Available online on 15.12.2025 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

*Copyright © 2025 The Author(s): This is an open-access article distributed under the terms of the CC BY-NC 4.0 which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited*

*Open Access Full Text Article*

Review Article

# Semaglutide: A Comprehensive Review of its Pharmacology, Clinical Applications, and Future Therapeutic Potential

Shalvi Sunil Pawar *, Pooja Balkrishna Rasal, Kiran Hemant Kulkarni, Suyash Balasaheb Pawar

Department of Pharmacology, SND College Of Pharmacy, Yeola 423401, Maharashtra, India

## Article Info:

### Article History:

Received 07 Aug 2025
Reviewed 20 Oct 2025
Accepted 18 Nov 2025
Published 15 Dec 2025

### Cite this article as:

Pawar SS, Rasal PB, Kulkarni KH, Pawar SB, Semaglutide: A Comprehensive Review of its Pharmacology, Clinical Applications, and Future Therapeutic Potential, Journal of Drug Delivery and Therapeutics. 2025; 15(12):103-114 *DOI: http://dx.doi.org/10.22270/jddt.v15i12.7452*

### *For Correspondence:

Shalvi Sunil Pawar, 3rd Year, PharmD, SND College of Pharmacy, Yeola, Maharashtra, India

## Abstract

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) that works for an extended period of time and has revolutionized the treatment of type 2 diabetes mellitus and obesity. By mimicking the endogenous incretin hormone GLP-1, semaglutide has a variety of physiological effects that help to improve metabolic control. It increases glucose-dependent insulin secretion while also reducing inappropriate appetite. Glucagon release, delayed gastric emptying, and increased satiety combine to produce better glycemic management and considerable weight reduction. Semaglutide differs from prior GLP-1 analogs in a crucial way: it comes in both subcutaneous injectable and oral tablet formulations, giving patients more options and ease. for patients, increasing adherence and long-term treatment outcomes.

Semaglutide has a long half-life of about a week, which makes it possible to administer the injectable form once a week. Its oral composition makes use of absorption-enhancing technology, which, despite the molecule's peptide composition, aids in gastrointestinal absorption. Its greater effectiveness in lowering glycated haemoglobin (HbA1c), decreasing body weight, and lowering the risk has been demonstrated by clinical trials, such as the SUSTAIN and PIONEER programs. of significant negative cardiovascular events when compared with conventional treatments. Mild to moderate gastrointestinal discomfort, such as nausea and vomiting, is a common side effect, and it typically subsides with time.

Beyond diabetes and obesity, emerging evidence suggests semaglutide's potential in addressing metabolic-associated steatotic liver disease, cardiovascular prevention, and neuroprotective applications. As research advances, semaglutide continues to exemplify the integration of peptide pharmacology and innovative drug delivery, marking a milestone in personalized management of metabolic disorders.

**Keywords:** Semaglutide, GLP-1 receptor agonist, type 2 diabetes mellitus, obesity, SNAC [sodium N–(8-[2-hydroxybenzoyl] amino)caprylate] , STEP program.

## Introduction

Type 2 diabetes mellitus (T2DM) continues to pose a major global health burden due to its increasing prevalence and strong association with cardiovascular, renal, and metabolic complications [1]. Conventional therapies often fail to provide adequate long-term glycaemic

control without causing hypoglycaemia or weight gain. This limitation has led to the emergence of incretin-based therapies that exploit the physiological role of glucagon-like peptide-1 (GLP-1).

GLP-1 is an intestinal hormone that stimulates insulin secretion in a glucose-dependent manner while suppressing glucagon release. However, native GLP-1 is rapidly degraded by dipeptidyl peptidase-4 (DPP-4), resulting in a very short half-life [2]. To overcome this, synthetic GLP-1 receptor agonists (GLP-1 RAs) were developed to provide prolongedactivity and enhanced metabolic effects.

Semaglutide, a novel GLP-1 RA developed by Novo Nordisk, represents the latest generation of this therapeutic class. It is structurally engineered to resist enzymatic degradation and bind to albumin, leading to an extended half-life that permits once-weekly subcutaneous administration [3]. In addition, the formulation of an oral tablet incorporating the absorption enhancer sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC) has made it the first peptide-based GLP-1 RA suitable for oral use [4].

According to the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD), GLP-1 RAs with proven cardiovascular benefit—such as semaglutide—are recommended for patients with established atherosclerotic cardiovascular disease or at high risk of such events [5]. Beyond glucose regulation, semaglutide has also shown promising effects on body-weight reduction and lipid metabolism,making it an important component of obesity and metabolic-syndrome management[6].

The following sections explore semaglutide's origin, chemical design, pharmacology, pharmacokinetics, therapeutic roles, and safety profile, along with emerging evidence supporting its use in conditions such as non-alcoholic fatty liver disease and cardiovascular risk reduction.

## Discovery and Development

The development of semaglutide arose from decades of research into the incretin system, aiming to overcome the short half-life and administration challenges associated with earlier GLP-1 receptor agonists. Native GLP-1 is rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4), limiting its therapeutic use. Therefore, researchers focused on modifying the GLP-1 molecule to enhance its metabolic stability and binding affinity to serum albumin [7].

Semaglutide was developed by Novo Nordisk as part of an effort to design a once-weekly injectable GLP-1 analogue with a prolonged half-life and consistent pharmacological activity. This was achieved through targeted molecular alterations that confer resistance to DPP-4 degradation and enhance albumin association, thereby extending its systemic exposure [8].

Key structural modifications include the substitution of alanine at position 8 with α-aminoisobutyric acid (Aib), which protects the molecule from enzymatic cleavage, and the attachment of a C18 di-acid fatty chain via a hydrophilic spacer at lysine position 26, which promotes reversible albumin binding. An arginine substitution at position 34 further enhances molecular stability [9]. Collectively, these changes enable semaglutide to maintain receptor potency and provide sustained therapeutic action suitable for weekly dosing. (shown in fig.1.a&b )

In 2017, the U.S. Food and Drug Administration (FDA) approved subcutaneous semaglutide (Ozempic®) for adults with T2DM, followed by the oral formulation (Rybelsus®) in 2019, which marked the first orally available GLP-1 RA for clinical use [10]. These approvals represented significant progress in peptide-based drug design and patient-centered diabetes management.

Figure 1: a) Chemistry of semaglutide, b) Structure of semaglutide (subcutaneous formulation)

1. The enzymatic stability (DPP4) is improved by replacing Ala with Aib at position 8.
2. A linker and C18 di-acid chain at position 26 provide tight albumin binding.
3. At position 34, the replacement of Lys with Arg blocks the incorrect binding of C18 fatty acids.

