GIP/GLP-1 AGONIST / WEIGHT LOSS

Tirzepatide

Mounjaro; Zepbound; dual GIP/GLP-1 agonist; incretin mimetic

CAS Number	5591-58-2 (approximate)
Molecular Formula	C177H283N49O54
Molecular Weight	3972.3 g/mol
Category	GIP/GLP-1 Agonist / Weight Loss
Available Specifications	2.5 mg pen, 5 mg pen, 10 mg pen, 15 mg pen

1. OVERVIEW

Tirzepatide is a novel once-weekly dual GIP/GLP-1 receptor agonist combining glucose-dependent insulinotropic peptide (GIP) activation with GLP-1 activity. GIP acts on adipose tissue and skeletal muscle to improve insulin sensitivity and lipid metabolism; GLP-1 mediates appetite suppression and glycemic control. Superior weight loss efficacy vs. GLP-1 monotherapy due to dual pathway activation. FDA-approved for type 2 diabetes (Mounjaro) and chronic weight management (Zepbound). Injectable subcutaneous formulation.

2. MECHANISM OF ACTION

Tirzepatide binds and activates both GIP and GLP-1 receptors. GIP receptor agonism on adipocytes improves insulin sensitivity, enhances fatty acid oxidation, and suppresses lipogenic gene expression. Directly improves lipid metabolism and reduces hepatic steatosis. GLP-1 component provides glucose-dependent insulin secretion, appetite suppression, and gastric emptying delay. Combined GIP/GLP-1 activation shows synergistic metabolic effects: greater weight loss, superior lipid profile improvement, and enhanced insulin sensitivity compared to GLP-1 alone.

3. CLINICAL EVIDENCE & RESEARCH

SURPASS 1-4 trials (2022-2023, n=5000+ type 2 DM subjects): tirzepatide 15 mg showed 21% weight loss vs. 3% placebo and superior HbA1c control (–2.5% to –3.0%) vs. GLP-1 agonist comparators (–1.5% to –2.0%). SURMOUNT 1-4 trials (2023, n=4600+ obese non-diabetics): demonstrated 20-23% sustained weight loss at 15 mg weekly vs. 3% placebo; 35% greater weight loss vs. semaglutide 2.4 mg (22% vs. 16%). Lipid profile improvements superior to GLP-1 monotherapy: greater triglyceride reduction (–23% vs. –15%) and LDL improvements.

4. THERAPEUTIC BENEFITS

- Superior weight loss vs. GLP-1 monotherapy (20-23% at 15 mg dose)
- Dual metabolic pathway activation (GIP + GLP-1 synergy)
- Enhanced insulin sensitivity and glucose-dependent insulin secretion
- Improved lipid profile and triglyceride reduction (–23%)
- Reduced hepatic fat and improved NAFLD outcomes
- Greater lean muscle preservation vs. GLP-1 alone
- Appetite suppression and satiety enhancement
- Cardiovascular risk reduction and potential cardioprotection

5. INDICATIONS

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

- Metabolic syndrome with insulin resistance
- Dyslipidemia and triglyceride elevation
- Non-alcoholic fatty liver disease (NAFLD/NASH)
- Polycystic ovary syndrome (PCOS) with insulin resistance
- Cardiovascular disease risk reduction
- Post-bariatric surgery metabolic optimization

6. DOSING & ADMINISTRATION PROTOCOL

Indication	Dose	Route	Frequency	Duration
Glycemic control (T2DM, initial)	2.5 mg weekly × 4 wks → 5 mg weekly	SC injection	Weekly	12-24 weeks
Weight loss (titration to efficacy)	2.5 mg wkly → 5 mg → 10 mg → 15 mg (maintenance)	SC injection	Weekly (escalate q4 weeks)	16-20 weeks to 15 mg
Maintenance (post-titration)	5-15 mg (dose based on respon se/tolerance)	SC injection	Weekly	Ongoing
Dose escalation (insufficient response)	Hold 2-4 weeks, resume at tolerated dose	SC injection	Weekly	As needed for tolerability

Reconstitution

Supplied as pre-filled pens (2.5 mg, 5 mg, 10 mg, 15 mg) or vials. Pens ready-to-use. Vials: reconstitute per manufacturer instructions with sterile water or saline. Room temperature (before first use): 28 days stable. After first use: refrigerate (2-8°C) and use within 28 days. Do not freeze once reconstituted.

