



REVIEW ARTICLE

Semaglutide as a Cornerstone Therapy in Obesity: Clinical and Pharmacological Insights

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ABSTRACT

Obesity is a chronic, relapsing disease associated with significant cardiometabolic, mechanical, and psychological consequences. Despite lifestyle interventions forming the cornerstone of therapy, long-term weight loss is difficult to sustain for many individuals, leading to growing interest in pharmacological options. Semaglutide, a long-acting glucagon-like peptide-1 receptor agonist, has emerged as an important therapeutic advancement due to its substantial weight-reduction effects and metabolic benefits. The objective of the study is to describe the clinical, pharmacological, and therapeutic profile of semaglutide in the context of obesity management, including mechanism of action, pharmacokinetic characteristics, efficacy, safety considerations, dosing strategies, and future directions. Relevant literature from clinical trials, mechanistic studies, regulatory reports, and real-world analyses was reviewed to summarize the therapeutic role of semaglutide in obesity. Particular attention was given to major clinical trial programs evaluating weight outcomes, metabolic parameters, and safety events. Semaglutide promotes weight loss through central and peripheral mechanisms that reduce appetite, enhance satiety, delay gastric emptying, and improve glucose homeostasis. Molecular modifications prolong its half-life, enabling convenient once-weekly dosing and consistent metabolic effects. Clinical evidence shows notable reductions in body weight, improvements in glycemic control, and favorable cardiometabolic changes in diverse patient groups. The most common adverse effects are gastrointestinal and tend to lessen with gradual dose escalation. Concerns such as pancreatitis, gallbladder disease, and thyroid-related risks are uncommon but require clinical awareness. High-dose oral formulations, extended indications, and combination therapies are under ongoing investigation and may further broaden clinical utility. Semaglutide represents a significant evolution in the medical treatment of obesity, offering durable weight loss and meaningful metabolic benefits. While cost, accessibility, and long-term safety considerations persist, current evidence supports its role as a cornerstone.

Keywords: Semaglutide, Obesity, Pharmacotherapy, GLP-1 receptor agonist, Weight management, Metabolism

INTRODUCTION

Obesity is defined as an abnormal or excessive accumulation of body fat that impairs health, with a body mass index (BMI) ≥ 30 kg/m² widely accepted as the diagnostic threshold¹. The severity of obesity is categorized as Class I

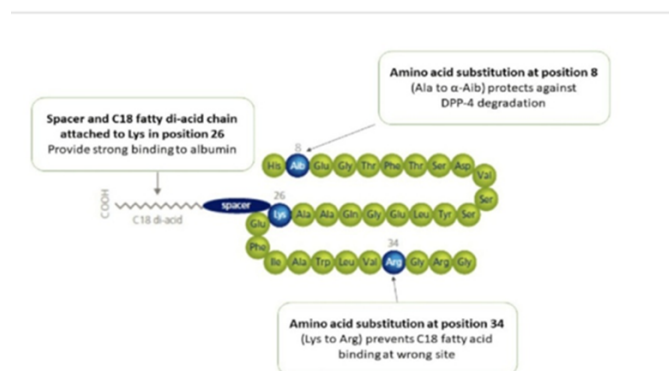
(BMI 30–34.9 kg/m²), Class II (35–39.9 kg/m²), and Class III (≥ 40 kg/m²), with higher classes conferring progressively greater morbidity risk². The global prevalence of obesity has risen sharply, with recent pooled analyses showing widespread increases across 200+ countries over the past three decades³. In India, the ICMR–INDIAB 2023 study

reported a combined overweight-and-obesity prevalence of 28.6%, highlighting the growing burden in both urban and rural populations³. Urban tertiary hospital studies indicate even higher rates, frequently ranging from 31% to 45%, reflecting lifestyle transitions, socioeconomic factors and reduced physical activity in metropolitan areas.³ Obesity contributes to a spectrum of complications including type 2 diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, osteoarthritis, obstructive sleep apnea and non-alcoholic fatty liver disease, thereby increasing all-cause mortality and posing significant public health challenges⁴. Metabolic syndrome, a closely related condition characterized by central obesity, insulin resistance, dyslipidemia and hypertension, further amplifies cardiometabolic risk⁵.

The limited sustainability of lifestyle interventions alone and the chronic, relapsing nature of obesity have intensified the need for effective pharmacotherapies⁶. Semaglutide, a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA), represents a major advancement in medical obesity management due to its substantial and durable weight-loss efficacy demonstrated across diverse populations⁶. The drug acts on key central and peripheral pathways regulating appetite, satiety and glucose homeostasis, offering meaningful improvements in metabolic parameters and obesity-related comorbidities⁶. With a rapidly expanding evidence base and regulatory approval for chronic weight management, semaglutide has become a cornerstone of modern pharmacological treatment strategies for obesity⁶.

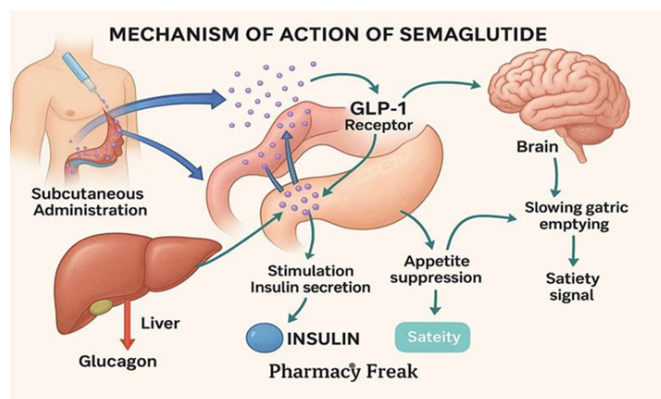
SEMAGLUTIDE STRUCTURE

Semaglutide is a structurally modified analogue of human GLP-1, incorporating specific amino acid substitutions and acylation with a C18 fatty-diacid side chain to enhance albumin binding and resist degradation by dipeptidyl peptidase-4 (DPP-4)⁷. These modifications prolong its half-life, enabling once-weekly dosing and sustained activation of GLP-1 receptors, thereby improving therapeutic adherence and metabolic efficacy⁷.



