

PHARMACOLOGICAL CHARACTERISTICS OF SEMAGLUTIDE

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Abstract: Semaglutide is a GLP-1 agonist, with a modified side chain, and can be administered subcutaneously or orally. It was approved for medical use in the USA in 2017. It is indicated: for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise, as monotherapy when metformin is considered inappropriate due to intolerance or contraindications, in addition to other diabetes medications. It works through numerous mechanisms, such as increasing insulin secretion (glucose-dependent), inhibiting the release of glucagon and suppressing hepatic gluconeogenesis. Semaglutide has pharmacokinetic characteristics compatible with once-weekly dosing and an elimination half-life of approximately 1 week. The maximum concentration is reached within 1 to 3 days after dosing. Steady-state exposure was achieved 4-5 weeks after the first one-week administration.

Key words: glucagon-like peptide-1 (GLP-1) agonists, type 2 diabetes, semaglutide, obesity, pharmacodynamic, pharmacokinetic.

1. INTRODUCTION

Semaglutide is a glucagon-like peptide 1 (GLP-1) analog used to manage type 2 diabetes along with lifestyle changes, such as dietary restrictions and increased physical activity. The subcutaneous injection is administered once weekly and the tablet is administered once a day. Semaglutide offers a competitive advantage over other drugs used to manage diabetes, which may require several daily doses. Clinical trials have determined that this drug reduces glycosylated hemoglobin (HbA1c) levels and reduces body weight, proving to be effective for patients with type 2 diabetes [1]. Semaglutide improves the efficiency of incretin function by activating the GLP-1 receptor. It works through numerous mechanisms, such as increasing insulin secretion (glucose-dependent), inhibiting the release of glucagon and suppressing hepatic gluconeogenesis, thereby reducing fasting and postprandial glucose levels [2], [3]. Semaglutide has pharmacokinetic characteristics compatible with once-weekly dosing and an elimination half-life of approximately 1 week. The maximum concentration is reached within 1 to 3 days after dosing. The absolute bioavailability of semaglutide is 89%. The mean volume of distribution in patients with type 2 diabetes is approximately 12.5 l, with semaglutide largely bound to plasma albumin (> 99%). Semaglutide is metabolized through proteolytic cleavage of the peptide chain and sequential β -oxidation of the fatty acid side chain. The primary routes of excretion include urine and faeces [6].

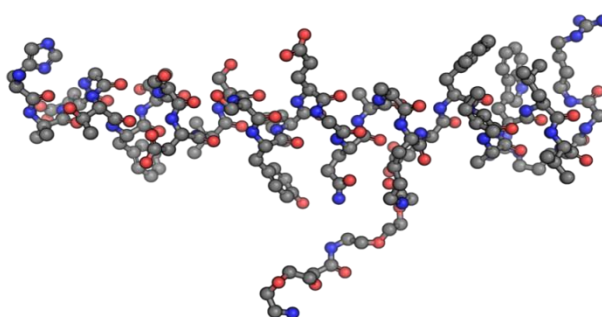


Figure 1 - Semaglutide structure

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2. PHARMACODYNAMIC CHARACTERISTICS AND MECHANISM OF ACTION

Semaglutide improves the efficiency of incretin function by activating the GLP-1 receptor. It works through numerous mechanisms, such as increasing insulin secretion (glucose-dependent), inhibiting the release of glucagon and suppressing hepatic gluconeogenesis, thereby reducing fasting and postprandial glucose levels. Semaglutide showed a favorable effect on proinsulin compared to insulin, indicating improved efficiency and functioning of β -cells and increased insulin production. Also, it showed an improvement in insulin sensitivity, which is probably mediated by a decrease in body weight, and the decrease in body weight is attributed to reduced energy intake and slowing of gastric motility [2]-[3]. Semaglutide is an agonist of the glucagon-like peptide-1 receptor, and its action leads to a decrease in blood glucose levels. This reduction is theorized to be caused by the incretin mimic, glucagon-like peptide-1. It also appears to improve the growth of pancreatic β -cells, which are responsible for the production and release of insulin. In addition, it inhibits the production of glucagon, thus affecting the release of stored carbohydrates from the liver and the synthesis of glucose. It leads to a decrease in food intake, because it reduces appetite and slows down the digestion of food in the stomach, thus helping to reduce body weight [4], [5].

