50 mm

SEMAGLUTIDE INJECTION

PRESCRIBING INFORMATION

91 8551 1 6039731

50 mm

PRESCRIBING INFORMATION

SEMAGLUTIDE INJECTION

91 8551 1 6039731

150 mm

To be sold by retail on the prescription of Endocrinologist, Internal medicine specialist only

PRESCRIBING INFORMATION

SEMAGLUTIDE INJECTION

1. Generic Name

Semaglutide Injection 0.68mg/ml (1 mg/1.5 ml Prefilled Pen)
Semaglutide Injection 1.34mg/ml (2 mg/1.5 ml Prefilled Pen)
Semaglutide Injection 1.34mg/ml (4 mg/3 ml Prefilled Pen)
Semaglutide Injection 2.68mg/ml (8 mg/3 ml Prefilled Pen)
(For use in Type 2 Diabetes Mellitus management - Please refer section 4.1 for details)

2. Qualitative and Quantitative Composition

Semaglutide Injection 0.68mg/ml (1 mg/1.5 ml Prefilled Pen)
Each 1 ml contains
Semaglutide.................................0.68mg
Phenol IP 5.50 mg
(As preservative)
Water for Injections IP q.s.
1.5 ml in prefilled pen capable of delivering 4 doses of 0.25 mg

Semaglutide Injection 1.34mg/ml (2 mg/1.5 ml Prefilled Pen)
Each 1 ml contains
Semaglutide.................................1.34mg
Phenol IP 5.50 mg
(As preservative)
Water for Injections IP q.s.
1.5 ml in prefilled pen capable of delivering 4 doses of 0.5 mg.

Semaglutide Injection 1.34mg/ml (4 mg/3 ml Prefilled Pen)
Each 1 ml contains
Semaglutide.................................1.34mg
Phenol IP 5.50 mg
(As preservative)
Water for Injections IP q.s.
3 ml in prefilled pen capable of delivering 4 doses of 1 mg.

Semaglutide Injection 2.68mg/ml (8 mg/3 ml Prefilled Pen)
Each 1 ml contains
Semaglutide.................................2.68mg
Phenol IP 5.50 mg
(As preservative)
Water for Injections IP q.s.
3 ml in prefilled pen capable of delivering 4 doses of 2 mg.

Each ml of solution also contains the following inactive ingredients: Disodium phosphate dihydrate, 1.42 mg; Propylene glycol, 14.0 mg; Phenol, 5.50 mg; and Water for injections. Hydrochloric acid or Sodium hydroxide may be added to adjust pH.

3. Dosage Form and Strengths

- Dosage Form: Solution for injection.
- Strengths:
  - Semaglutide Injection 0.68 mg/ml, 1 mg/1.5 ml Prefilled pen
  - Semaglutide Injection 1.34 mg/ml, 2 mg/1.5 ml prefilled pen
  - Semaglutide Injection 1.34 mg/ml, 4 mg/3 ml prefilled pen
  - Semaglutide Injection 2.68 mg/ml, 8 mg/3 ml prefilled pen

4. Clinical Particulars

4.1 Therapeutic Indication

Semaglutide is a glucagon-like peptide 1 (GLP-1) receptor agonist indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy, when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes

4.2 Posology and Method of Administration

Posology

The starting dose is 0.25 mg semaglutide once weekly. After 4 weeks the dose should be increased to 0.5 mg once weekly. After at least 4 weeks with a dose of 0.5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycemic control. After at least 4 weeks with a dose of 1 mg once weekly, the dose can be increased to 2 mg once weekly to further improve glycemic control.

Semaglutide 0.25 mg is not a maintenance dose. Weekly doses higher than 2 mg are not recommended.
When 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 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 hypoglycemia.
Self-monitoring of blood glucose is not needed in order to adjust the dose of semaglutide. Blood glucose self-monitoring is necessary to adjust the dose of sulfonylurea and insulin, particularly when semaglutide is started and insulin is reduced. A stepwise approach to insulin reduction is recommended.

