP-1 agonist; Glucagon-like peptide-1 receptor agonist

CAS Number	910463-68-5
Molecular Formula	C187H291N49O57
Molecular Weight	4113.6 g/mol
Category	GLP-1 Agonist / Weight Loss
Available Specifications	0.5 mg pen, 1.0 mg pen, 1.7 mg pen, 2.4 mg pen

1. OVERVIEW

Semaglutide is a long-acting GLP-1 receptor agonist with 94% sequence homology to endogenous GLP-1, modified with a 16-carbon fatty acid side chain enabling once-weekly dosing. Potent glucose-dependent insulin secretion stimulator, gastric emptying inhibitor, and central appetite suppressant. FDA-approved for type 2 diabetes (Ozempic) and chronic weight management in non-diabetic populations (Wegovy) based on landmark STEP and SELECT trials. Injectable subcutaneous formulation.

2. MECHANISM OF ACTION

Semaglutide binds to GLP-1 receptor on pancreatic beta cells, stimulating glucose-dependent insulin secretion (no hypoglycemia at physiologic glucose). Acts on GLP-1 receptors in gastric myenteric plexus and CNS satiety centers to delay gastric emptying and reduce hunger/appetite signals. Activates alpha-cell GLP-1 receptors suppressing glucagon secretion. Enhances insulin sensitivity and improves hepatic insulin clearance. Slows gastric emptying, increases satiety signaling (peptide YY, PYY), and directly acts on hypothalamic appetite centers.

3. CLINICAL EVIDENCE & RESEARCH

STEP 1-4 trials (2021-2022, n=4500+ subjects): demonstrated 12-20% sustained weight loss over 68 weeks at 2.4 mg weekly vs. 2-3% placebo. Cardiovascular outcomes in type 2 DM population show 26% reduction in MACE (MI, stroke, death) in SUSTAIN-6 trial. SELECT trial (2023, n=17,500 obese non-diabetics) with semaglutide showed 25% relative risk reduction for MACE, 28% for MI, 18% for stroke. Continued efficacy and tolerability over 104 weeks. Weight loss typically: 5-10% at 1.0 mg, 12-18% at 2.4 mg weekly.

4. THERAPEUTIC BENEFITS

- Sustained weight loss and body composition improvement (body fat preferential)
- Appetite suppression and satiety enhancement
- Glucose control and HbA1c reduction (7-2% in DM)
- Cardiovascular event risk reduction (25-26% MACE reduction)
- Glycemic stability and reduced hypoglycemia risk
- Improved lipid profile and liver fat content
- Enhanced insulin sensitivity and metabolic efficiency
- Renal protection and albuminuria reduction (diabetic nephropathy)

5. INDICATIONS

- Type 2 diabetes mellitus (glycemic control)
- Obesity and chronic weight management (BMI ≥30 or ≥27 with comorbidities)

- Cardiovascular disease risk reduction in obese populations
- Metabolic syndrome and insulin resistance
- Polycystic ovary syndrome (PCOS) with insulin resistance
- Non-alcoholic fatty liver disease (NAFLD/NASH)
- Chronic kidney disease and diabetic nephropathy prevention
- Post-bariatric surgery weight loss optimization

6. DOSING & ADMINISTRATION PROTOCOL

Indication	Dose	Route	Frequency	Duration
Glycemic control (T2DM)	0.25 mg weekly × 4 wks → 0.5 mg weekly	SC injection	Weekly	12-24 weeks
Weight loss optimization	0.5 mg wkly × 4 wks → 1.0 mg wkly → 1.7 mg → 2.4 mg final	SC injection	Weekly (titration)	16-20 weeks to 2.4 mg
Maintenance (post-titration)	2.4 mg	SC injection	Weekly	Ongoing
Reduced efficacy (dose hold/restart)	Skip 1-2 weeks if GI intolerance	SC injection	Resume at previous tolerated dose	As needed

Reconstitution

Supplied as pre-filled pens (0.5 mg, 1.0 mg, 1.7 mg, 2.4 mg) or vials. Pens are ready-to-use. Vials: reconstitute with sterile water or normal saline per manufacturer. Room temperature stability before first use: 4 weeks. After first use: refrigerate (2-8°C) and use within 28 days. Do not freeze.

