Sematide
(Semaglutide)

1 mg **0.50 mg** **0.25 mg**

Solution for Injection in a Single Dose Prefilled Syringe

سیماٹائیڈ
(سیماگلوٹائیڈ) پری فلڈ سرنج

SE-P-P-001

Composition:
Sematide 1 mg Injection
Solution for Injection in Prefilled Syringe
Each 0.75 mL contains:
Semaglutide.....1mg
Sematide 0.5 mg Injection
Solution for Injection in Prefilled Syringe
Each 0.375 mL contains:
Semaglutide.....0.5mg
Sematide 0.25 mg Injection
Solution for Injection in Prefilled Syringe
Each 0.188 mL contains:
Semaglutide.....0.25mg

WARNINGS:
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.
SUDDEN CHANGES TO YOUR EYESIGHT
If you notice a sudden loss of vision or rapidly worsening eyesight during treatment with semaglutide, urgently contact your doctor. This may be caused by a very rare side effect called non-arteritic anterior ischaemic optic neuropathy (NAION). Your doctor will refer you for an eye examination by an ophthalmologist and you may have to stop treatment with semaglutide.

DESCRIPTION
Semaglutide injection, for subcutaneous use, contains semaglutide, a human GLP-1 receptor agonist (or GLP-1 analog). Semaglutide peptide is synthesized by coupling of aminoacids through solid phase (Fmoc) method. 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 is C187H291N45O59 and the molecular weight is 4113.58 g/mol.
CLINICAL PARTICULARS
Therapeutic indications:
Sematide (Semaglutide) is indicated:
• As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
• To reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease.
• As monotherapy when metformin is considered inappropriate due to intolerance or contraindications
• In addition to other medicinal products for the treatment of diabetes.
Limitations of Use
• Semaglutide has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
• Semaglutide is not indicated for use in patients with type 1 diabetes mellitus.
Posology and method of administration
Important Administration Instructions
• Subcutaneous use. Sematide (Semaglutide) is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed without dose adjustment. Sematide (Semaglutide) should not be administered intravenously or intramuscularly.
• Inspect Sematide (Semaglutide) visually before use. It should appear clear and colorless. Do not use Sematide (Semaglutide) if particulate matter and coloration is seen.
• Administer Sematide (Semaglutide) once weekly, on the same day each week, at any time of the day, with or without meals.
• Inject Sematide (Semaglutide) subcutaneously to the abdomen, thigh, or upper arm. Instruct patients to use a different injection site each week when injecting in the same body region.
• When using Sematide (Semaglutide) with insulin, instruct patients to administer as separate injections and to never mix the products. It is acceptable to inject Sematide (Semaglutide) and insulin in the same body region, but the injections should not be adjacent to each other.
Recommended Dosage
• Initiate Sematide (Semaglutide) with a dosage of 0.25 mg injected subcutaneously once weekly for 4 weeks. The 0.25 mg dosage is intended for treatment initiation and is not effective for glycemic control.
• After 4 weeks on the 0.25 mg dosage, increase the dosage to 0.5 mg once weekly.
• If additional glycemic control is needed after at least 4 weeks on the 0.5 mg dosage, the dosage may be increased to 1 mg once weekly.
• If additional glycemic control is needed after at least 4 weeks on the 1 mg dosage, the dosage may be increased to 2 mg once weekly. The maximum recommended dosage is 2 mg once weekly.
• Semaglutide 0.25 mg is not a maintenance dose.
• The day of weekly administration can be changed if necessary as long as the time between two doses is at least 2 days (>48 hours).
• When Sematide (Semaglutide) is added to existing metformin and/or thiazolidinedione therapy or to a sodium-glucose cotransporter 2 (SGLT2) inhibitor, the current dose of metformin and/or thiazolidinedione or SGLT2 inhibitor can be continued unchanged.
• When Sematide (Semaglutide) is added to existing therapy of sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia
• Self-monitoring of blood glucose is not needed in order to adjust the dose of Sematide (Semaglutide). Blood glucose self-monitoring is necessary to adjust the dose of sulfonylurea and insulin, particularly when Sematide (Semaglutide) is started and insulin is reduced. A stepwise approach to insulin reduction is recommended.
• If a dose is missed, administer Sematide (Semaglutide) as soon as possible within 5 days after the missed dose. If more than 5 days have passed, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.
Special populations
Elderly No dose adjustment is required based on age. Therapeutic experience in patients
≥75 years of age is limited.
Renal impairment No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience with the use of semaglutide in patients with severe renal impairment is limited. Semaglutide is not recommended for use in patients with endstage 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.
