Semaglutide Use in Clinical Practice

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Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist available in two different formulations: oral Rybelsus and injectable Wegovy or Ozempic. Rybelsus is approved for glycemic control in type 2 diabetes mellitus (T2DM), whereas the injectable forms are approved for glycemic control, improving cardiovascular outcomes in patients with diabetes and for weight loss in patients with a body mass index (BMI) >30 kg/m^2 or >27 kg/m^2 with at least one obesity related complication like DM or hypertension. Ozempic is not available in India.

Formulation

It is a human GLP-1 analogue with 94% structural homology,[1] modified at positions 8, 26, and 34 to enhance stability and extend its half-life to 160 hours. At the eighth position, alanine is replaced with alpha-aminoisobutyric acid, which protects it from degradation by dipeptidyl peptidase-4 (DPP-4) enzymes. At the 26th position, the C-18 fatty acid chain is attached to lysine, which provides strong binding to albumin. At the 34th position, lysine is replaced with arginine to prevent the wrong binding of the C-18 fatty diacid chain at the wrong position[2].

As a peptide, it has low oral bioavailability (0.01%) due to degradation by proteolytic enzymes, low gastric pH, and poor permeation through the gastrointestinal epithelium caused by its high molecular weight[3]. Co-formulation with sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC), a fatty acid derivative, increases semaglutide's bioavailability 100-fold to approximately 1% by elevating localized pH, protecting against enzymatic and acidic degradation, and facilitating transcellular transport across the gastric epithelium. Impact of SNAC is time- and concentration-dependent and fully reversible[4].

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Heuristics

The injectable from is a prefilled, multi-dose, disposable pen containing clear, colorless solution (pH 7.4) of semaglutide in a 1.5 mL or 3 mL glass cartridge. The pens are available in five dosage strengths: 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, and 2.4 mg. The non-medicinal ingredients in the pen include disodium phosphate dihydrate, propylene glycol, phenol, and water for injections.

The injectable dose is given once a week subcutaneously with gradual dose escalation. It starts at 0.25 mg (weeks 1-4), followed by 0.5 mg (weeks 5-8), 1 mg (weeks 9-12), 1.7 mg (weeks 13-16), and reaches 2.4 mg from week 17 onward.

Patient progress should be evaluated after 12 weeks on the maintenance dose (2.4 mg or maximum tolerated dose), with discontinuation considered if clinically meaningful BMI improvement is not achieved. Subcutaneous semaglutide exhibits high bioavailability (89%), with peak plasma concentrations reached within 1 to 3 days following administration[5]. Steady-state exposure is typically achieved after 4 to 5 weeks of weekly dosing, with exposure increasing proportionally with doses up to 2.4 mg.

The medicine is administered subcutaneously in the thigh or arm, once a week, without any relation to food. It should never be given as intravenous or intramuscular injections. The site of administration must be rotated. In case of a missed dose, if the duration is less than 48 hours, then take the dose as soon as possible with the next dose at its usual time. If the duration is more than 48 hours, skip the dose and take the next dose at the scheduled time.

Oral semaglutide demonstrates a low bioavailability range of 0.4% to 1% and the absorption is significantly influenced by gastric fluid composition, with food intake and increased water volumes reducing the bioavailability of oral semaglutide[6]. The tablet as of now is available in 3 mg, 7 mg and 14 mg tablets. It must be taken on an empty stomach, at least 30 minutes before the first food, beverage, or other oral medications of the day, as shorter intervals may reduce semaglutide absorption. The tablet should be swallowed whole with no more than 120 mL (half

a glass) of water, as larger volumes may decrease absorption. Splitting, crushing, or chewing the tablet is not permitted to ensure proper delivery and efficacy of the medication. It is initiated at 3 mg daily for 30 days to initiate treatment and minimize gastrointestinal side effects. This is followed by an increase to 7 mg daily for an additional 30 days which can then be escalated to 14 mg daily if needed. No dose adjustment is needed for oral or subcutaneous semaglutide in patients with hepatic or mild renal impairment[7,8].