## Mechanism of Action

Semaglutide acts as a highly selective agonist of the glucagon-like peptide-1 receptor (GLP-1R), which is expressed in multiple metabolically active tissues including the pancreatic β-cells, gastrointestinal tract, central nervous system (CNS), and cardiovascular system. By binding to this receptor, semaglutide reproduces and amplifies the physiological functions of endogenous GLP-1, thereby modulating glucose metabolism, appetite regulation, and cardiovascular homeostasis. Activation of GLP-1R initiates a series of intracellular signaling cascades, primarily mediated by cyclic AMP (cAMP), which ultimately enhance insulin secretion, inhibit glucagon release, and improve overall energy balance.

In pancreatic β-cells, semaglutide stimulates glucose-dependent insulin secretion, enhancing the body's ability to maintain normal blood glucose levels in response to food intake. Concurrently, it suppresses glucagon secretion from pancreatic α-cells, leading to decreased hepatic glucose production. These complementary actions contribute to improved fasting and postprandial glycemic control. Within the gastrointestinal system, semaglutide delays gastric emptying, slowing the rate at which glucose and nutrients enter the bloodstream, which further aids in stabilizing postprandial glucose levels.

In the central nervous system, particularly within the hypothalamic nuclei responsible for appetite regulation, GLP-1R activation by semaglutide influences neuronal pathways associated with hunger and satiety. This results in reduced appetite, lower caloric intake, and enhanced feelings of fullness, making it effective not only for glycemic regulation but also for weight management. Neuroimaging studies have demonstrated that semaglutide decreases activity in brain regions associated with food craving and reward, providing a mechanistic basis for its appetite-suppressing effects[11].

Additionally, semaglutide exerts favorable cardiovascular effects, which are thought to result from improvements in endothelial function, reduced inflammation, and decreased oxidative stress. Clinical outcome trials have shown that treatment with semaglutide significantly reduces major adverse cardiovascular events (MACE), along with beneficial changes in body weight, lipid parameters, and systolic blood pressure [12]. These effects underline its importance not only as an antidiabetic agent but also as a cardioprotective therapeutic option.(shown in fig.2.a)

### 1. Role of Semaglutide

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1RA**)**. It mimics the action of endogenous GLP-1, a hormone that regulates glucose metabolism. When absorbed into systemic circulation, semaglutide binds to GLP-1 receptors located on pancreatic β-cells, stimulating insulin secretion in a glucose-dependent manner**.** It also suppresses glucagon release**,** delays gastric emptying**,** and promotes satiety**,** thereby helping in both glycemic control and weight management.

### 2. Role of SNAC in Oral Absorption

Semaglutide is a large peptide molecule that is normally degraded in the stomach and poorly absorbed through the intestinal wall. The absorption enhancer SNAC [sodium N–(8-[2-hydroxybenzoyl]amino)caprylate] helps overcome these barriers through several coordinated actions:

**Local pH Modulation:** SNAC temporarily increases the pH in the stomach microenvironment around the tablet. This neutralization reduces the acidic degradation of semaglutide, preserving its structural stability.

**Protection Against Enzymatic Degradation:** By creating a localized neutral zone, SNAC minimizes the activity of gastric proteolytic enzymes (such as pepsin) that would otherwise break down the peptide.

**Facilitating Transcellular Transport:** SNAC promotes the **transcellular (through-cell)** absorption of semaglutide across the gastric epithelial membrane. It enhances the lipophilicity of semaglutide, allowing the molecule to cross the cell membranes and enter systemic circulation.

**Rapid Systemic Entry:** Once across the epithelial barrier, semaglutide enters the **bloodstream** where it exerts its GLP-1 receptor-mediated effects.(shown in fig.2.b)

Figure 2(a):Mechanism of action of semaglutide

Figure 2(b): Mechanism of absorption of semaglutide and SNAC co-formulation tablet

## Pharmacology

### Pharmacokinetics

Semaglutide possesses unique pharmacokinetic properties that make it suitable for both once-weekly subcutaneous administration and once-daily oral dosing. Its prolonged duration of action is mainly attributed to two major mechanisms: high affinity for plasma albumin binding and resistance to enzymatic degradation. These characteristics slow its clearance from the systemic circulation and protect the molecule from rapid metabolic breakdown, allowing it to maintain therapeutically effective plasma concentrations for an extended period[13].

The albumin-binding capability of semaglutide plays a crucial role in its pharmacokinetic behavior. By attaching to albumin, semaglutide remains in circulation longer, resulting in a gradual and sustained release into target tissues. This tight but reversible binding reduces renal

filtration and enzymatic degradation, contributing to its long elimination half-life of approximately one week.

In addition, structural modifications in semaglutide enhance its enzymatic stability. Specifically, substitutions in its peptide backbone and the presence of a fatty acid side chain make the molecule less susceptible to cleavage by dipeptidyl peptidase-4 (DPP-4) and other proteolytic enzymes. As a result, semaglutide remains active in the body for a longer duration, providing consistent glycaemic control with infrequent dosing.

These combined pharmacokinetic features—albumin binding, enzymatic resistance, and slow systemic clearance—allow semaglutide to deliver stable therapeutic effects over extended intervals, thereby improving patient adherence and simplifying treatment regimens for individuals with type 2 diabetes and obesity [13].

## Absorption

Following subcutaneous administration, semaglutide exhibits slow and sustained absorption from the injection site into systemic circulation. Peak plasma concentrations (Tmax) are typically achieved within 1 to 3 days, reflecting its gradual uptake. The absolute bioavailability after subcutaneous dosing is approximately 89%, indicating efficient absorption and minimal loss during this process. This steady absorption contributes to the drug's consistent plasma exposure and supports its once-weekly dosing regimen [14].

In contrast, the oral formulation of semaglutide displays considerably lower bioavailability, estimated between 0.4% and 1%, which is primarily due to enzymatic degradation and poor permeability across the gastrointestinal mucosa. Peptide-based drugs like semaglutide are typically unstable in the acidic gastric environment and prone to hydrolysis by digestive enzymes, leading to limited systemic availability.