Paediatric population The safety and efficacy of semaglutide in children and adolescents below 18 years have not yet been established. No data are available.
Contraindication
Semaglutide is contraindicated in patients with:
• A personal or family history of MTC or in patients with MEN 2
• A serious hypersensitivity reaction to semaglutide or to any of the excipients. Serious hypersensitivity reactions including anaphylaxis and angioedema have been reported with semaglutide.
Warnings and precautions
General Semaglutide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Semaglutide is not a substitute for insulin. 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. There is no experience in patients with congestive heart failure NYHA class IV and semaglutide is therefore not recommended in these patients.
Sudden Changes to Your Eyesight If you notice a sudden loss of vision or rapidly worsening eyesight during treatment with semaglutide, urgently contact your doctor. This may be caused by a very rare side effect called non-arteritic anterior ischaemic optic neuropathy (NAION). Your doctor will refer you for an eye examination by an ophthalmologist and you may have to stop treatment with semaglutide.
Gastrointestinal effects Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions. This should be considered when treating patients, with impaired renal function as nausea, vomiting, and diarrhoea may cause dehydration which could cause a deterioration of renal function.
Risk of Thyroid C-Cell Tumors In mice and rats, semaglutide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure at clinically relevant plasma exposures. It is unknown whether semaglutide causes thyroid C-cell tumors, including MTC, in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined.
Pancreatitis Acute pancreatitis has been observed with the use of GLP-1 receptor agonists.
Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, semaglutide should be discontinued; if confirmed, semaglutide should not be restarted. Caution should be exercised in patients with a history of pancreatitis.
Diabetic Retinopathy Complications In a 2-year trial involving patients with type 2 diabetes and high cardiovascular risk, more events of diabetic retinopathy complications occurred in patients treated with semaglutide (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline (semaglutide 8.2%, placebo 5.2%) than among patients without a known history of diabetic retinopathy (semaglutide 0.7%, placebo 0.4%).
Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. 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 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 dose 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 postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis, in patients treated with GLP-1 receptor agonists. 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 in patients reporting severe adverse gastrointestinal reactions.
Hypersensitivity Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported in patients treated with semiglutide. If hypersensitivity reactions occur, discontinue use of semiglutide; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity to semiglutide. Anaphylaxis and angioedema have been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema or anaphylaxis with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to anaphylaxis with semiglutide.
Acute Gallbladder Disease Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and postmarketing. In placebo-controlled trials, cholelithiasis was reported in 1.5% and 0.4% of patients-treated with semiglutide 0.5 mg and 1 mg, respectively. Cholelithiasis was not reported in placebo-treated patients. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.
Use in specific populations
Pregnancy Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. 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.

Breast-feeding In lactating rats, semaglutide was excreted in milk. As a risk to a breast-fed child cannot be excluded, semaglutide should not be used during breast-feeding.
Fertility The effect of semaglutide on fertility in humans is unknown. Semaglutide did not affect male fertility in rats. In female rats, an increase in oestrous length and a small reduction in number of ovulations were observed at doses associated with maternal body weight loss.
Females and Males of Reproductive Potential Women of childbearing potential are recommended to use contraception when treated with semaglutide. Discontinue semaglutide in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide.

Drug & Other Interactions

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.
Oral Medications Semaglutide causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, semaglutide did not affect the absorption of orally administered medications to any clinically relevant degree. Nonetheless, caution should be exercised when oral medications are concomitantly administered with semaglutide.