Semaglutide reduces fasting and postprandial glucose levels. In patients with type 2 diabetes, treatment with semaglutide 1 mg resulted in a reduction in glucose in terms of absolute change from baseline (mmol/l) and relative change, compared to placebo (%), for fasting glucose (1.6 mmol/l; 22%), postprandial glucose, after 2 hours (4.1 mmol/l; 37%), for the mean glucose level after 24 hours (1.7 mmol/l; 22%) and the change of glucose after meals during three meals compared to placebo (0.6-1.2 mmol/l) [6].

Compared with placebo, semaglutide improved the first and second phases of the insulin response with a threefold and twofold increase, respectively, and an increased β -cell secretory capacity, in patients with type 2 diabetes. In addition, semaglutide treatment caused an increase in fasting insulin concentrations relative to on placebo. In patients with type 2 diabetes, administration of semaglutide resulted in the following relative reductions in glucagon compared to placebo: fasting glucagon (8-21%), postprandial glucagon response (14-15%), mean glucagon concentration over 24 hours (12%). Semaglutide lowers high blood glucose levels by stimulating insulin secretion and reducing glucagon secretion in a glucose-dependent manner. With semaglutide, the rate of insulin secretion in patients with type 2 diabetes was comparable to that in healthy subjects [6].

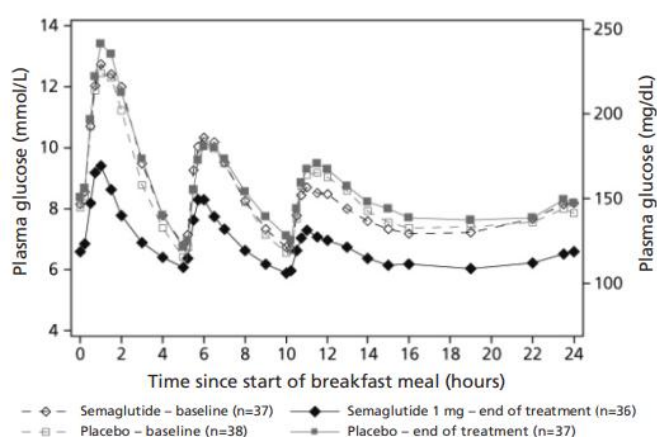


Figure 2 - Mean 24-hour plasma glucose profiles in patients with type 2 diabetes (baseline) and after 12 weeks of semaglutide or placebo

During induced hypoglycemia, compared with placebo, semaglutide did not alter the counterregulatory responses to increased glucagon, and did not reduce C-peptide secretion in patients with type 2 diabetes. It caused a smaller delay in early postprandial gastric emptying, thereby reducing the rate of appearance of glucose in the circulation after a meal. Compared to placebo, semaglutide reduced the energy intake of three consecutive *ad libitum* meals by 18-35%. This is supported by semaglutide-induced appetite suppression, both in the fasted and postprandial state, improved food control, reduced food cravings, and a relative lower preference for high-fat foods. Compared to

placebo, semaglutide reduced fasting triglyceride and VLDL levels by 12% and 21%, respectively. Postprandial triglyceride levels and VLDL after a high-fat meal were reduced by > 40% [6].

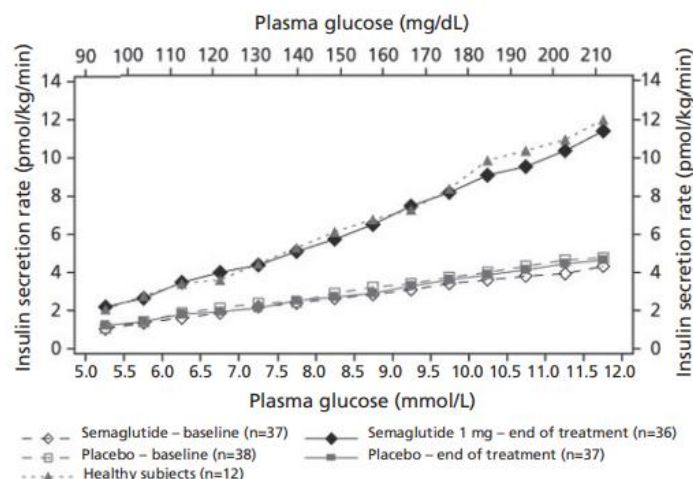


Figure 3 - Mean insulin secretion rate versus glucose concentration in patients with type 2 diabetes during graded glucose infusion (baseline) and after 12 weeks of semaglutide or placebo compared with healthy, untreated subjects