To overcome these challenges, semaglutide is co-formulated with sodium N-[8-(2-hydroxybenzoyl)amino] caprylate (SNAC)—a specialized absorption enhancer. SNAC plays a dual role in promoting gastric absorption:

- It temporarily increases the local pH around the tablet, thereby protecting semaglutide from acid-induced degradation and deactivation by gastric enzymes.
- It facilitates transcellular transport by altering membrane fluidity in the gastric epithelial cells, allowing semaglutide to diffuse directly through the cell membranes into the bloodstream rather than passing through the intestinal route [15].

This mechanism enables semaglutide to be absorbed directly from the stomach, an uncommon feature for peptide-based drugs. Although oral bioavailability remains low compared to the injectable form, the SNAC-assisted formulation ensures that sufficient drug levels are achieved for therapeutic efficacy. Overall, the combination of slow subcutaneous absorption and SNAC-mediated oral uptake contributes to semaglutide's flexible dosing options and consistent pharmacological effects across different administration routes [16,17].

## Distribution

Semaglutide demonstrates extensive plasma protein binding, with more than 99% of the drug bound to albumin under physiological conditions. This high degree of albumin association serves several pharmacokinetic purposes. By binding tightly yet reversibly to albumin, semaglutide remains protected from rapid enzymatic degradation and renal filtration, effectively prolonging its residence time in systemic circulation. This binding creates a drug reservoir that slowly releases semaglutide into the bloodstream, maintaining stable therapeutic concentrations over extended periods [18].

The strong affinity for albumin also contributes significantly to its prolonged elimination half-life, which averages around one week. This property ensures consistent plasma exposure and supports a once-weekly dosing schedule without major fluctuations in drug levels. Furthermore, albumin binding limits the drug's distribution to peripheral tissues, ensuring that semaglutide remains primarily within the vascular compartment where it can exert sustained pharmacological effects.

Interestingly, both oral and subcutaneous formulations of semaglutide exhibit comparable efficacy and gastrointestinal tolerability despite differences in exposure levels, suggesting that its strong plasma protein binding and slow systemic release maintain therapeutic activity across various administration routes [19]. Pharmacokinetic studies indicate that this consistent exposure-response relationship is a key factor supporting the flexibility of semaglutide formulations and reinforces the clinical reliability of its long-acting mechanism [19].

Overall, the combination of high plasma protein binding, gradual systemic release, and restricted tissue distribution is central to semaglutide's long-acting profile and underpins its efficacy in maintaining steady glycaemic control with infrequent dosing [18,19].

## Metabolism

Semaglutide undergoes systemic metabolic degradation through a combination of proteolytic cleavage and β-oxidation processes. The primary metabolic pathway involves enzymatic cleavage of its peptide backbone, which breaks the molecule into smaller peptide fragments. In parallel, the fatty acid side chain attached to the peptide undergoes sequential β-oxidation, a metabolic pathway similar to that used for endogenous fatty acids. These reactions gradually dismantle the parent molecule into inactive metabolites that can be safely excreted from the body [20].

Unlike many small-molecule drugs, semaglutide is not metabolized in a single organ, such as the liver. Instead, its breakdown occurs throughout various tissues via widely distributed proteolytic enzymes. This non–organ-specific metabolism minimizes the likelihood of drug accumulation and reduces dependence on hepatic

function for clearance, making semaglutide suitable for patients with mild to moderate hepatic impairment.

The resulting degradation products are eliminated through multiple excretory pathways, primarily via urine and faeces, with no single route dominating the process. This balanced elimination mechanism contributes to semaglutide's favorable safety and tolerability profile, as it avoids excessive metabolic burden on any single organ system [21].

In summary, semaglutide's enzymatic breakdown through proteolysis and β-oxidation, combined with its multi-organ elimination, underpins its predictable pharmacokinetic behavior and supports its use in diverse patient populations.

### Elimination

After subcutaneous administration, semaglutide displays a prolonged terminal elimination half-life ranging from 155 to 184 hours, which underlies its suitability for once-weekly dosing. This extended half-life is a direct result of its strong albumin binding and slow systemic clearance, allowing the drug to remain in circulation for an extended duration while maintaining stable plasma levels [22].

Because of this long elimination phase, semaglutide achieves steady-state plasma concentrations—where the rate of drug input equals the rate of elimination—after approximately four to five weeks of continuous dosing. At this stage, consistent therapeutic exposure is maintained throughout the dosing interval without significant peak-to-trough variability, ensuring steady glycaemic control.

Elimination of semaglutide involves multiple clearance pathways, including both renal and hepatic routes, where the inactive metabolites produced through proteolytic degradation and β-oxidation are excreted via urine and faeces. The absence of a single dominant elimination route contributes to its predictable pharmacokinetics and minimizes the impact of mild organ impairment on overall clearance.

Overall, semaglutide's long terminal half-life, slow elimination rate, and multi-pathway excretion explain its sustained efficacy with weekly dosing and support its favorable pharmacokinetic profile for long-term therapy in type 2 diabetes and obesity management [22].

### Pharmacodynamics

Semaglutide exhibits dose-dependent effects on glycaemic control and body weight. The pharmacodynamic profile is consistent between subcutaneous and oral formulations, as both achieve comparable receptor activation once plasma levels are sufficient [23].

By mimicking endogenous GLP-1 activity, semaglutide:

- Promotes the release of insulin in response to glucose
- Inhibits the release of glucagon
- Delays gastric emptying
- Decreases caloric intake and appetite

Clinical trials have demonstrated reductions in HbA1c levels of 1.0–1.8% and weight loss ranging from 4 to 15% depending on dose and duration of therapy [24].

## Pharmacological Action

### 1. Glucose Regulation

Semaglutide plays a pivotal role in maintaining glucose homeostasis by exerting a balanced effect on both insulin and glucagon secretion. As a GLP-1 receptor agonist, it mimics the natural activity of endogenous glucagon-like peptide-1, enhancing the body's ability to regulate blood glucose levels in a glucose-dependent manner. Upon receptor activation in the pancreatic β-cells, semaglutide stimulates insulin secretion when blood glucose concentrations are elevated. This ensures that insulin release aligns with physiological needs, thereby minimizing the likelihood of hypoglycaemia [25].

At the same time, semaglutide acts on pancreatic α-cells to inhibit glucagon secretion, which in turn decreases hepatic glucose production through reduced gluconeogenesis and glycogenolysis. This coordinated modulation of pancreatic hormone secretion leads to lower fasting and postprandial plasma glucose levels.

Furthermore, semaglutide's effect on gastric emptying indirectly supports glucose regulation by slowing the absorption of dietary carbohydrates, which blunts postprandial glucose spikes. This mechanism, combined with its direct pancreatic actions, contributes to a smoother glycaemic profile and improved HbA1c reduction over time.