Missed dose: If a dose is missed, it should be administered as soon as possible and within 5 days after the missed dose. If more than 5 days have passed, the missed dose should be skipped, and the next dose should be administered on the regularly scheduled day. In each case, patients can then resume their regular "once weekly dosing" schedule.
Changing the dosing day: The day of weekly administration can be changed, if necessary, as long as the time between two doses is at least 3 days (>72 hours). After selecting a new dosing day, once-weekly dosing should be continued.
Special Population:
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 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 semaglutide in children (below 18 years) have not been established.

Method of Administration

Subcutaneous use

Semaglutide is to be injected subcutaneously into the abdomen, in the thigh or in the upper arm. The injection site can be changed without dose adjustment. Semaglutide should not be administered intravenously or intramuscularly.
Semaglutide is to be administered once weekly at any time of the day, with or without meals.

4.3 Contraindication

- A personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- A serious hypersensitivity reaction to semaglutide or to any of the excipients.

4.4 Special warnings and precautions for use

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 who 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.

Pulmonary Aspiration during General Anesthesia or Deep Sedation

Semaglutide injection delays gastric emptying. There have been rare cases of pulmonary aspiration reported in patients receiving GLP-1 receptor agonists undergoing general anesthesia or deep sedation. Therefore, the increased risk of residual gastric content due to delayed gastric emptying should be considered prior to performing procedures with general anesthesia or deep sedation.

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 diarrhea may cause dehydration which could cause a deterioration of renal function.

Acute 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.

Hypoglycemia

Patients treated with semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with semaglutide.

Diabetic Retinopathy

In patients with diabetic retinopathy treated with insulin and semaglutide, an increased risk of developing diabetic retinopathy complications has been observed. Caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin. These patients should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. There is no experience with semaglutide 2 mg in patients with type 2 diabetes with uncontrolled or potentially unstable diabetic retinopathy and semaglutide 2 mg is therefore not recommended in these patients.

Acute Kidney Injury due to Volume Depletion

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. 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 Reactions

Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported in patients treated with Semaglutide. If hypersensitivity reactions occur, discontinue use of Semaglutide; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity to Semaglutide.
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 semaglutide.

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. In placebo-controlled trials, cholelithiasis was reported in 1.5% and 0.4% of patients treated with Semaglutide 0.5 mg and 1 mg, respectively. Cholelithiasis was not reported in placebo-treated patients.

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.
Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the post-marketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans.

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with semaglutide. Such monitoring may increase the risk of unnecessary procedures, due to the low-test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin value may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. 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.

4.5 Drug Interactions

Semaglutide delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. Semaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption.

Paracetamol
Semaglutide delays the rate of gastric emptying as assessed by paracetamol pharmacokinetics during a standardized meal test. Paracetamol AUC0-60min and Cmax were decreased by 27% and 23%, respectively, following concomitant use of semaglutide 1 mg. The total paracetamol exposure (AUC0-5h) was not affected. No clinically relevant effect on the rate of gastric emptying was observed with semaglutide 2.4 mg, following 20 weeks of administration of semaglutide, probably due to a tolerance effect. No dose adjustment of paracetamol is necessary when administered with semaglutide.
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.
Oral contraceptives
Semaglutide is not anticipated to decrease the effect of oral contraceptives as semaglutide did not change the overall exposure of ethinylestradiol and levonorgestrel to a clinically relevant degree when an oral contraceptive combination medicinal product (0.03 mg ethinylestradiol/0.15 mg levonorgestrel) was co-administered with semaglutide. Exposure of ethinylestradiol was not affected; an increase of 20% was observed for levonorgestrel exposure at steady state. Cmax was not affected by any of the compounds.
Atorvastatin
Semaglutide did not change the overall exposure of atorvastatin following a single dose administration of atorvastatin (40 mg). Atorvastatin Cmax was decreased by 38%. This was assessed not to be clinically relevant.
Digoxin
Semaglutide did not change the overall exposure or Cmax of digoxin following a single dose of digoxin (0.5 mg).
Metformin
Semaglutide did not change the overall exposure or Cmax of metformin following dosing of 500 mg twice daily over 3.5 days.
Warfarin and other coumarin derivatives
Semaglutide did not change the overall exposure or Cmax of R- and S-warfarin following a single dose of warfarin (25 mg), and the pharmacodynamic effects of warfarin as measured by the international normalized ratio (INR) were not affected in a clinically relevant manner. However, 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.

4.6 Use in Special Populations

Pregnant Women

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.