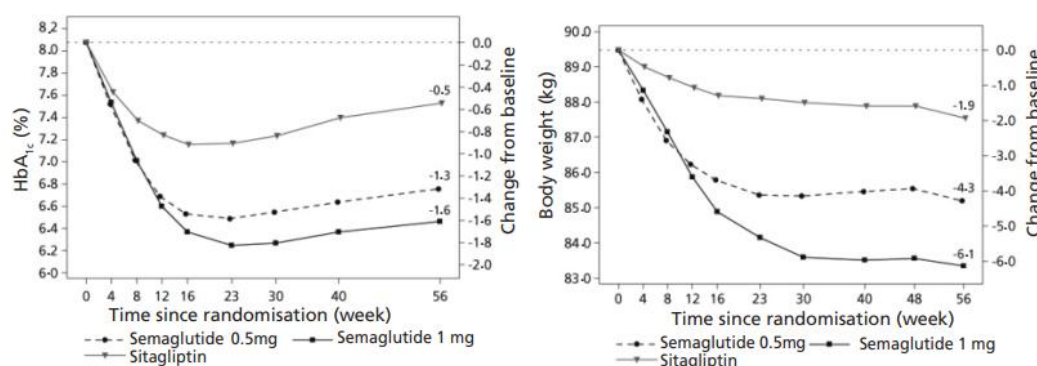


Figure 4 - Change in HbA_{1c} (%) and body weight (kg) (initial value and after 56 weeks)

Both improvement of glycemic control and reduction of cardiovascular morbidity and mortality are integral to the treatment of type 2 diabetes. The efficacy and safety of semaglutide, at doses of 0.5 mg and 12 mg once weekly, were evaluated in six randomized controlled phase 3a trials, which included 7215 patients with (of which 4107 were tested with semaglutide). Five studies (SUSTAIN 1-5) had as their primary objective the assessment of glycemic efficiency, while one trial (SUSTAIN 6) had as their primary objective the assessment of objective cardiovascular outcome. The efficacy and safety of semaglutide (2 mg once weekly) was evaluated in a phase 3b study (SUSTAIN FORTE), which included 961 patients. In addition, a phase 3b trial (SUSTAIN 7) involving 1201 patients was conducted to compare the efficacy and safety of semaglutide (0.5 mg and 1 mg once weekly) versus dulaglutide (0.75 mg and 1, 5 mg once a week). A phase 3b trial (SUSTAIN 9) was also conducted to test the efficacy and safety of semaglutide as an adjunct to treatment with SGLT2 inhibitors. Semaglutide treatment was shown to be durable, statistically superior and clinically significant for reducing HbA_{1c} and body weight up to 2 years compared to placebo and currently active treatment (sitagliptin, insulin glargine, exenatide and dulaglutide). Age, gender, race, ethnicity, initial BMI, body weight, duration of type 2 diabetes, and level of kidney function impairment did not affect the effectiveness of semaglutide. Results target the treatment period in all randomized subjects (analyses based on mixed models for repeated measures or multiple imputation). In addition to the above, a phase 3b trial (SUSTAIN 11) was also conducted to examine the effect of semaglutide in relation to insulin aspart, and as an addition to metformin and optimized insulin glargine (U100) [6].

3. PHARMACOKINETIC CHARACTERICS

Semaglutide has pharmacokinetic characteristics compatible with once-weekly dosing and an elimination half-life of approximately 1 week. The maximum concentration is reached within 1 to 3 days after dosing. Steady-state exposure was achieved 4-5 weeks after the first one-week administration. In patients with type 2 diabetes, the mean concentrations after subcutaneous administration of 0.5 mg and 1 mg semaglutide were approximately 16 nmol/l and 30 nmol/l, respectively. Semaglutide exposure increases proportionally to the dose, for doses of 0.5 mg and 1 mg. Similar exposure was achieved by subcutaneous administration of semaglutide in the abdomen, thigh or upper arm. The absolute bioavailability of semaglutide is 89%. The mean volume of distribution in patients with type 2 diabetes is approximately 12.5 l, with semaglutide largely bound to plasma albumin (> 99%). Semaglutide is metabolized through proteolytic cleavage of the peptide chain and sequential β -oxidation of the fatty acid side chain. The primary routes of excretion include urine and faeces. About 3% of the dose is excreted unchanged in the urine. The 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 approximately 5 weeks from the last administered dose [6].