Carcinogenesis, Mutagenesis, Impairment of fertility

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity or genotoxicity.
Non-lethal thyroid C-cell tumours observed in rodents are a class effect for GLP-1 receptor agonists. In 2-year carcinogenicity studies in rats and mice, semaglutide caused thyroid C-cell tumours at clinically relevant exposures. No other treatment related tumours were observed. The rodent C-cell tumours are caused by a nongenotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. The relevance for humans is considered to be low, but cannot be completely excluded.
Semaglutide was not mutagenic or clastogenic in a standard battery of genotoxicity tests (bacterial mutagenicity (Ames), human lymphocyte chromosome aberration, rat bone marrow micronucleus).
In a combined fertility and embryo-fetal development study in rats, subcutaneous doses of 0.01, 0.03 and 0.09 mg/kg/day (0.06-, 0.2-, and 0.6-fold the MRHD) were administered to male and female rats. Males were dosed for 4 weeks prior to mating, and females were dosed for 2 weeks prior to mating and throughout organogenesis until Gestation Day 17. No effects were observed on male fertility. In females, an increase in estrus cycle length was observed at all dose levels, together with a small reduction in numbers of corpora lutea at ≥0.03 mg/kg/day. These effects were likely an adaptive response secondary to the pharmacological effect of semaglutide on food consumption and body weight.

Adverse Reactions

Frequencies are defined as: very common: (≥1/10); common: (≥1/100 to <1/10); uncommon: (≥1/1 000 to <1/100); rare: (≥1/10 000 to <1/1 000); very rare:(<1/10 000) and not known: cannot be estimated from available data.
Very common: Hypoglycaemia when used with insulin or sulfonylurea, Nausea, Diarrhoea.
Common: Hypoglycaemia when used with other OADs, Decreased appetite, Dizziness, Diabetic retinopathy complications, Vomiting, Abdominal pain, Abdominal distension, Constipation, Dyspepsia, Gastritis, Gastrooesophageal reflux disease, Eructation, Flatulence, Cholelithiasis, Fatigue, Increased Lipase, Increased amylase, Weight Decreased.
Uncommon: Hypersensitivity, Dysgeusia, Increased heart rate, Acute pancreatitis Delayed gastric emptying, Injection site reactions.
Rare: Anaphylactic reaction
Very Rare (may affect up to 1 in 10 000 people)
A medical condition of the eye called non-arteritic anterior ischaemic optic neuropathy (NAION), which may cause loss of vision to one of your eyes without any pain. You should immediately contact your doctor if you notice sudden or gradually worsening eyesight.
Not known: Angioedema
Immunogenicity: Consistent with the potentially immunogenic properties of medicinal products containing proteins or peptides, patients may develop antibodies following treatment with semaglutide. The proportion of patients tested positive for anti-semaglutide antibodies at any time point post-baseline was low (1–3%) and no patients had anti- semaglutide neutralising antibodies or anti-semaglutide antibodies with endogenous
GLP-1 neutralising effect at end-of-trial.
Postmarketing Experience: Ileus, anaphylaxis, angioedema, rash, urticaria, cholecystitis, cholecystectomy.

Reporting of side effects

If you get any side effects, talk to your doctor, or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly https://bfbio.com/drug-safety/.
By reporting side effects, you can help provide more information on the safety of this medicine.

Effects on ability to drive and use machines

Semaglutide has no or negligible influence on the ability to drive or use machines.
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.

Overdosage

Overdoses of up to 4 mg in a single dose, and up to 4 mg in a week have been reported in clinical trials. The most commonly reported adverse reaction was nausea.
All patients recovered without complications. There is no specific antidote for overdose with semaglutide. 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 for these symptoms may be necessary, taking into account the long half-life of semaglutide of approximately 1 week.

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.