Lactating Women

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.

Women of Childbearing potential

Women of childbearing potential are recommended to use contraception when treated with semaglutide.

Pediatric Patients

Safety and efficacy of semaglutide have not been established in pediatric patients (younger than 18 years).

Geriatric Patients

No overall differences in safety or efficacy were detected between these older patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

4.7 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 hypoglycemia while driving and using machines.

4.8 Undesirable effects

Summary of safety profile

The information provided below is derived from the phase III study conducted by Intas Pharmaceuticals (Study code: 0130-24). The Safety profile of Intas semaglutide subcutaneous injection against Innovator semaglutide subcutaneous injection, Ozempic was evaluated in a randomized, open-label, multicenter, active-controlled, parallel-group, phase III study in participants with type 2 diabetes (T2D) who had poor glycaemic control after lifestyle modification and who were inadequately controlled on metformin.
In Study 0130-24, all the 223 randomized participants received at least one dose of study medication and were included in the safety analysis set: 112 participants in the Test arm and 111 participants in the Reference arm.
The most frequently reported treatment emergent adverse events during the study were Diarrhea (7.6 % participants), Nausea (7.6 % participants) and Vomiting (7.6 % participants).
In general, these reactions were mild or moderate in severity and of short duration. The clinical trial safety data generated by the Intas Pharmaceuticals demonstrated a safety profile comparable to that reported in published clinical studies, indicating concordance across data sources.

Table 1: Lists of adverse reactions based on System organ Class from study 0130-24

System Organ Class	MedDRA (PT) (Version 28.1)	Semaglutide Test (N=112) n (%) e	Semaglutide-Reference (N=111) n (%) e	Total (N=223) n (%) e
Blood and lymphatic system disorders	Anaemia	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
	Leukocytosis	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
	Thrombocytopenia	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
Congenital, familial and genetic disorders	Hydrocele	0 (0.0) 0	1 (0.9) 2	1 (0.4) 2
Eye disorders	Cataract	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
	Macular oedema	1 (0.9) 2	0 (0.0) 0	1 (0.4) 2
Gastrointestinal disorders	Abdominal discomfort	4 (3.6) 4	4 (3.6) 5	8 (3.6) 9
	Abdominal distension	3 (2.7) 4	6 (5.4) 7	9 (4.0) 11
	Constipation	7 (6.3) 17	0 (0.0) 0	7 (3.1) 17
	Diarrhoea	7 (6.3) 31	10 (9.0) 14	17 (7.6) 45
	Dyspepsia	2 (1.8) 4	1 (0.9) 1	3 (1.3) 5
	Flatulence	4 (3.6) 4	2 (1.8) 2	6 (2.7) 6
	Gastritis	7 (6.3) 8	6 (5.4) 6	13 (5.8) 14
	Gastrooesophageal reflux disease	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
	Hyperchlorhydria	2 (1.8) 5	4 (3.6) 4	6 (2.7) 9
	Nausea	8 (7.1) 9	9 (8.1) 9	17 (7.6) 18
	Vomiting	7 (6.3) 7	10 (9.0) 10	17 (7.6) 17
General disorders and administration site conditions	Asthenia	3 (2.7) 3	6 (5.4) 7	9 (4.0) 10
	Fatigue	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
	Pain	2 (1.8) 2	2 (1.8) 2	4 (1.8) 4
	Pyrexia	4 (3.6) 4	0 (0.0) 0	4 (1.8) 4
Infections and infestations	Candida infection	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
	Furuncle	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
	Nasopharyngitis	1 (0.9) 1	1 (0.9) 1	2 (0.9) 2
	Tinea versicolour	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
	Upper respiratory tract infection	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
Investigations	Glomerular filtration rate decreased	1 (0.9) 1	1 (0.9) 1	2 (0.9) 2
	Lipase increased	2 (1.8) 2	0 (0.0) 0	2 (0.9) 2
	Low density lipoprotein increased	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
	Weight decreased	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
Metabolism and nutrition disorders	Decreased appetite	3 (2.7) 3	8 (7.2) 8	11 (4.9) 11
	Hypercalcitoninaemia	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
	Hyperglycaemia	6 (5.4) 9	3 (2.7) 4	9 (4.0) 13
	Hyperkalaemia	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
	Hypertriglyceridaemia	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
	Hypoglycaemia	6 (5.4) 8	7 (6.3) 9	13 (5.8) 17
Musculoskeletal and connective tissue disorders	Back pain	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
	Musculoskeletal stiffness	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
	Pain in extremity	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
Nervous system disorders	Dizziness	2 (1.8) 2	1 (0.9) 1	3 (1.3) 3
	Headache	3 (2.7) 3	1 (0.9) 1	4 (1.8) 4
Renal and urinary disorders	Haematuria	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
	Proteinuria	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
Reproductive system and breast disorders	Dysmenorrhoea	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
Respiratory, thoracic and mediastinal disorders	Cough	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
	Dyspnoea	1 (0.9) 1	0 (0.0) 0	1 (0.4) 1
Total		61 (54.5) 152	43 (38.7) 98	104 (46.6) 250

