JOURNAL OF PHARMA INSIGHTS AND RESEARCH ISSN NO. 3048-5428

REVIEW ARTICLE

Pharmacology and Clinical Efficacy of Semaglutide in the Management of Type 2 Diabetes Mellitus

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Publication history: Received on 22nd July 2025; Revised on 2nd September 2025; Accepted on 7th September 2025

Article DOI: 10.69613/9dd27k52

Abstract: Semaglutide, a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist, represents a significant development in the therapeutic landscape for type 2 diabetes mellitus (T2DM). Its molecular structure, featuring 94% homology to human GLP-1 with modifications for albumin binding and resistance to dipeptidyl peptidase-4 (DPP-4) degradation, confers an extended half-life of approximately one week. This profile permits once-weekly subcutaneous or, uniquely, once-daily oral administration facilitated by the absorption enhancer sodium N-(8-[2-hydroxybenzoyl]-amino) caprylate (SNAC). The mechanism of action involves glucose-dependent stimulation of insulin secretion, suppression of inappropriate glucagon release, and delayed gastric emptying. Apart from glycemic control, semaglutide exerts central effects on appetite regulation, leading to significant reductions in body weight. Large-scale clinical trial programs (SUSTAIN for subcutaneous, PIONEER for oral) have shown robust reductions in HbA1c and body weight compared to placebo and active comparators, including other GLP-1 receptor agonists and SGLT2 inhibitors. Moreover, dedicated cardiovascular outcome trials have established its benefit in reducing major adverse cardiovascular events (MACE) in patients with T2DM and high cardiovascular risk. Its clinical utility extends to chronic weight management, with higher-dose formulations approved for obesity. The primary adverse events are gastrointestinal in nature, including nausea, vomiting, and diarrhea, which are typically dose-dependent and transient. Therapeutic monitoring include potential risks for diabetic retinopathy complications and the class-specific boxed warning regarding thyroid C-cell tumors, derived from rodent studies.

Keywords: Semaglutide; Type 2 Diabetes Mellitus; GLP-1 Receptor Agonist; Glycemic Control; Weight Loss

1. Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. Its prevalence has reached pandemic proportions, with global health organizations estimating that hundreds of millions of adults are affected worldwide, a figure projected to rise substantially [2]. The disorder is a major source of morbidity and mortality, primarily through its association with long-term complications. Chronic hyperglycemia is a key driver of microvascular damage, leading to retinopathy, nephropathy, and neuropathy, as well as macrovascular complications such as coronary artery disease, peripheral arterial disease, and cerebrovascular events [3, 4].

Diabetes mellitus is broadly classified into distinct types. Type 1 diabetes (T1D), often diagnosed in youth but possible at any age, is an autoimmune condition defined by the progressive destruction of pancreatic β-cells, resulting in absolute insulin deficiency [5]. Type 2 diabetes (T2DM) accounts for the vast majority of cases (approximately 90%) and is characterized by the dual pathophysiology of peripheral insulin resistance and a progressive decline in β-cell insulin secretory capacity [6]. Gestational diabetes mellitus (GDM) refers to glucose intolerance that is first recognized during pregnancy. Given its prevalence and complex pathophysiology linked to obesity, T2DM presents a significant and ongoing therapeutic challenge.

Traditional management of T2DM often involves lifestyle modifications and oral antidiabetic agents, progressing to injectable therapies as β-cell function declines. However, many conventional treatments, such as sulfonylureas and exogenous insulin, are associated with significant limitations, including the risk of hypoglycemia and weight gain, both of which can be barriers to achieving optimal glycemic targets [7].

A critical advancement in T2DM pharmacology stemmed from the characterization of the incretin effect. This physiological phenomenon describes the observation that an oral glucose load elicits a much larger insulin response than an isoglycemic

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intravenous glucose infusion [8]. This effect is mediated by gut-derived hormones, principally glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). In individuals with T2DM, the incretin effect is significantly diminished, largely due to reduced GLP-1 secretion and responsiveness [9]. This deficit identified the GLP-1 pathway as a prime therapeutic target.

