Sem-O™

(Semaglutide)

سیم او

Tablets 3mg, 7mg & 14mg

DESCRIPTION

Sem-O (Semaglutide) Tablets, for oral use, contain semaglutide, a GLP-1 receptor agonist. The main protraction mechanism of semaglutide is albumin binding, facilitated by modification of position 26 lysine with a hydrophilic spacer and a C18 fatty di-acid. Furthermore, semaglutide is modified in position 8 to provide stabilization against degradation by the enzyme dipeptidyl-peptidase 4 (DPP-4). A minor modification was made in position 34 to ensure the attachment of only one fatty di-acid. The molecular formula of Semaglutide is $C_{187}H_{291}N_{45}O_{59}$.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Sem-O (Semaglutide) is available for oral administration as:

Sem-O Tablet 3mg
Each tablet contains:
Semaglutide…3mg

Sem-O Tablet 7mg
Each tablet contains:
Semaglutide…7mg

Sem-O Tablet 14mg
Each tablet contains:
Semaglutide…14mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Semaglutide is a GLP-1 analogue with 94% sequence homology to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. GLP-1 is a physiological hormone that has multiple actions on glucose, mediated by the GLP-1 receptors. The principal mechanism of protraction resulting in the long half-life of Semaglutide is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, Semaglutide is stabilized against degradation by the DPP-4 enzyme. Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase.

Pharmacokinetics

Absorption

Orally administered Semaglutide has a low absolute bioavailability and a variable absorption. Daily administration according to the recommended posology in combination with a long half-life reduces day-to-day fluctuation of the exposure. Following oral administration, maximum plasma concentration of Semaglutide occurred 1 hour post dose. Steady-state exposure was reached after 4-5 weeks of once-daily administration. In patients with type 2 diabetes, the average steady-state concentrations were approximately 6.7nmol/L and 14.6nmol/L with Semaglutide 7mg and 14mg, respectively; with 90% of subjects treated with Semaglutide 7mg having an average concentration between 1.7 and 22.7nmol/L and 90% of subjects treated with Semaglutide 14mg having an average concentration between 3.7 and 41.3nmol/L. Systemic exposure of Semaglutide increased in a dose-proportional manner. Based on *in vitro* data, salcaprozate sodium facilitates absorption of Semaglutide. The absorption of Semaglutide predominantly occurs in the stomach. The estimated bioavailability of Semaglutide is approximately 1% following oral administration. The between-subject variability in absorption was high (coefficient of variation was approximately 100%). Absorption of Semaglutide is decreased if taken with food or large volumes of water. A longer post-dose fasting period results in higher absorption.

Distribution

The estimated absolute volume of distribution is approximately 8L in subjects with type 2 diabetes. Semaglutide is extensively bound to plasma proteins (>99%).

Metabolism

Semaglutide is metabolised through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid side chain. The enzyme neutral endopeptidase (NEP) is expected to be involved in the metabolism of Semaglutide.

Elimination

The primary excretion routes of Semaglutide-related material are via the urine and feces. Approximately 3% of the absorbed dose is excreted as intact Semaglutide via the urine. With an elimination half-life of approximately 1 week, Semaglutide will be present in the circulation for about 5 weeks after the last dose. The clearance of Semaglutide in patients with type 2 diabetes is approximately 0.04L/h.

Switching between oral and subcutaneous administration

The effect of switching between oral and subcutaneous Semaglutide cannot easily be predicted because of the high pharmacokinetic variability of oral Semaglutide. Exposure after oral Semaglutide 14mg once daily is comparable to subcutaneous Semaglutide 0.5mg once weekly. An oral dose equivalent to 1.0mg of subcutaneous Semaglutide has not been established.

Special Population

Body weight

Body weight had an effect on the exposure of Semaglutide. Higher body weight was associated with lower exposure. Semaglutide provided adequate systemic exposure over the body weight range of 40-188 kg evaluated in the clinical trials.

Hepatic impairment & Renal impairment

Hepatic impairment *& renal impairment* did not impact the pharmacokinetics of Semaglutide in a clinically relevant manner.

Upper GI tract disease

Upper GI tract disease (chronic gastritis and/or gastroesophageal reflux disease) did not impact the pharmacokinetics of Semaglutide in a clinically relevant manner.