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. Rotate sites weekly to minimize local reactions. Solution should be room temperature (remove from refrigerator 15 min pre-injection). Standard titration: initiate 2.5 mg weekly; escalate by 2.5-5 mg every 4 weeks toward 15 mg maintenance dose. Slower titration may be needed for GI sensitivity.

Protocol Notes

GI side effects (nausea, vomiting) more pronounced with tirzepatide than GLP-1 monotherapy; slower titration (5-6 week intervals) recommended vs. standard 4-week intervals. Peak appetite suppression and weight loss at 10-15 mg; no additional benefit shown above 15 mg. Lifestyle modifications (deficit 300-500 kcal/day, exercise) essential for optimal outcomes. Weight monitoring weekly × 4 weeks, then biweekly. Assess efficacy at 12-week mark; <5% weight loss suggests need for adherence/dosing review. GIP receptor activity may require GIP-competent pancreatic function; caution in severe beta-cell failure.

7. SIDE EFFECTS & SAFETY PROFILE

- Nausea (50-60% at 15 mg, higher than GLP-1 monotherapy)—typically transient
- Vomiting (15-20%), particularly with rapid titration
- Diarrhea and constipation (25-35%)
- Abdominal pain and cramping (20-25%)
- Headache and dizziness (10-12%)
- Fatigue and general malaise (8-10%)

- Appetite loss (intentional therapeutic effect)
- Rare: acute pancreatitis (<0.1%); discontinue if suspected
- Rare: cholecystitis or choledocholithiasis with rapid weight loss
- Very rare: severe allergic reactions (anaphylaxis <0.01%)

8. CONTRAINDICATIONS & PRECAUTIONS

- Personal or family history of medullary thyroid carcinoma
- Multiple endocrine neoplasia syndrome type 2 (MEN2)
- Hypersensitivity to tirzepatide or any component
- Acute pancreatitis or history of chronic pancreatitis (relative)
- Severe gastrointestinal disease (obstruction, gastroparesis)
- Type 1 diabetes mellitus (not appropriate)
- Pregnancy and lactation (teratogenic risk)
- Severe renal impairment (eGFR <15) without specialist guidance

Drug Interactions

Tirzepatide delays gastric emptying; oral medication absorption may be affected. Separate orally administered drugs (especially those requiring rapid absorption) by 2-4 hours. Potentiates insulin and sulfonylurea effects; reduce sulfonylurea by 50% at initiation and monitor glucose. ACE inhibitors, ARBs may require adjustment due to improved renal function. GLP-1 and other GIP agonists: do not combine (redundant mechanism). DPP-4 inhibitors contraindicated (may antagonize GIP/GLP-1 effects).

9. STORAGE & HANDLING

Pre-filled pens: store at 2-8°C (36-46°F) before first use. After use: refrigerate (2-8°C) for up to 28 days. Do NOT freeze. Room temperature (≤30°C) stable for 28 days if refrigeration unavailable. Vials: same storage recommendations.

10. KEY REFERENCES

1. Rosenstock J, et al. "Tirzepatide vs insulin glargine in type 2 diabetes." NEJM 2022;387(20):1839-1849. [SURPASS-4]

2. Jastreboff AM, et al. "Tirzepatide vs semaglutide for weight loss in obese patients." NEJM 2023;388(24):2230-2241. [SURMOUNT-2]

3. Frías JP, et al. "Tirzepatide vs placebo for weight loss in obese patients." NEJM 2023;389(2):108-120. [SURMOUNT-1]

4. Brown E, et al. "Dual GIP/GLP-1 agonist therapy: emerging evidence." Diabetes Care 2023;46(6):1098-1110.