2. The GLP-1 Endocrine System

2.1. Physiological Role of Glucagon-Like Peptide-1 (GLP-1)

GLP-1 is a peptide hormone secreted from enteroendocrine L-cells in the distal ileum and colon in response to nutrient ingestion [10]. It exerts its metabolic effects by binding to the GLP-1 receptor (GLP-1R), a G-protein-coupled receptor expressed in numerous tissues, including pancreatic islets, the brain, the gastrointestinal tract, and the heart [11]. The primary glucoregulatory actions of GLP-1 are multifaceted. It potentiates glucose-dependent insulin secretion from pancreatic β-cells, meaning it stimulates insulin release only when blood glucose levels are elevated, thereby carrying a very low intrinsic risk of hypoglycemia [12]. Concurrently, it suppresses the secretion of glucagon from pancreatic α-cells, particularly in the postprandial state when it is pathologically elevated in T2DM. This action reduces hepatic gluconeogenesis [13]. Beyond its pancreatic effects, GLP-1 slows gastric emptying, which attenuates the rate of postprandial glucose absorption, and acts centrally on hypothalamic appetite centers to promote satiety and reduce food intake [14].

2.2. Limitations of Native GLP-1 and Therapeutic Analogues

The therapeutic utility of native human GLP-1 is nullified by its extremely short plasma half-life of less than two minutes [15]. This rapid clearance is mediated by two mechanisms: (1) enzymatic degradation by dipeptidyl peptidase-4 (DPP-4) and (2) renal clearance. This limitation prompted the development of two distinct therapeutic classes: DPP-4 inhibitors, which prolong the action of endogenous GLP-1, and GLP-1 receptor agonists (GLP-1 RAs), which are analogues of GLP-1 engineered to resist DPP-4 degradation and extend plasma half-life. Semaglutide is a member of this latter class.

3. Semaglutide: A Novel GLP-1 Receptor Agonist

3.1. Molecular Structure and Pharmacology

Semaglutide is a human GLP-1 analogue that shares 94% sequence homology with the native peptide [16]. Its development incorporated three key structural modifications to optimize its pharmacokinetic profile. First, the alanine at position 8 is substituted with α-aminoisobutyric acid (Aib), a non-natural amino acid that renders the peptide backbone highly resistant to degradation by the DPP-4 enzyme [17]. Second, the lysine at position 26 is acylated with a C18 fatty di-acid chain via a short polyethylene glycol (PEG) spacer. This modification facilitates strong, non-covalent, reversible binding to serum albumin [18]. This albumin binding sequesters the molecule, protecting it from renal clearance and further enzymatic degradation, thereby dramatically extending its elimination half-life to approximately 168 hours (one week) [19]. Third, the lysine at position 34 is substituted with arginine to ensure correct attachment of the fatty acid chain. This extended half-life is the basis for its utility as a once-weekly subcutaneous injection.

3.2. Mechanism of Action

Semaglutide functions by selectively binding to and activating the GLP-1R [14]. Its glucoregulatory effects mirror the physiology of native GLP-1 but with a sustained, long-acting pharmacodynamic profile. It enhances glucose-dependent insulin secretion, inhibits glucagon release, and slows gastric motility [20]. Moreover, semaglutide crosses the blood-brain barrier and activates GLP-1Rs in brain regions associated with appetite regulation, such as the hypothalamus and brainstem. This central action is pivotal to its observed effects on reducing energy intake, increasing feelings of fullness, and altering food preferences, which collectively drive significant weight loss [21].

3.2. Pharmacokinetics and Pharmacodynamics

3.2.1. Subcutaneous Administration

Following subcutaneous (SC) injection, semaglutide exhibits high bioavailability (approximately 89%). Peak plasma concentrations are achieved within 1 to 3 days, and steady-state concentrations are reached after 4 to 5 weeks of consistent once-weekly dosing [19].