Drug-drug interaction studies have shown no clinically significant changes in semaglutide exposure when co-administered with commonly used medications, including omeprazole, lisinopril, warfarin, metformin, digoxin, ethinylestradiol/levonorgestrel, rosuvastatin, and furosemide[9].

However, a modest 33% increase in levothyroxine exposure (90% CI: 125-142) was observed when administered with a 600 mcg dose alongside oral semaglutide[10]. To mitigate potential interactions, patients on levothyroxine are advised to adhere strictly to a dosing schedule, taking levothyroxine at least 30 minutes after oral semaglutide, and to monitor their thyroid function to ensure optimal therapeutic outcomes regularly.

Precautions While Using

While no adjustment is required >65 years of age, there is limited experience in people >75 years of age.

While it has not affected mild-moderate renal impairment, it is not recommended in end-stage renal disease due to limited experience.

It is associated with an increase in heart rate and prolongation of the PR interval on electrocardiograms; therefore, it should be used with caution in patients with tachyarrhythmias or those with pre-existing conduction abnormalities. A recent meta-analysis, however, showed that semaglutide is protective against atrial fibrillation[11].

Semaglutide has caused necrotizing pancreatitis in multiple case reports, but meta-analyses has not shown any increased risk[12]. however, it should be avoided in patients with a history of chronic pancreatitis or a recent (past 6 months) history of acute pancreatitis.

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy[13].

There have been some reports of acute kidney injury and worsening chronic renal failure in semaglutide-treated patients, sometimes requiring hemodialysis, particularly in those with gastrointestinal adverse events (e.g., nausea, vomiting, diarrhea) leading to volume depletion[14]. Adequate hydration must be ensured in patients on the medication.

Semaglutide should be discontinued at least 2 months before a planned pregnancy due to its long half-life, and treatment should be stopped if pregnancy occurs.

Contraindications

It should not be used during hyperglycemic emergencies like diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, as it has been shown to induce ketosis in non-diabetic patients. It is contraindicated in people with hypersensitivity to the drug or other ingredients (Hydrochloric acid, sodium chloride, sodium hydroxide, sodium phosphate dibasic heptahydrate).

While systematic review has not demonstrated any increased risk for medullary or papillary thyroid carcinoma with semaglutide[15] it is contraindicated in people with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2. It is contraindicated in patients with class IV heart failure. Its use is contraindicated in patients with a history of suicide attempts or active suicidal ideation. It is contraindicated during pregnancy and breastfeeding. Animal studies with subcutaneous semaglutide have shown reproductive and developmental toxicity at exposures below or similar to human exposure levels[16].

Adverse Events

About 41.9% of participants receiving continued semaglutide 2.4 mg experienced gastrointestinal AEs, including nausea, vomiting, diarrhea, constipation, and abdominal cramps, which eventually decreased over time[17]. A meta-analysis of 76 randomized controlled trials (RCTs) involving 103,371 patients demonstrated that GLP-1 receptor agonists including semaglutide, were associated with an increased risk of gallbladder and biliary diseases, such as cholelithiasis, cholecystitis, and other biliary disorders[18].

The risk was found to be dose- and duration-dependent, with higher doses and longer treatment durations correlating with elevated incidences of these adverse events, highlighting the need for careful monitoring during prolonged or high-dose GLP-1 receptor agonists therapy.

For the oral semaglutide, the main side effects included gastrointestinal adverse reactions, including nausea, vomiting, and diarrhea, which predominantly occurred during dose escalation[19].

Conclusion

Semaglutide, a GLP-1 receptor agonist, is a significant advancement in the management of T2DM, providing enhanced glycemic control, improved cardiovascular outcomes, and effective weight management. Its multifaceted mechanism targets central and peripheral pathways regulating glucose and

energy homeostasis, making it a promising therapeutic agent for metabolic and potentially neurodegenerative disorders. Ongoing research is exploring its applications in non-diabetic conditions and evaluating its long-term safety profile. Continued pharmacological analyses are essential to confirm its efficacy and ensure patient safety across diverse clinical contexts.

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