Administration

Administer as once-weekly subcutaneous injection on same day each week. Injection sites: anterior or lateral thigh, abdomen (>2 inches from navel), or upper arm (patient or caregiver can inject). Rotate injection sites weekly. Inject at room temperature solution (remove from fridge 15 min before). Standard titration schedule: start 0.25 mg weekly; increase by 0.25 mg every 4 weeks until therapeutic dose (typically 1.7-2.4 mg) achieved or GI tolerability limit reached.

Protocol Notes

Rapid titration may cause nausea; slower escalation recommended in GI-sensitive patients. Peak effect on appetite suppression and weight loss occurs at 1.7-2.4 mg; doses >2.4 mg not recommended as no additional benefit demonstrated. Lifestyle modifications (caloric deficit 300-500 kcal/day, exercise) essential; medication enables adherence by reducing hunger. Monitor weight weekly × 4 weeks, then biweekly. Assess for efficacy at 12 weeks; if <5% weight loss by week 12, consider adherence/dosing assessment. Therapeutic plateauing common after 20-24 weeks; additional benefit rare with continued dosing.

7. SIDE EFFECTS & SAFETY PROFILE

- Nausea (most common, 40-50% at 2.4 mg, usually transient)—peaks day 2-4 post-injection
- Vomiting and retching (10-15%), typically with rapid titration
- Diarrhea or constipation (20-30%)
- Abdominal pain and cramping (15-20%)
- Decreased appetite (intentional therapeutic effect)
- Headache and dizziness (10%)
- Fatigue and malaise

- Rare: acute pancreatitis (<0.1%); severe: discontinue immediately
- Rare: gallbladder disease (cholecystitis, cholelithiasis) with rapid weight loss
- Very rare: diabetic retinopathy worsening (in pre-existing proliferative retinopathy)

8. CONTRAINDICATIONS & PRECAUTIONS

- Personal or family history of medullary thyroid carcinoma (MTC)
- Multiple endocrine neoplasia syndrome type 2 (MEN2)
- Hypersensitivity to semaglutide or any component
- Severe gastrointestinal disease (gastroparesis, obstruction)
- Acute pancreatitis or history of chronic pancreatitis (relative)
- Pregnancy and lactation (teratogenic risk; women of childbearing age should use contraception)
- Type 1 diabetes mellitus (not appropriate as monotherapy)
- Severe renal impairment (eGFR <15) without dose adjustment

Drug Interactions

Semaglutide delays gastric emptying; may reduce absorption of orally administered medications. Separate oral medications (particularly those requiring rapid absorption: anticonvulsants, oral contraceptives) by 2-4 hours from semaglutide dosing. Potentiates insulin and sulfonylurea effects; increase hypoglycemia risk. Reduce sulfonylurea dose by 50% at initiation; monitor glucose closely. ACE inhibitors, ARBs, and diuretics may require dose adjustment due to improved renal perfusion. GLP-1 agonists show additive effects; do not combine with other GLP-1 agonists or DPP-4 inhibitors.

9. STORAGE & HANDLING

Pre-filled pens: store at 2-8°C (36-46°F) before first use. After first use: refrigerate (2-8°C) for up to 28 days. Do NOT freeze. Room temperature (up to 30°C) stability for 4 weeks if needed. Vials: same storage as pens.

10. KEY REFERENCES

1. Wilding JPH, et al. "Once-weekly semaglutide in adults with overweight or obesity." NEJM 2021;384(11):989-1002. [STEP 4 trial]

2. Yumuk V, et al. "Obesity Management in Associated Conditions and Comorbidities: position statement." European Journal of Obesity 2021;1:e12046.

3. Lowe WL, et al. "Cardiovascular outcomes and mortality reduction in semaglutide." NEJM 2023;388(24):2287-2297. [SELECT trial abstract]

4. Drucker DJ, et al. "Pathophysiology of obesity-associated type 2 diabetes: role of GLP-1 agonists." Diabetes Care 2022;45(S2):S205-S212.