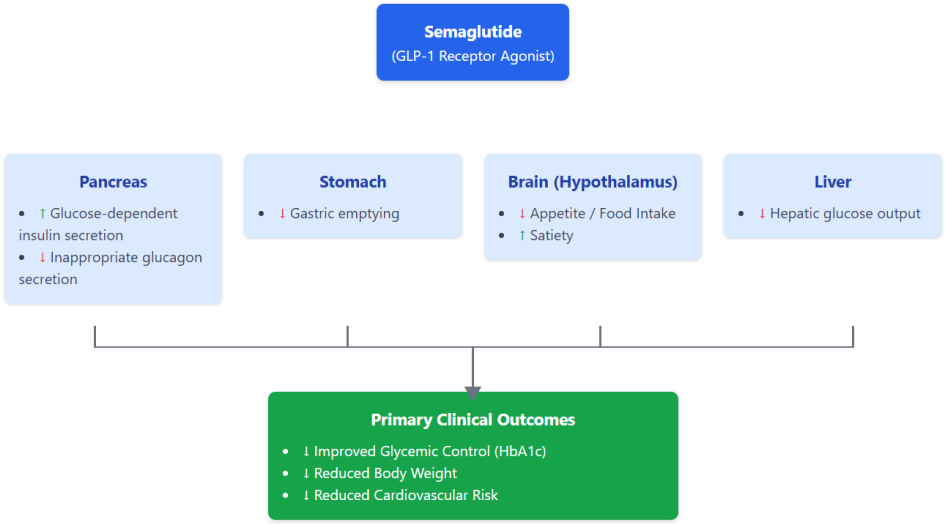

Figure 1. Mechanism of Action of Semaglutide (GLP-1 Receptor Agonist)

Table 1. Pharmacokinetic Profile of Subcutaneous vs. Oral Semaglutide

Parameter	**Subcutaneous Semaglutide (Ozempic®/Wegovy®)**	**Oral Semaglutide (Rybelsus®)**
Dosing Frequency	Once-weekly	Once-daily
Absorption Enhancer	None	Sodium N-(8-[2-hydroxybenzoyl]amino) caprylate (SNAC)
Bioavailability	~89%	0.4% – 1.0%
Time to Peak (Tmax)	1–3 days	~1 hour (post-dose)
Elimination Half-life	~168 hours (1 week)	~168 hours (1 week)
Metabolism	Proteolytic cleavage & β-oxidation	Proteolytic cleavage & β-oxidation
Administration Precautions	Independent of meals. Rotate injection site.	Must be taken fasting with 120 mL (4 oz) of water, 30 min before first food, beverage, or other oral medication.

3.2.2. Oral Administration

The development of an oral formulation of a peptide like semaglutide represented a major pharmaceutical challenge due to its susceptibility to gastric acid degradation and poor permeability across the gastric mucosa.

Figure 2. Recommended Dose Titration Schedules for Semaglutide Formulations

This was overcome by co-formulating semaglutide with an absorption enhancer, sodium N-(8-[2-hydroxybenzoyl]amino) caprylate (SNAC) [22]. SNAC is believed to act locally by buffering the gastric pH to protect semaglutide from proteolysis and by facilitating its transcellular absorption across the gastric epithelium [23]. This oral formulation (Rybelsus®) must be administered in a fasting state with a small amount of water (no more than 120 mL) at least 30 minutes before any other food, drink, or medication to ensure optimal absorption. Despite these measures, the oral bioavailability remains low (0.4–1.0%) but is sufficiently consistent to produce the desired clinical effects [24].

3.2.3. Metabolism and Elimination

Semaglutide is metabolized primarily via the proteolytic cleavage of its peptide backbone and subsequent β-oxidation of its fatty acid side chain [16]. It is not significantly metabolized by CYP450 enzymes, suggesting a low potential for pharmacokinetic drug-drug interactions. The elimination half-life of approximately one week is consistent for both SC and oral routes, with metabolites excreted primarily in the urine and feces [19, 24].