Overall, through its dual influence on insulin enhancement and glucagon suppression, semaglutide provides precise, glucose-dependent control of blood sugar, offering effective management of hyperglycaemia without posing a substantial risk of hypoglycaemia [25].

### 2. Appetite and Weight Control

Semaglutide has a big impact on the central nervous system (CNS), which helps lower body weight and curb hunger. It works by serving as an agonist for the GLP-1 receptor. triggers receptors in important appetite-regulating areas of the hypothalamus, such as the arcuate nucleus (ARC) and paraventricular nucleus (PVN). When these neural circuits are activated, satiety signals are increased while hunger cues are decreased, resulting in a lower total caloric intake [26].

Semaglutide stimulates pro-opiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons within the arcuate nucleus, which contribute to satiety, while simultaneously suppressing neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons, which promote hunger. By simultaneously affecting two different neurons, this helps to establish a physiological equilibrium that promotes lower food intake and appetite.

Semaglutide affects brain reward centers like the nucleus accumbens and amygdala, which are responsible for the hedonic (pleasure-driven) aspects of eating, in addition to its effects on the hypothalamus. Neuroimaging studies have demonstrated that semaglutide lowers activation in

these brain areas when people are exposed to visual or sensory food cues, suggesting a reduction in food-related reward perception and craving [26].

These central effects translate clinically into significant and sustained weight loss, as patients experience less desire to eat and greater satisfaction with smaller meals. The combined action on satiety, hunger control, and reduced reward-driven eating underscores semaglutide's effectiveness as a pharmacological agent for both glycaemic regulation and obesity management [26].

### 3. Gastric Emptying

Semaglutide plays an important role in modulating gastrointestinal motility, primarily by delaying gastric emptying, which significantly influences postprandial glucose regulation. Through activation of GLP-1 receptors located on the vagal afferent nerves and in the smooth muscle layers of the stomach, semaglutide slows the rate at which gastric contents are released into the small intestine. This delay reduces the speed of nutrient and glucose absorption, thereby preventing sharp increases in blood glucose levels following meals[27].

The prolongation of gastric emptying not only enhances postprandial glycaemic control but also contributes to prolonged satiety. By keeping food in the stomach for a longer duration, semaglutide increases the feeling of fullness and decreases the frequency of hunger signals between meals. This leads to reduced caloric intake and supports its weight-lowering effects.

Furthermore, the modulation of gastric motility is dose-dependent and tends to diminish slightly with chronic therapy as the body adapts, yet it continues to contribute to sustained metabolic and appetite-regulating benefits.

Overall, the gastric-emptying effect of semaglutide represents a critical component of its pharmacological profile, reinforcing its dual role in postprandial glucose management and long-term appetite suppression [27].

### 4. Cardiovascular Effects

In addition to lowering glucose and decreasing weight, semaglutide has cardioprotective benefits that help lower the risk of cardiovascular (CV) problems, which are common in patients with type 2 diabetes. By its action as a GLP-1 receptor agonist, semaglutide affects a number of physiological routes that, taken as a whole, enhance cardiometabolic health[15]. One of the main processes entails lowering body weight and blood pressure, both of which are significant modifiable cardiovascular risk factors. Semaglutide-induced weight reduction results in lower arterial stiffness, better endothelial function, and less systemic inflammation—all of which promote vascular health. Furthermore, semaglutide causes mild drops in systolic blood pressure, adding to its cardioprotective profile[15].

Additionally, semaglutide has positive impacts on lipid metabolism, such as somewhat raising HDL cholesterol while lowering LDL cholesterol and triglyceride levels. These lipid enhancements aid in lowering the development of atherosclerotic plaque and slowing the course of cardiovascular illness[15].

According to clinical outcome trials like the SUSTAIN-6 study, semaglutide therapy is linked to a large decrease in major adverse cardiovascular events (MACE), which includes non-fatal stroke, non-fatal myocardial infarction, and cardiovascular death in comparison to placebo[15]. Semaglutide is demonstrated by these results to be a useful treatment option for people with diabetes since it offers both efficient glycemic control and significant cardiovascular protection for patients with type 2 diabetes with a significant cardiovascular risk[15].

Semaglutide's cardiovascular advantages are due to its overall effects on body weight, blood pressure, lipid levels, and vascular function, which collectively contribute to its positive effects—decreasing the frequency of significant cardiovascular events and enhancing long-term results in diabetic people[15].

### 5. Oral Formulation and SNAC Technology

The oral formulation of semaglutide represents a major advancement in peptide drug delivery, made possible through its co-formulation with sodium N-[8-(2-hydroxybenzoyl)amino] caprylate (SNAC)—a unique absorption enhancer that enables effective gastric uptake of the peptide. Normally, peptide-based drugs are degraded in the stomach and poorly absorbed in the gastrointestinal tract; however, the inclusion of SNAC overcomes these physiological barriers and allows systemic bioavailability through the gastric mucosa [16].

SNAC functions through multiple complementary mechanisms. First, it transiently elevates the local pH in the microenvironment surrounding the tablet. This temporary neutralization of gastric acidity protects semaglutide from acid-catalyzed degradation and minimizes its exposure to proteolytic enzymes such as pepsin. By preserving the structural integrity of the peptide, SNAC ensures that a greater proportion of the active drug remains intact for absorption.

Second, SNAC enhances transcellular permeability across the gastric epithelium. It interacts with the phospholipid bilayer of gastric epithelial cells, increasing membrane fluidity and facilitating the direct passage of semaglutide through the cells rather than relying on paracellular diffusion. This mechanism allows semaglutide to enter systemic circulation directly from the stomach, bypassing the small intestine where enzymatic degradation and low permeability would otherwise limit absorption.

As a result of these synergistic effects, the SNAC-assisted oral formulation achieves therapeutically relevant plasma concentrations comparable to those attained with subcutaneous injections. This innovation marks a breakthrough in peptide pharmacotherapy, as it demonstrates that large, biologically active peptides can be delivered orally with clinically meaningful efficacy—a milestone previously unattainable for this drug class [16].

In summary, the incorporation of SNAC technology transforms semaglutide into a viable oral therapeutic option, offering patients a more convenient and non-

invasive alternative while maintaining the robust pharmacological efficacy and safety associated with injectable GLP-1 receptor agonists.