THERAPEUTIC INDICATIONS

Sem-O (Semaglutide) Tablet is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise:

- As monotherapy when metformin is considered inappropriate due to intolerance or contraindications.
- In combination with other medicinal products for the treatment of diabetes.

DOSAGE AND ADMINISTRATION

The starting dose of Sem-O (Semaglutide) Tablet is 3mg once daily for one month. After one month, the dose should be increased to a maintenance dose of 7mg once daily. After at least one month with a dose of 7mg once daily, the dose can be increased to a maintenance dose of 14mg once daily to further improve glycemic control. The maximum recommended single daily dose of Sem-O (Semaglutide) Tablet is 14mg. When Sem-O (Semaglutide) Tablet is used in combination with metformin and/or a sodium-glucose co-transporter-2 inhibitor (SGLT2i) or thiazolidinedione, the current dose of metformin and/or SGLT2i or thiazolidinedione can be continued. When Sem-O (Semaglutide) Tablet is used in combination with a sulfonylurea or with insulin, a reduction in the dose of sulfonylurea or insulin may be considered to reduce the risk of hypoglycaemia. Self-monitoring of blood glucose is not needed in order to adjust the dose of Sem-O (Semaglutide) Tablet. Blood glucose self-monitoring is necessary to adjust the dose of sulfonylurea and insulin, particularly when Sem-O (Semaglutide) Tablet is started and insulin is reduced. A stepwise approach to insulin reduction is recommended.

Missed dose

If a dose is missed, the missed dose should be skipped and the next dose should be taken the following day.

Special Population

Elderly

No dose adjustment is required based on age.

Renal impairment

No dose adjustment is required for patients with mild, moderate or severe renal impairment. Semaglutide is not recommended in patients with end-stage renal disease.

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment. Experience with the use of Semaglutide in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with Semaglutide.

Pediatric population

The safety and efficacy of Sem-O (Semaglutide) Tablet in children and adolescents below 18 years have not been established.

Method of Administration

Sem-O (Semaglutide) Tablet is a tablet for once-daily oral use.

- It should be taken on an empty stomach in the morning.
- It should be swallowed whole with a sip of water (up to half a glass of water equivalent to 120 ml). Do not take Semaglutide with other liquids besides water.
- Tablets should not be split, crushed or chewed.
- Patients should wait at least 30 minutes before eating or drinking or taking other oral medicinal products. Waiting less than 30 minutes decreases the absorption of Semaglutide.
- Do not take more than one tablet per day.

Switching from Sem-P (Semaglutide) Injection to Sem-O (Semaglutide) Tablets

- One week after discontinuing 0.5mg of subcutaneous Sem-P (Semaglutide) Injection, start 7mg or 14mg of Sem-O (Semaglutide) Tablets orally once daily.
- Switching recommendations for patients taking Sem-P (Semaglutide) Injection 0.25mg, 1mg, or 2mg subcutaneously once weekly to Sem-O (Semaglutide) Tablets are not available.

ADVERSE REACTIONS

Very common

Hypoglycaemia when used with insulin or sulfonylurea, nausea and diarrhea.

Common

Hypoglycemia when used with other oral antidiabetic products, decreased appetite, diabetic retinopathy complications, vomiting, abdominal pain, abdominal distension, constipation, dyspepsia, gastritis, gastrooesophageal reflux disease, flatulence, fatigue, increased lipase, increased amylase and dizziness.

Uncommon

Hypersensitivity, increased heart rate, eructation delayed gastric emptying, cholelithiasis, weight decreased and dysgeusia.

Rare

Anaphylactic reaction and acute pancreatitis.

Not Known

Intestinal obstruction.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
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).
- A prior serious hypersensitivity reaction to Semaglutide or to any of the excipients in Semaglutide Tablet. Serious hypersensitivity reactions including anaphylaxis and angioedema have been reported with Semaglutide Tablet.

PRECAUTIONS

WARNING: RISK OF THYROID C-CELL TUMORS
- In rodents, Semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether Semaglutide causes thyroid C-cell tumors, including Medullary Thyroid Carcinoma (MTC), in humans as human relevance of Semaglutide-induced rodent thyroid C-cell tumors has not been determined.
- Semaglutide is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Semaglutide and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Semaglutide.