4. Clinical Efficacy of Semaglutide in Type 2 Diabetes

The clinical development of semaglutide was conducted through two extensive Phase 3 trial programs: SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) for the SC formulation and PIONEER (Peptide Innovation for Early Diabetes Treatment) for the oral formulation.

4.1. Glycemic Control

The SUSTAIN program (SUSTAIN 1-7) consistently shown superior glycemic control with once-weekly SC semaglutide across the continuum of T2DM care [25]. When compared to placebo, semaglutide (at 0.5 mg and 1.0 mg doses) provided robust reductions in HbA1c, typically ranging from 1.2% to 1.8% [26]. In active-comparator trials, SC semaglutide was superior to sitagliptin (a DPP-4 inhibitor), exenatide extended-release (a weekly GLP-1 RA), and insulin glargine in reducing HbA1c [26, 27].

The PIONEER program (PIONEER 1-8) established the efficacy of the oral formulation. Oral semaglutide (at 7 mg and 14 mg doses) provided statistically significant and clinically meaningful HbA1c reductions compared to placebo [28]. It also showed superiority over active comparators, including the SGLT2 inhibitor empagliflozin (PIONEER 2) and the DPP-4 inhibitor sitagliptin (PIONEER 3) [29, 30].

4.2. Impact on Body Weight and Metabolism

A distinguishing feature of semaglutide therapy is its profound effect on body weight. In both the SUSTAIN and PIONEER programs, semaglutide treatment was associated with significant, dose-dependent weight loss, typically ranging from 3.5 kg to 6.5 kg, far exceeding the modest weight loss or weight neutrality of comparators [25, 28]. This effect is primarily attributed to its central appetite-suppressing mechanism. The potent effect on weight led to the development of a higher 2.4 mg weekly SC dose (Wegovy®), which is specifically approved for chronic weight management in individuals with or without T2DM [31].

Table 2. Outcomes from SUSTAIN and PIONEER Phase 3 Trials

Trial	Population (T2DM)	Semaglutide Dose	Comparator	Mean ΔHbA1c (Sema vs. Comp)	Mean ΔWeight (Sema vs. Comp)
SUSTAIN 1	Monotherapy, drug-naïve	1.0 mg SC weekly	Placebo	-1.6% vs. -0.0%	-4.5 kg vs. -1.0 kg
SUSTAIN 7	Add-on to metformin	1.0 mg SC weekly	Dulaglutide 1.5 mg weekly	-1.8% vs. -1.4%	-6.5 kg vs. -3.0 kg
PIONEER 2	Add-on to metformin	14 mg oral daily	Empagliflozin 25 mg daily	-1.3% vs. -0.9%	-3.8 kg vs. -3.7 kg
PIONEER 3	Add-on to metformin SGLT2i	14 mg oral daily	Sitagliptin 100 mg daily	-1.3% vs. -0.8%	-3.1 kg vs. -0.6 kg
PIONEER 4	Add-on to metformin SGLT2i	14 mg oral daily	Liraglutide 1.8 mg daily	-1.2% vs. -1.1%	-4.4 kg vs. -3.1 kg

(Δ= Change from baseline. All comparisons shown were statistically significant in favor of semaglutide, except for weight in PIONEER 2 and HbA1c in PIONEER 4 which was non-inferior)

4.3. Cardiovascular and Renal Outcomes

Cardiovascular outcome trials (CVOTs) are now a regulatory requirement to establish the cardiovascular safety of new antidiabetic agents.

The SUSTAIN 6 trial evaluated SC semaglutide in over 3,200 patients with T2DM and established cardiovascular disease (CVD) or high CV risk [32]. Over a median follow-up of 2.1 years, semaglutide significantly reduced the primary composite endpoint (MACE: cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) by 26% compared to placebo. This benefit was largely driven by a significant 39% reduction in non-fatal stroke [32].