Pharmacodynamics

Semaglutide lowers fasting and postprandial blood glucose and reduces body weight. All pharmacodynamic evaluations were performed after 12 weeks of treatment (including dose escalation) at steady state with semaglutide 1 mg.
Fasting and postprandial glucose Semaglutide reduces fasting and postprandial glucose concentrations. In patients with type 2 diabetes, treatment with semaglutide 1 mg resulted in reductions in glucose in terms of absolute change from baseline (mmol/L) and relative reduction compared to placebo (%) for fasting glucose (1.6 mmol/L; 22% reduction), 2 hour postprandial glucose (4.1 mmol/L; 37% reduction), mean 24 hour glucose concentration (1.7 mmol/L; 22% reduction) and postprandial glucose excursions over 3 meals (0.6-1.1 mmol/L) compared with placebo. Semaglutide lowered fasting glucose after the first dose.
Beta-cell function and insulin secretion Semaglutide improves beta-cell function. Compared to placebo, semaglutide improved first- and second-phase insulin response with a 3– and 2–fold increase, respectively, and increased maximal beta-cell secretory capacity in patients with type 2 diabetes. In addition, semaglutide treatment increased fasting insulin concentrations compared to placebo.
Glucagon secretion Semaglutide lowers the fasting and postprandial glucagon concentrations. In patients with type 2 diabetes, semaglutide resulted in the following relative reductions in
glucagon compared to placebo: fasting glucagon (8–21%), postprandial glucagon response (14–15%) and mean 24 hour glucagon concentration (12%).
Glucose dependent insulin and glucagon secretion Semaglutide lowered high blood glucose concentrations by stimulating insulin secretion and lowering glucagon secretion in a glucose dependent manner. With semaglutide, the insulin secretion rate in patients with type 2 diabetes was comparable to that of healthy subjects. During induced hypoglycaemia, semaglutide compared to placebo did not alter the counter regulatory responses of increased glucagon and did not impair the decrease of C-peptide in patients with type 2-diabetes.
Gastric emptying Semaglutide caused a minor delay of early postprandial gastric emptying, thereby reducing the rate at which glucose appears in the circulation postprandially.
Appetite, energy intake and food choice. Semaglutide compared to placebo lowered the energy intake of 3 consecutive ad libitum meals by 18-35%. This was supported by a semaglutide-induced suppression of appetite in the fasting state as well as postprandially, improved control of eating, less food cravings and a relative lower preference for high fat food.
Fasting and postprandial lipids Semaglutide compared to placebo lowered fasting triglyceride and very low density lipoproteins (VLDL) cholesterol concentrations by 12% and 21%, respectively. The postprandial triglyceride and VLDL cholesterol response to a high fat meal was reduced by >40%.
Cardiac electrophysiology (QTc) The effect of semaglutide on cardiac repolarization was tested in a thorough QTc trial. Semaglutide did not prolong QTc intervals at dose levels up to 1.5 mg at steady state.

Pharmacokinetics

Compared to native GLP-1, semaglutide has a prolonged half-life of around 1 week making it suitable for once weekly subcutaneous administration. The principal mechanism of protraction is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilised against degradation by the DPP-4 enzyme.
Absorption Maximum concentration was reached 1 to 3 days post dose. Steady state exposure was achieved following 4–5 weeks of once weekly administration. Semaglutide exposure increased in a dose proportional manner for doses of 0.5 mg, 1 mg and 2 mg. Similar exposure was achieved with subcutaneous administration of semaglutide in the abdomen, thigh, or upper arm. Absolute bioavailability of subcutaneous semaglutide was 89%.
Distribution The mean volume of distribution of semaglutide following subcutaneous administration in patients with type 2 diabetes was approximately 12.5 L. Semaglutide was extensively bound to plasma albumin (>99%).
Elimination The apparent clearance of semaglutide in patients with type 2 diabetes is approximately 0.05 L/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for about 5 weeks after the last dose.
Metabolism The primary route of elimination for semaglutide is metabolism following 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.
Excretion The primary excretion routes of semaglutide-related material are via the urine and feces. Approximately 2/3 of semaglutide-related material were excreted in urine and approximately 1/3 in faeces. Approximately 3% of the dose is excreted in the urine as intact semaglutide.
Special population
Body weight Body weight has an effect on the exposure of semaglutide. Higher body weight
results in lower exposure; a 20% difference in body weight between individuals will result in an approximate 16% difference in exposure. Semaglutide doses of 0.5 mg and 1 mg provide adequate systemic exposure over a body weight range of 40–198 kg.

STORAGE

Refrigerate at 2°C to 8°C. Do not Freeze.

INSTRUCTIONS

Keep out of reach of children. Protect from heat and light.
To be sold on Prescription of a registered medical practitioner only.
Do not shake the prefilled syringe.

Manufactured by:
BF BIOSCIENCES
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