General
Semaglutide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Diabetic ketoacidosis has been reported in insulin-dependent patients whom had rapid discontinuation or dose reduction of insulin when treatment with a GLP-1 receptor agonist is started.

Gastrointestinal Effects and Dehydration
Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions that can cause dehydration, which in rare cases can lead to a deterioration of renal function. Patients treated with Semaglutide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Risk of Thyroid C-Cell Tumors
Semaglutide Tablet is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of Semaglutide Tablet and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Semaglutide Tablet. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

Acute Pancreatitis
Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists, including Semaglutide Tablet. After initiation of Semaglutide Tablet, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, discontinue Semaglutide Tablet and initiate appropriate management.

Diabetic Retinopathy Complications
The effect of long-term glycemic control with Semaglutide on diabetic retinopathy complications has not been studied. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin
Patients receiving Semaglutide Tablet in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dosage of sulfonylurea (or other concomitantly administered insulin secretagogue) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

Acute Kidney Injury
There have been post marketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis, in patients treated with GLP-1 receptor agonists, including Semaglutide. Some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Monitor renal function when initiating or escalating doses of Semaglutide Tablet in patients reporting severe adverse gastrointestinal reactions.

Severe Gastrointestinal Adverse Reactions
Use of Semaglutide Tablet has been associated with gastrointestinal adverse reactions, sometimes severe. Semaglutide Tablet is not recommended in patients with severe gastroparesis.

Hypersensitivity Reactions
Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported in patients treated with Semaglutide Tablet. If hypersensitivity reactions occur, discontinue use of Semaglutide Tablet; treat promptly per standard of care, and monitor until signs and symptoms resolve.

Acute Gallbladder Disease
Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and post marketing. If cholelithiasis or cholecystitis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

Pulmonary Aspiration during General Anesthesia or Deep Sedation
Semaglutide Tablet delays gastric emptying. There have been rare post marketing reports of pulmonary aspiration in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation who had residual gastric contents despite reported adherence to preoperative fasting recommendations. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking Semaglutide Tablet.

Heart Failure
There is no therapeutic experience in patients with congestive heart failure and Semaglutide is therefore not recommended in these patients.

Effects on ability to drive and use machines
Semaglutide has no or negligible influence on the ability to drive or use machines. However, dizziness can be experienced mainly during dose escalation. Driving or use of machines should be done cautiously if dizziness occurs. When it is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.

Pregnancy
Semaglutide should not be used during pregnancy. Women of childbearing potential are recommended to use contraception when treated with Semaglutide. If a patient wishes to become pregnant, or pregnancy occurs, Semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life.

Nursing Mothers
No measurable concentrations of Semaglutide were found in breast milk of lactating women. Salcaprozate sodium was present in breast milk and some of its metabolites were excreted in breast milk at low concentrations. As a risk to a breast-fed child cannot be excluded, Semaglutide should not be used during breast-feeding.

DRUG INTERACTIONS
Semaglutide delays gastric emptying which may influence the absorption of other oral medicinal products.

Thyroxine
Total exposure (AUC) of thyroxine (adjusted for endogenous levels) was increased by 33% following administration of a single dose of levothyroxine. Maximum exposure (C_{max}) was unchanged. Monitoring of thyroid parameters should be considered when treating patients with Semaglutide at the same time as levothyroxine.

Warfarin and Other Coumarin Derivatives
Cases of decreased INR have been reported during concomitant use of acenocoumarol and Semaglutide. Upon initiation of Semaglutide treatment in patients on warfarin or other coumarin derivatives, frequent monitoring of INR is recommended.

Concomitant use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin
Semaglutide stimulates insulin release in the presence of elevated blood glucose concentrations. Patients receiving Semaglutide in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. When initiating Semaglutide, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia.

OVERDOSAGE
Effects of overdose with Semaglutide in clinical studies may be associated with gastrointestinal disorders. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment of the symptoms may be necessary, taking into account the long half-life of Semaglutide of approximately 1 week. There is no specific antidote for overdose with Semaglutide.

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Sem-O (Semaglutide) Tablets 3mg is available in blister pack of 14's.
Sem-O (Semaglutide) Tablets 7mg is available in blister pack of 14's.
Sem-O (Semaglutide) Tablets 14mg is available in blister pack of 14's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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