## Dosing and Administration

### Subcutaneous Formulation (Ozempic®)[26].

**Initiation:** 0.25 mg once weekly for 4 weeks

**Titration:** Increase to 0.5 mg once weekly; may further escalate to 1 mg or 2 mg if additional control is required [25].

**Administration:** Injected in the abdomen, thigh, or upper arm, independent of meals.

**Missed Dose:** If a dose is missed, it should be administered within 5 days; otherwise, the next scheduled dose should be taken

### Oral Formulation (Rybelsus®)

**Initiation:** 3 mg once daily for 30 days, then increased to 7 mg daily.

**Maintenance:** May be escalated to 14 mg daily for optimal effect [27].

**Administration:** Must be taken on an empty stomach with up to 120 mL of water, at least 30 minutes before eating or taking other medications. Tablets should not be split, crushed, or chewed [28].

## Drug–Food and Drug–Drug Interactions

### Food Interactions

Food intake significantly reduces semaglutide absorption in the oral form; therefore, strict fasting before dosing is required. Clinical pharmacokinetic studies indicate that food can decrease drug exposure by up to 80% [29].

### Drug Interactions

Semaglutide has a low potential for pharmacokinetic drug interactions due to its protein nature and non–cytochrome P450 metabolism.

**Co-administration with omeprazole** slightly increases exposure but without clinical relevance [30].

**Concomitant use with metformin, warfarin, lisinopril, or digoxin** has shown no significant changes in drug levels or therapeutic effect [31].

**Delayed gastric emptying** may influence absorption of orally administered drugs; hence, caution is advised with medications requiring rapid absorption (e.g., paracetamol) [32].

**Special Populations**: Renal or hepatic impairment does not significantly affect semaglutide pharmacokinetics, and no dose adjustment is generally required [32].

## Management of Obesity

Semaglutide has emerged as a highly effective pharmacological option for obesity management, extending its therapeutic benefits beyond glycaemic control. Its anti-obesity effects stem primarily from mechanisms involving both the central nervous system (CNS) and the gastrointestinal (GI) tract, mediated through GLP-1 receptor activation [33].

In the CNS, semaglutide acts on GLP-1 receptors located within the hypothalamic nuclei—particularly the arcuate nucleus and paraventricular nucleus—which are key regions responsible for appetite regulation and energy balance. Activation of these receptors enhances satiety signaling by stimulating pro-opiomelanocortin (POMC) neurons and inhibiting neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons. This dual neuronal modulation reduces hunger sensations and food-seeking behavior, leading to a significant decrease in caloric intake over time.

Beyond its central effects, semaglutide exerts important peripheral actions that complement appetite suppression. By delaying gastric emptying, the drug slows the rate at which nutrients leave the stomach and enter the small intestine, which prolongs the feeling of fullness after meals. This mechanism not only supports portion control but also smooths postprandial glucose excursions, further reinforcing metabolic benefits.

Clinical trials have consistently demonstrated dose-dependent reductions in body weight among individuals treated with semaglutide compared to placebo. Participants receiving semaglutide therapy often achieve substantial reductions in total body weight, body mass index (BMI), and waist circumference, with improvements evident in both diabetic and non-diabetic populations. These effects are attributed primarily to caloric restriction and improved satiety, rather than to increased energy expenditure.

Moreover, long-term data indicate that semaglutide-induced weight loss contributes to the improvement of cardiometabolic parameters, including better lipid profiles, reduced systolic blood pressure, and lower markers of inflammation. These outcomes collectively reduce the overall risk of obesity-related comorbidities, such as type 2 diabetes, cardiovascular disease, and metabolic syndrome.

In summary, semaglutide's weight management efficacy arises from its multifactorial mechanisms, combining central appetite suppression, delayed gastric emptying, and metabolic optimization. These actions make it one of the most promising pharmacological agents for the sustained treatment of obesity and metabolic disorders [34].

### Clinical Evidence

The *Semaglutide Treatment Effect in People with Obesity (STEP)* trials demonstrated significant weight reduction in adults with or without type 2 diabetes. In *STEP 1*, participants receiving semaglutide 2.4 mg once weekly achieved an average weight loss of approximately 15% of their baseline body weight after 68 weeks compared with 2.4% in the placebo group[35]

In *STEP 2* and *STEP 3* trials, similar outcomes were observed, confirming semaglutide's superior efficacy over other anti-obesity medications. Furthermore, semaglutide improved cardiometabolic markers such as waist circumference, blood pressure, fasting glucose, and

lipid profiles [36].Meta-analyses comparing semaglutide with other weight-loss agents—including liraglutide, orlistat, and phentermine/topiramate—consistently rank semaglutide as one of the most effective and best-tolerated pharmacotherapies for obesity management [37].

**Management of Obesity**

Semaglutide's weight reduction is primarily mediated through hypothalamic pathways that regulate appetite and reward behavior. By reducing activity in brain regions associated with food cravings and enhancing satiety signals, semaglutide effectively reduces caloric intake [38] . This mechanism explains its efficacy in individuals with or without diabetes, providing a potential role in obesity treatment independent of glycaemic control.

## Adverse Events

While semaglutide is generally well tolerated, some adverse effects are dose-dependent and primarily gastrointestinal in nature. Understanding these events is essential for optimizing treatment adherence and minimizing patient discomfort during therapy.

### Gastrointestinal Reactions

The most commonly reported adverse effects of semaglutide involve the gastrointestinal (GI) system, including nausea, vomiting, diarrhea, and constipation, especially during the early dose-escalation phase. These reactions are thought to be related to delayed gastric emptying and direct activation of GLP-1 receptors in the gastrointestinal tract, which influence motility and appetite regulation [39]. Nausea is the most frequent symptom and tends to occur shortly after initiation or dose increases. It is typically transient, improving as the patient's tolerance develops over several weeks. Vomiting and diarrhea may also occur but are usually mild to moderate in intensity. Constipation, though less frequent, can result from slowed gastric emptying and decreased intestinal transit.

To manage these GI reactions, gradual dose titration is strongly recommended. Starting with the lowest possible dose and increasing slowly allows the gastrointestinal system to adapt to semaglutide's effects, thereby minimizing discomfort. Patient education plays a vital role; advising individuals to eat smaller, low-fat meals and avoid overeating can help reduce nausea. Maintaining adequate hydration and fiber intake can also alleviate constipation. In rare cases, if symptoms are severe or persistent, temporary dose reduction or discontinuation may be necessary [39].