The PIONEER 6 trial was a CVOT designed to establish the cardiovascular safety of oral semaglutide in a similar high-risk population [33]. The trial met its primary endpoint of non-inferiority to placebo for MACE. While it showed a 21% reduction in MACE, the trial was not powered to show statistical superiority for this endpoint, though it did show a significant reduction in all-cause mortality [33]. These trials confirm that semaglutide provides cardiovascular benefits in addition to its glycemic and weight-lowering effects.

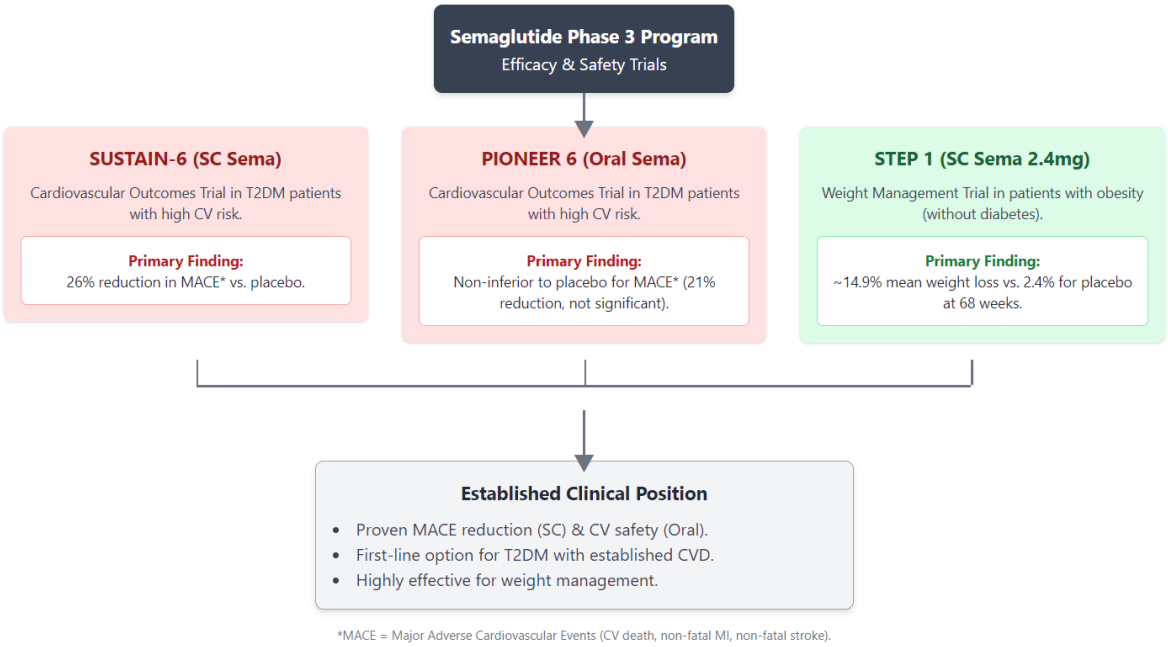

Figure 3. Cardiovascular and Metabolic Outcome Trials

5. Therapeutic Versatility

5.1. Semaglutide Versus Other GLP-1 Receptor Agonists

Semaglutide has shown superior efficacy in head-to-head trials against other GLP-1 RAs. The SUSTAIN 7 trial directly compared once-weekly SC semaglutide (0.5 mg and 1.0 mg) with once-weekly dulaglutide (0.75 mg and 1.5 mg) [27]. Semaglutide at both doses was superior to dulaglutide at both doses for reductions in both HbA1c and body weight. Similarly, oral semaglutide was shown to be superior to the once-daily GLP-1 RA liraglutide in the PIONEER 4 trial for non-inferior HbA1c reduction and superior weight loss [34].