Oral semaglutide has low absolute bioavailability and variable absorption. Daily administration according to the recommended dose in combination with a long half-life reduces the daily fluctuation of exposure. The pharmacokinetics of semaglutide have been extensively characterised in healthy subjects and patients with type 2 diabetes. Following oral administration, peak plasma concentrations of semaglutide occurred 1 hour post-dose. Steady-state exposure was achieved after 4-5 weeks of once daily dosing. In patients with type 2 diabetes, mean steady-state concentrations were approximately 6.7 nmol/l and 14.6 nmol/l with semaglutide 7 mg and 14 mg, respectively, with 90% of subjects treated with semaglutide 7 mg having mean concentrations between 1.7 and 22.7 nmol/l and 90% of subjects treated with 14 mg semaglutide had a mean concentration between 3.7 and 41.3 nmol/l. Systemic exposure to semaglutide increased in a dose-proportional manner. Based on *in vitro* data, salcaprosate sodium facilitates the absorption of semaglutide. Absorption of semaglutide occurs predominantly in the stomach. The estimated bioavailability of semaglutide is approximately 1% after oral administration. Inter-subject variability in absorption was high (coefficient of variation was approximately 100%). Variability estimation of intra-subject bioavailability was not reliable. Absorption of semaglutide is reduced when taken with food or large amounts of water. A longer fasting period after dosing results in greater absorption. The estimated absolute volume of distribution is approximately 8 l in subjects with type 2 diabetes. Semaglutide is largely bound to plasma proteins (> 99%). Semaglutide is metabolized through proteolytic cleavage of the peptide backbone and sequential β -oxidation of the fatty acid side chain. The enzyme neutral endopeptidase (NEP) is expected to be involved in the metabolism of semaglutide. The primary routes of excretion of semaglutide-related material are via urine and feces. Approximately 3% of the absorbed dose is excreted as unchanged semaglutide via urine. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for approximately 5 weeks after the last dose. The clearance of semaglutide in patients with type 2 diabetes is approximately 0.04 l/h. The effect of switching between oral and subcutaneous semaglutide cannot be easily predicted due to the large pharmacokinetic variability of oral semaglutide. Exposure after oral semaglutide 14 mg once daily is comparable to subcutaneous semaglutide 0.5 mg once weekly. An oral dose equivalent to 1.0 mg of subcutaneous semaglutide has not been determined [7], [8], [9].

Age had no effect on the pharmacokinetics of semaglutide based on data from phase 3a studies, which included patients aged 20 to 86 years. Gender, race, and ethnicity had no effect on the pharmacokinetics of semaglutide. Body weight affects semaglutide exposure. Higher body weight results in lower exposure; a 20% difference in body weight between individuals will result in approximately a 16% difference in exposure. Semaglutide doses of 0.5 mg and 1 mg provide adequate systemic exposure across the body weight range of 40-198 kg. Renal impairment did not affect the pharmacokinetics of semaglutide in a clinically relevant manner. This was demonstrated when a single dose of 0.5 mg was administered to patients with varying degrees of renal impairment. renal impairment (mild, moderate, severe, dialysis patients) compared to patients with normal renal

function. This has also been shown for subjects with type 2 diabetes and impaired renal function based on data from phase 3a studies, and if the experience in patients with end-stage renal disease was limited. The same was shown in patients with impaired liver function, where it was concluded that generalization of liver function has no effect on the pharmacokinetics of semaglutide [6], [10], [11].

4. CONCLUSION

Semaglutide is a GLP-1 agonist, with a modified side chain, and can be administered subcutaneously or orally. It was approved for medical use in the USA in 2017. It is indicated: for the treatment of adults with insufficiently controlled type 2 diabetes as a supplement to diet and exercise, as monotherapy when metformin is considered inappropriate due to intolerance or contraindications, or in addition to other drugs for the treatment of diabetes. Its antihyperglycemic activity was established for the first time in a series of clinical studies on adult, elderly and obese patients with or without kidney/liver damage or cardiovascular disorders. Although gastrointestinal symptoms are relatively common, it is generally well tolerated, and at the same time provides better control of hypoglycemia as a monotherapy, and patient adherence is very good compared to other hypoglycemic treatments. Semaglutide has pharmacokinetic characteristics compatible with once-weekly dosing and an elimination half-life of approximately 1 week. The maximum concentration is reached within 1 to 3 days after dosing. The absolute bioavailability of semaglutide is 89%. The mean volume of distribution in patients with type 2 diabetes is approximately 12.5 l, with semaglutide largely bound to plasma albumin (> 99%). Semaglutide is metabolized through proteolytic cleavage of the peptide chain and sequential β -oxidation of the fatty acid side chain. The primary routes of excretion include urine and faeces.

5. REFERENCES

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