### Hypoglycaemia

Semaglutide has a glucose-dependent mechanism of action, stimulating insulin secretion only when blood glucose levels are elevated, and reducing glucagon secretion during hyperglycemia. Therefore, when used as monotherapy or in combination with metformin, it carries a low intrinsic risk of hypoglycaemia [40]. This characteristic provides a major safety advantage over agents such as sulfonylureas or insulin, which can cause hypoglycaemia regardless of glucose levels. However, when semaglutide is combined with insulin or insulin secretagogues (e.g., sulfonylureas), the risk of hypoglycaemia increases significantly. In such cases, dose adjustment of the concomitant medication is necessary to prevent excessive glucose lowering. Patients should also be counseled on recognizing early symptoms of hypoglycaemia, such as dizziness, sweating, or confusion, and advised to carry fast-acting carbohydrates.

### Other Adverse Effects

Aside from gastrointestinal symptoms and hypoglycaemia, semaglutide may be associated with other, less frequent adverse reactions. Reports have documented gallbladder-related disorders such as cholelithiasis and cholecystitis, possibly linked to rapid weight loss or alterations in bile composition [41]. A modest increase in heart rate has been observed, though its clinical relevance remains uncertain. In some patients with pre-existing diabetic retinopathy, progression of retinopathy has been noted, likely due to rapid improvements in glycemic control [41]. Pancreatitis, although rare, has been reported; clinicians should maintain a high index of suspicion if patients present with severe, persistent abdominal pain radiating to the back, accompanied by nausea or vomiting [42]. Discontinuation of therapy is warranted if pancreatitis is suspected or confirmed.

### Cardiovascular Safety

The cardiovascular profile of semaglutide has been rigorously evaluated in large outcome studies. The SUSTAIN-6 and PIONEER-6 trials demonstrated that semaglutide not only meets cardiovascular safety standards but also provides substantial protective effects against major adverse cardiovascular events (MACE), including nonfatal myocardial infarction and stroke [43]. These findings are particularly noteworthy because cardiovascular disease remains the leading cause of morbidity and mortality among patients with type 2 diabetes. The cardioprotective benefits of semaglutide are thought to result from multiple mechanisms, including weight reduction, improved glycemic control, reduced inflammation, and favorable effects on lipid metabolism. Moreover, semaglutide's ability to lower blood pressure and body weight further contributes to its cardiovascular advantages.

Overall, semaglutide's adverse event profile is well characterized and manageable with appropriate clinical oversight. Gastrointestinal side effects are the most common but typically transient and dose-dependent. The low risk of hypoglycaemia, along with proven cardiovascular benefits, positions semaglutide as a highly effective and safe therapeutic option for managing type 2 diabetes and obesity, provided that patients are closely monitored and educated throughout the course of therapy [39–43].

## Future Scope

The therapeutic potential of semaglutide continues to expand beyond diabetes and obesity. Ongoing investigations are exploring its use in conditions such as non-alcoholic steatohepatitis (NASH), neuro-

degenerative diseases, and polycystic ovary syndrome (PCOS) [44].Early studies indicate improvements in hepatic steatosis and inflammation, suggesting a role in the management of metabolic liver disease [45].

In addition, combination therapy with the amylin analogue cagrilintide is under development to enhance weight loss outcomes, as demonstrated in phase II trials showing synergistic effects [46]. Further research is also evaluating semaglutide's potential neuroprotective and anti-inflammatory effects by modulating oxidative stress and inflammatory pathways in the brain [47].

The future of semaglutide therapy lies in personalised medicine integrating genetic, metabolic, and behavioural profiling to optimise therapeutic response. Continued research will help define its role across broader metabolic and cardiovascular disease spectrums.

**Table 1: Key Advantages and Limitations of Semaglutide**

| Advantages | Limitations |
|---|---|
| Increases treatment adaptability by being offered in oral and injectable forms. | For maximum absorption, the oral tablet needs rigorous fasting conditions |
| Shows better weight loss and glycemic control than many other agonists of the GLP-1 receptor. | Some individuals may find gastrointestinal adverse effects such as nausea, vomiting, and diarrhoea to be intolerable—increases treatment adaptability by being offered in oral and injectable forms. |
| Proven cardiovascular benefits, reducing the risk of major adverse cardiovascular events. | High cost and limited access in low-resource settings. |
| Convenient once-weekly injection or once-daily oral dosing improves adherence. | Long-term safety in specific populations (e.g., adolescents, pregnancy) remains under evaluation. |

(Adapted and summarised from multiple clinical and pharmacological sources [48],[49]).

## Conclusion

One of the most important therapeutic breakthroughs in the management of obesity and type 2 diabetes mellitus is semaglutide. Its molecular structure provides extended activity, high receptor affinity, and resistance to enzymatic breakdown, which translates into convenient dosing schedules and improved patient adherence.

The oral formulation's advent has revolutionized incretin-based treatment even more by offering a viable non-injectable option without sacrificing effectiveness. When compared to prior GLP-1 receptor agonists, semaglutide has been consistently shown to be superior in clinical studies in terms of glycemic control, weight loss, and cardiovascular risk management.

Despite the fact that gastrointestinal side effects are still the most prevalent constraint, they can usually be overcome with patient education and a slow dose increase. The possible uses of semaglutide in non-alcoholic fatty liver illness, neuroprotection, and combination regimens with the objective of improving metabolic results are still being investigated in future studies.

Semaglutide has proven to be a vital component of metabolic therapy, effectively connecting diabetes and obesity treatment with a single pharmaceutical agent. It will probably have a significant long-term impact on the metabolic health of the planet and establish a new benchmark for the development of peptide-based medicines.

**Conflict of interest:** There are no conflicts of interest by authors regarding the publication of this paper.

**Author Contributions:** All authors have equal contributions in the preparation of the manuscript and compilation.

**Source of Support:** Nil

**Funding:** The authors declared that this study has received no financial support.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** The data supporting this paper are available in the cited references.