5.2. Semaglutide Versus Other Oral Antidiabetic Agents

As established in the PIONEER trials, oral semaglutide provides superior HbA1c and weight reduction compared to market-leading oral agents from other classes. Its superiority over both empagliflozin (SGLT2 inhibitor) and sitagliptin (DPP-4 inhibitor) positions it as a highly effective oral therapy, particularly for patients in whom weight loss and potent glycemic control are primary goals [29, 30].

Table 3. Comparison of Semaglutide with Other Antidiabetic Drug Classes

Drug Class	Example Agents	Typical HbA1c Reduction	Effect on Body Weight	Cardiovascular (MACE) Benefit	Renal (Progression) Benefit	Adverse Events
GLP-1 RA	Semaglutide, Dulaglutide	High (1.0–1.8%)	Significant Loss	Proven	Proven	Nausea, vomiting, diarrhea
SGLT2 Inhibitors	Empagliflozin, Dapagliflozin	Moderate (0.6–1.0%)	Moderate Loss	Proven	Proven	Genitourinary infections, euglycemic DKA (rare)
DPP-4 Inhibitors	Sitagliptin, Linagliptin	Modest (0.5–0.8%)	Neutral	Neutral	Neutral	Generally well-tolerated, pancreatitis (rare)
Sulfonylureas	Glimepiride, Gliclazide	Moderate-High (1.0–1.5%)	Gain	Neutral	None	Hypoglycemia, weight gain
Metformin	Metformin	Moderate (1.0–1.5%)	Neutral / Modest Loss	Neutral (Proven in UKPDS)	None	GI upset, lactic acidosis (rare)

6. Safety, Tolerability, and Risk Management

6.1. Common Adverse Events

The safety profile of semaglutide is well-characterized and consistent with the GLP-1 RA class [35]. The most frequently reported adverse events are gastrointestinal (GI) in nature. These include nausea, vomiting, diarrhea, and constipation [36]. These events are typically mild to moderate in severity, dose-dependent, and transient, occurring most frequently during the initial dose-escalation period and attenuating over time. A slow, stepwise dose titration is essential to mitigate these GI effects and optimize patient tolerability and adherence.

Table 4. Common Adverse Events and Safety for Semaglutide

Adverse Event / Safety Point	Typical Incidence (Trial Data)	Clinical Management
Nausea	20–44% (Dose-dependent)	Mild-to-moderate and transient. Mitigated by slow dose-escalation.
Diarrhea	15–30% (Dose-dependent)	Typically mild. Manage hydration. Attenuates over time.
Vomiting	10–24% (Dose-dependent)	Less common than nausea. Mitigated by slow dose-escalation.
Constipation	~15–25%	Dietary management. Attenuates over time.
Diabetic Retinopathy	Increased risk of complications seen in SUSTAIN 6 (3.0% vs 1.8% placebo)	Hypothesized to be from rapid glucose lowering. Monitor patients with pre-existing retinopathy.
Pancreatitis	Rare (Incidence not clearly above placebo in CVOTs)	Discontinue permanently if acute pancreatitis is suspected.
Thyroid C-Cell Tumors	(Rodent finding)	Boxed Warning. Contraindicated in patients with a personal or family history of Medullary Thyroid Carcinoma (MTC) or MEN 2 syndrome.

6.2. Clinical Scrutiny

6.2.1. Pancreatitis

An increased risk of acute pancreatitis has been a theoretical concern for the incretin class of therapies. However, analyses of large-scale clinical trial data, including the CVOTs, and real-world evidence studies have not established a definitive causal association between GLP-1 RA use and pancreatitis [37].

6.2.2. Diabetic Retinopathy

An unexpected finding in the SUSTAIN 6 trial was a statistically significant increase in the risk of diabetic retinopathy complications (such as vitreous hemorrhage or need for photocoagulation) in the semaglutide group compared to placebo [32]. This risk was highest among patients with pre-existing diabetic retinopathy at baseline. It is widely hypothesized that this finding is not a direct drug-induced toxicity but rather a consequence of the rapid and substantial improvement in glycemic control, a phenomenon that has also been observed with intensive insulin therapy [38]. Patients with a history of diabetic retinopathy should be monitored when initiating semaglutide.