MECHANISM OF ACTION

Semaglutide exerts its effects by binding to GLP-1 receptors in the hypothalamus, promoting satiety, reducing appetite and lowering caloric intake⁸. It delays gastric emptying, enhances glucose-dependent insulin secretion, suppresses glucagon release and improves pancreatic β -cell responsiveness⁸. Additionally, its central effects extend to reward pathways, reducing cravings and hedonic eating, which contributes significantly to weight loss in individuals with obesity⁸.



PHARMACOKINETICS

Semaglutide exhibits high bioavailability with subcutaneous administration, achieving slow and sustained absorption due to strong albumin binding, which prolongs its half-life to approximately one week⁹. Its pharmacokinetics remain consistent across age groups and in mild-to-moderate renal or hepatic impairment, allowing predictable drug exposure without major dose adjustments⁹. Oral semaglutide utilizes absorption enhancer Salscaprozate sodium (SNAC) to facilitate gastric mucosal uptake, although with lower bioavailability than injectable preparations⁹.

Following systemic absorption, semaglutide undergoes proteolytic degradation and β -oxidation rather than cytochrome P450 metabolism, minimizing the risk of drug-drug interactions⁹. Excretion occurs primarily through the urine and feces as inactive metabolites, and steady-state concentrations are achieved after four to five weeks of weekly dosing, consistent with its extended half-life¹⁰.

ADVERSE DRUG REACTIONS

Gastrointestinal adverse effects such as nausea, vomiting, diarrhea and constipation are the most common and arise from delayed gastric emptying and increased central satiety signaling¹². Alopecia has been reported infrequently and is thought to result from rapid weight loss-induced telogen effluvium rather than a direct drug effect¹². Ocular adverse effects, including transient blurred vision, may occur due to rapid glycemic improvements altering lens hydration

dynamics¹². Pancreatitis is a rare but serious concern, potentially linked to GLP-1–related effects on pancreatic exocrine cells and gallstone formation from weight loss¹². Thyroid-related risks, including C-cell hyperplasia observed in rodents, underline theoretical concerns, although human evidence remains limited¹².

Following clinical trials have been conducted:

Trial Name	Population	Dose	Outcome	Inference
STEP 1, 2, 3, 4 ¹¹	Adults with overweight / obesity	2.4 mg weekly	~10–15% weight loss	Robust and sustained weight reduction across cohorts.
SUSTAIN Trials ¹¹	Type 2 diabetes	0.5–1 mg weekly	Improved glycemic control + modest weight loss	Effective for diabetes with metabolic benefits.
STEP 2 Trial ¹⁴	T2DM + obesity	2.4 mg weekly vs placebo and 1 mg	Greater weight loss vs placebo and 1 mg	Confirms efficacy of higher-dose semaglutide in diabetes-associated obesity.

CONTRAINDICATIONS

Semaglutide is contraindicated in individuals with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 due to preclinical findings of C-cell tumors in rodents¹³. It should be avoided in patients with severe gastrointestinal disorders such as gastroparesis, as delayed gastric emptying may worsen symptoms¹³. Hypersensitivity to the formulation constitutes another contraindication¹³. Use during pregnancy is discouraged because intentional weight loss is contraindicated and human fetal safety data remain insufficient¹³.

DOSE

For obesity management, semaglutide is initiated at 0.25 mg weekly and titrated gradually to the target dose of 2.4 mg weekly to minimize gastrointestinal intolerance¹⁴. Oral semaglutide follows a stepwise increase to 14 mg daily for glycemic control, while higher-dose oral formulations for obesity are under active evaluation¹⁴.

COST

Cost-effectiveness analyses indicate that semaglutide 2.4 mg is economically viable in high-income countries due to reductions in diabetes progression, cardiovascular events and healthcare utilization¹⁵. However, its high retail cost

remains a barrier in resource-limited settings, highlighting the need for pricing negotiations and broader insurance coverage to improve accessibility¹⁵.

FUTURE FORMULATIONS

Future directions include expanded indications for obesity with comorbidities like metabolic liver disease, heart failure and addiction disorders¹⁶. Oral semaglutide (Rybelsus) formulations currently available include 3 mg, 7 mg and 14 mg tablets, with higher-dose tablets 25 mg and 50 mg are under investigation in OASIS trials for improved weight-loss efficacy¹⁶. Pen-injector (Ozempic) semaglutide is available as 0.25 mg, 0.5 mg, 1 mg and 2.4 mg pre-filled pens designed for once-weekly dosing¹⁶. Ongoing innovations aim to improve delivery systems, enhance potency and develop combination therapies to further optimize outcomes¹⁶. Possible fixed drug combinations are under investigation:

- **Semaglutide + Amylin analog** (enhanced appetite suppression)
- **Semaglutide + GIP/GLP-1 dual agonist** (complementary metabolic effects)
- **Semaglutide + SGLT2 inhibitor** (cardiometabolic additive effect)

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