**Ethical approval:** Not applicable.

## References

1. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycemia in type 2 diabetes, 2018: A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018;41(12):2669-701. https://doi.org/10.2337/dci18-0033 PMid:30291106 PMCid:PMC6245208

2. American Diabetes Association. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes 2019. Diabetes Care. 2019;42(Suppl 1):S90-S102. https://doi.org/10.2337/dc19-S009 PMid:30559235

3. Lau J, Bloch P, Schäffer L, Pettersson I, Spetzler J, Kofoed J, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. J Med Chem. 2015;58(18):7370-80. https://doi.org/10.1021/acs.jmedchem.5b00726 PMid:26308095

4. Knudsen LB, Lau J. The discovery and development of liraglutide and semaglutide. Front Endocrinol (Lausanne). 2019;10:155.

https://doi.org/10.3389/fendo.2019.00155 PMid:31031702 PMCid:PMC6474072

5. Kapitza C, Nosek L, Jensen L, Hartvig H, Jensen CB, Flint A. Semaglutide, a once-weekly human GLP-1 analog, does not reduce the bioavailability of the combined oral contraceptive, ethinylestradiol/levonorgestrel. J Clin Pharmacol. 2015;55(5):497-504. https://doi.org/10.1002/jcph.443 PMid:25475122 PMCid:PMC4418331

6. Jensen L, Helleberg H, Rofel A, van Lier JJ, Bjørnsdottir I, Pedersen PJ, et al. Absorption, metabolism and excretion of the GLP-1 analogue semaglutide in humans and nonclinical species. Eur J Pharm Sci. 2017;108:101-10. https://doi.org/10.1016/j.ejps.2017.03.020

7. Buckley ST, Bækdal TA, Vegge A, Maarbjerg SJ, Pyke C, Ahnfelt-Rønne J, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. Sci Transl Med. 2018;10(467):eaar7047. https://doi.org/10.1126/scitranslmed.aar7047 PMid:30429357

8. Granhall C, Donsmark M, Blicher TM, Golor G, Søndergaard FL, Thomsen M, et al. Safety and pharmacokinetics of single and multiple ascending doses of the novel oral human GLP-1 analogue, oral semaglutide, in healthy subjects and subjects with type 2 diabetes. Clin Pharmacokinet. 2019;58(6):781-91. https://doi.org/10.1007/s40262-018-0728-4 PMid:30565096

9. Buckley ST, Schéele SG, Kirk RK, Knudsen LB. Mechanism of absorption mediated by SNAC in an oral formulation of semaglutide. Diabetes. 2017;66(Suppl 1):A322.

10. Neumiller JJ. Incretin-based therapies. Med Clin North Am. 2015;99(1):107-29. https://doi.org/10.1016/j.mcna.2014.08.013 PMid:25456646

11. Buckley ST, Schéele SG, Kirk RK, Knudsen LB. Mechanism of absorption mediated by SNAC in an oral formulation of semaglutide. Diabetes. 2017;66(Suppl 1):A322.

12. Buckley ST, Bækdal TA, Vegge A, Maarbjerg SJ, Pyke C, Ahnfelt-Rønne J, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. Sci Transl Med. 2018;10(467):eaar7047. https://doi.org/10.1126/scitranslmed.aar7047 PMid:30429357

13. European Medicines Agency. Rybelsus: Summary of Product Characteristics. Available from: https://www.ema.europa.eu/en/documents/product-information/rybelsus-epar-product-information_en.pdf.

14. Connor A, Donsmark M, Hartoft-Nielsen ML, Søndergaard FL, Bækdal TA. A pharmacoscintigraphic study of the relationship between tablet erosion and pharmacokinetics of oral semaglutide. Diabetes. 2017;66(Suppl 1):S319.

15. Bækdal TA, Borregaard J, Donsmark M, Breitschaft A, Søndergaard FL. Evaluation of the effects of water volume with dosing and post-dose fasting period on pharmacokinetics of oral semaglutide. Diabetes. 2017;66(Suppl 1):A315.

16. Maarbjerg SJ, Borregaard J, Breitschaft A, Donsmark M, Søndergaard FL. Evaluation of the effect of food on the pharmacokinetics of oral semaglutide. Diabetes. 2017;66(Suppl 1):A321.

17. Hauge C, Breitschaft A, Hartoft-Nielsen ML, Jensen S, Bækdal T. A drug-drug interaction trial of oral semaglutide with levothyroxine and multiple co-administered tablets. J Endocr Soc. 2019;3(Suppl 1):SAT-140. https://doi.org/10.1210/js.2019-SAT-140 PMCid:PMC6552044

18. Overgaard RV, Navarria A, Hertz CL, Ingwersen SH. Similar efficacy and gastrointestinal tolerability versus exposure for oral and subcutaneous semaglutide. Diabetes Technol Ther. 2020;22(Suppl 1):A187-8.

19. Granhall C, Søndergaard FL, Thomsen M, Anderson TW. Pharmacokinetics, safety and tolerability of oral semaglutide in subjects with renal impairment. Clin Pharmacokinet. 2018;57(12):1571-80. https://doi.org/10.1007/s40262-018-0649-2 PMid:29623579 PMCid:PMC6267549

20. Baekdal TA, Thomsen M, Kupčová V, Hansen CW, Anderson TW. Pharmacokinetics, safety, and tolerability of oral semaglutide in subjects with hepatic impairment. J Clin Pharmacol. 2018;58(10):1314-23. doi:10.1002/jcph.1131. https://doi.org/10.1002/jcph.1131 PMid:29693715 PMCid:PMC6175428

21. Bækdal TA, Breitschaft A, Navarria A, Hansen CW. A randomized study investigating the effect of omeprazole on the pharmacokinetics of oral semaglutide. Expert Opin Drug Metab Toxicol. 2018;14(8):869-77. https://doi.org/10.1080/17425255.2018.1488965 PMid:29897249

22. Bækdal TA, Borregaard J, Hansen CW, Thomsen M, Anderson TW. Effect of oral semaglutide on the pharmacokinetics of lisinopril, warfarin, digoxin, and metformin in healthy subjects. Clin Pharmacokinet. 2019;58(9):1193-203. https://doi.org/10.1007/s40262-019-00756-2 PMid:30945118 PMCid:PMC6719321

23. Enebo LB, Berthelsen KK, Kankam M, Lund MT, Rubino DM, Satylganova A, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2.4 mg for weight management: A randomised, controlled, phase 1b trial. Lancet. 2021;397(10286):1736-48. https://doi.org/10.1016/S0140-6736(21)00845-X PMid:33894838

24. Isaacs D, Prasad-Reddy L, Srivastava SB. Role of glucagon-like peptide 1 receptor agonists in management of obesity. Am J Health Syst Pharm. 2016;73(19):1493-507. https://doi.org/10.2146/ajhp150990 PMid:27521241

25. US Food and Drug Administration. FDA requests the withdrawal of weight-loss drug Belviq, Belviq XR (Lorcaserin) from the market: Potential risk of cancer outweighs the benefits. Center for Drug Evaluation and Research. Washington DC; 2020.

26. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021;384(11):989-1002. https://doi.org/10.1056/NEJMoa2032183 PMid:33567185

27. Rodbard HW, Lingvay I, Reed J, de la Rosa R, Rose L, Sugimoto D, et al. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): A randomized, controlled trial. J Clin Endocrinol Metab. 2018;103(6):2291-301. https://doi.org/10.1210/jc.2018-00070 PMid:29688502 PMCid:PMC5991220

28. Sorli C, Harashima SI, Tsoukas GM, Unger J, Karsbøl JD, Hansen T, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): A double-blind, randomised, placebo-controlled, multinational, multicentre phase 3a trial. Lancet Diabetes Endocrinol. 2017;5(4):251-60. https://doi.org/10.1016/S2213-8587(17)30013-X PMid:28110911

29. Zinman B, Bhosekar V, Busch R, Holst I, Ludvik B, Thielke D, et al. Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): A randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2019;7(5):356-67. https://doi.org/10.1016/S2213-8587(19)30066-X PMid:30833170

30. Aroda VR, Rosenstock J, Terauchi Y, Altuntas Y, Lalic NM, Morales Villegas EC, et al. Pioneer 1: Randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes. Diabetes Care. 2019;42(9):1724-32. https://doi.org/10.2337/dc19-0749 PMid:31186300

31. Mosenzon O, Blicher TM, Rosenlund S, Eriksson JW, Heller S, Hels OH, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): A placebo-controlled, randomised, phase 3a trial. Lancet Diabetes Endocrinol. 2019;7(7):515-27. https://doi.org/10.1016/S2213-8587(19)30192-5 PMid:31189517

32. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381(9):841-51. https://doi.org/10.1056/NEJMoa1901118 PMid:31185157

33. Center for Drug Evaluation and Research. Guidance for industry: Developing products for weight management. Washington DC: FDA; 2007. Available from: http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071612.pdf .

34. Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: A systematic review and meta-analysis. JAMA. 2016;315(22):2424-34. https://doi.org/10.1001/jama.2016.7602 PMid:27299618 PMCid:PMC5617638

35. Apovian CM, Aronne L, Rubino D, Still C, Wyatt H, Burns C, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). Obesity (Silver Spring). 2013;21(5):935-43. https://doi.org/10.1002/oby.20309 PMid:23408728 PMCid:PMC3739931

36. Finer N, James WPT, Kopelman PG, Lean ME, Williams G. One-year treatment of obesity: A randomized, double-blind, placebo-controlled, multicentre study of orlistat, a gastrointestinal lipase inhibitor. Int J Obes Relat Metab Disord. 2000;24(3):306-13. https://doi.org/10.1038/sj.ijo.0801128 PMid:10757623

37. Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiers ML, Najarian T, et al. Controlled-release phentermine/topiramate in severely obese adults: A randomized controlled trial (EQUIP). Obesity (Silver Spring). 2012;20(2):330-42. https://doi.org/10.1038/oby.2011.330 PMid:22051941 PMCid:PMC3270297

38. Fidler MC, Sanchez M, Raether B, Weissman NJ, Smith SR, Shanahan WR, et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: The BLOSSOM trial. J Clin Endocrinol Metab. 2011;96(10):3067-77. https://doi.org/10.1210/jc.2011-1256 PMid:21795446

39. Lyseng-Williamson KA. Glucagon-like peptide-1 receptor agonists in type 2 diabetes: Their uses and differential features. Clin Drug Investig. 2019;39(8):805-19. https://doi.org/10.1007/s40261-019-00826-0 PMid:31317516 PMCid:PMC6746674

40. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834-44. https://doi.org/10.1056/NEJMoa1607141 PMid:27633186

41. Granhall C, Donsmark M, Blicher TM, Golor G, Søndergaard FL, Thomsen M, et al. Safety and pharmacokinetics of single and multiple ascending doses of the novel oral human GLP-1 analogue, oral semaglutide, in healthy subjects and subjects with type 2 diabetes. Clin Pharmacokinet. 2019;58(6):781-91. https://doi.org/10.1007/s40262-018-0728-4 PMid:30565096

42. Overgaard RV, Navarria A, Hertz CL, Ingwersen SH. Similar efficacy and gastrointestinal tolerability versus exposure for oral and subcutaneous semaglutide. Diabetes Technol Ther. 2020;22(Suppl 1):A187-8.

43. Baekdal TA, Borregaard J, Donsmark M, Breitschaft A, Søndergaard FL. Evaluation of the effects of water volume with dosing and post-dose fasting period on pharmacokinetics of oral semaglutide. Diabetes. 2017;66(Suppl 1):A315.

44. Granhall C, Søndergaard FL, Thomsen M, Anderson TW. Pharmacokinetics, safety and tolerability of oral semaglutide in subjects with renal impairment. Clin Pharmacokinet. 2018;57(12):1571-80. https://doi.org/10.1007/s40262-018-0649-2 PMid:29623579 PMCid:PMC6267549

45. Baekdal TA, Thomsen M, Kupčová V, Hansen CW, Anderson TW. Pharmacokinetics, safety, and tolerability of oral semaglutide in subjects with hepatic impairment. J Clin Pharmacol. 2018;58(10):1314-23. https://doi.org/10.1002/jcph.1131 PMid:29693715 PMCid:PMC6175428

46. Bækdal TA, Breitschaft A, Navarria A, Hansen CW. Effect of omeprazole on the pharmacokinetics of oral semaglutide. Expert Opin Drug Metab Toxicol. 2018;14(8):869-77. https://doi.org/10.1080/17425255.2018.1488965 PMid:29897249

47. Bækdal TA, Borregaard J, Hansen CW, Thomsen M, Anderson TW. Effect of oral semaglutide on pharmacokinetics of lisinopril, warfarin, digoxin, and metformin in healthy subjects. Clin Pharmacokinet. 2019;58(9):1193-203. https://doi.org/10.1007/s40262-019-00756-2 PMid:30945118 PMCid:PMC6719321

48. Enebo LB, Berthelsen KK, Kankam M, Lund MT, Rubino DM, Satylganova A, et al. Safety and pharmacodynamics of cagrilintide with semaglutide 2.4 mg for weight management: A randomised, controlled, phase 1b trial. Lancet. 2021;397(10286):1736-48. https://doi.org/10.1016/S0140-6736(21)00845-X PMid:33894838

49. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381(9):841-51. https://doi.org/10.1056/NEJMoa1901118 PMid:31185157