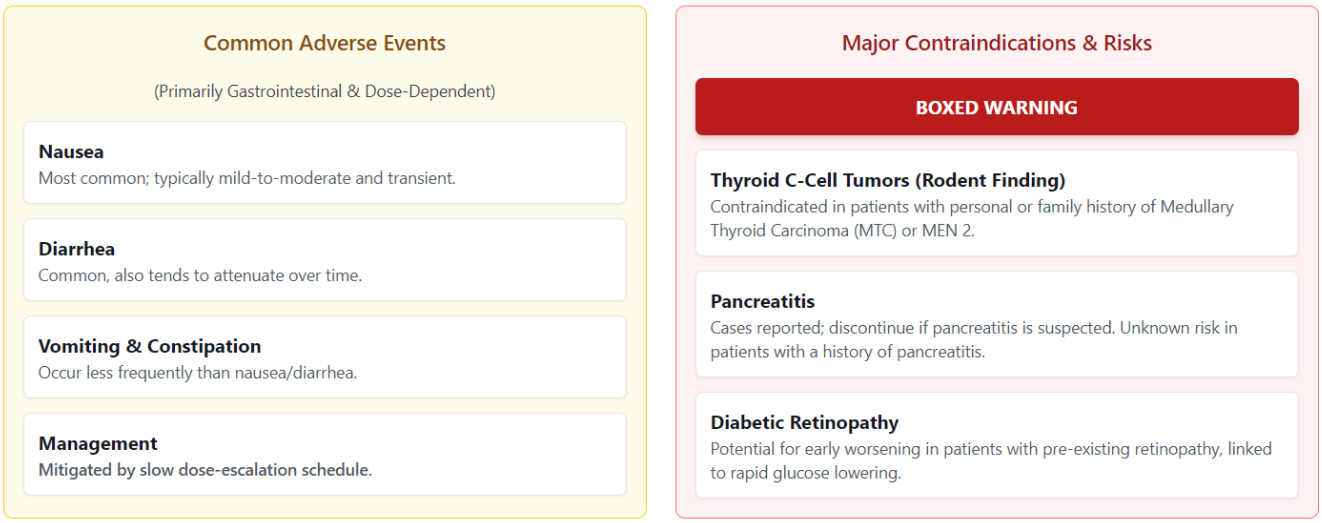

Figure 4. Safety Profile and Risk Management of Semglutide

6.3. Contraindications and Boxed Warning

Semaglutide, like all GLP-1 RAs, carries a boxed warning from the U.S. Food and Drug Administration regarding the risk of thyroid C-cell tumors. This warning is based on dose- and duration-dependent increases in thyroid C-cell tumors (adenomas and carcinomas) observed in rodent studies [16, 39]. The clinical relevance of this finding to humans is considered low, as human thyroid C-cells express significantly fewer GLP-1 receptors than rodent C-cells. Nevertheless, semaglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

7. Conclusion

Semaglutide, available in both once-weekly subcutaneous and once-daily oral formulations, has established itself as a highly effective agent for the management of type 2 diabetes. It offers a powerful combination of potent glycemic lowering, substantial and sustained weight loss, and proven cardiovascular risk reduction. Its mechanism of action, which leverages the native incretin system while providing central appetite suppression, overcomes multiple core pathophysiological defects of T2DM and its common comorbidities. While its safety profile is manageable, dominated by transient gastrointestinal effects, clinicians must be mindful of the contraindication regarding thyroid C-cell tumor history and the need for monitoring in patients with pre-existing retinopathy. Current research also focusses on its additional benefits in non-alcoholic steatohepatitis (NASH), chronic kidney disease, and expanded cardiovascular indications. Semaglutide thus can be vital in modern metabolic therapy for managing T2DM and related cardiometabolic disease.

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