Safety conclusion from the study 0130-24

A total of 250 TEAEs (Treatment-Emergent Adverse Events) were reported by 104 (46.6%) of the 223 participants during the conduct of study, of which 152 TEAEs were reported by 61 (54.5%) of 112 participants from Test Arm-T and 98 TEAEs were reported by 43 (38.7%) of 111 participants from Reference Arm-R.
Of the 250 TEAEs, 172 TEAEs were AESI (Adverse Events of Special Interest) reported in 72 (32.3%) participants; 103 AESI were reported by 39 participants (34.8%) in Test Arm (T) and 69 AESI were reported by 33 participants (29.7%) in Reference Arm (R).
Out of the 250 TEAEs, 225 TEAEs were mild, 24 TEAEs were moderate and 1 TEAE was severe in nature.
The causality assessment was judged as unlikely for 43 TEAEs, as probable/likely for 147 TEAEs, as certain for 26 TEAEs and as possible for 34 AEs.

Adverse reactions from published clinical trial

The information provided below is derived from all phases 3 trials (including the long-term cardiovascular outcomes trial) and post-marketing reports in patients with type 2 diabetes mellitus. The most frequently reported adverse reactions in published/reported clinical trials were gastrointestinal disorders, including nausea (very common), diarrhoea (very common) and vomiting (common). In general, these reactions were mild or moderate in severity and of short duration.
The frequencies of the adverse reactions (except diabetic retinopathy complications, see footnote in Table 2) are based on a pool of the phase IIIa trials excluding the cardiovascular outcomes trial.

Table 2: List of Adverse reactions from published clinical Trials

MedDRA system organ Class	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)	Not Known (No estimation)
Immune system disorders			Hypersensitivity[c]	Anaphylactic reaction	
Metabolism and nutrition disorders	Hypoglycemia[a] when used with insulin or sulfonylurea	Hypoglycemia[a] when used with other oral antidiabetics (OAD), Decreased appetite			
Nervous system disorders		Dizziness	Dyspepsia		
Eye disorders		Diabetic retinopathy complications[b]			
Cardiac disorders			Increased heart rate		
Gastrointestinal disorders	Nausea, Diarrhea	Vomiting, Abdominal pain, Abdominal distension, Constipation, Dyspepsia,Gastritis, Gastro- esophageal Reflux disease, Eructation, Flatulence	Acute pancreatitis, Delayed gastric emptying		Intestinal Obstruction
Hepatobiliary disorders		Cholelithiasis			
Skin and subcutaneous tissue disorders					Angioedema[d]
General disorders and administration site conditions		Fatigue	Injection site reactions		
Investigations		Increased lipase, Increased amylase, Weight decreased			

a) Hypoglycemia defined as severe (requiring the assistance of another person) or symptomatic in combination with a blood glucose <3.1 mmol/L. b) Diabetic retinopathy complications is a composite of retinal photocoagulation, treatment with intravitreal agents, vitreous hemorrhage, diabetes-related blindness (uncommon). Frequency based on cardiovascular outcomes trial. c) Grouped term covering also adverse events related to hypersensitivity such as rash and urticaria. d) From post-marketing reports.

Description of selected adverse reactions

Hypoglycemia

No episodes of severe hypoglycemia were observed when semaglutide was used as monotherapy. Severe hypoglycemia was primarily observed when semaglutide was used with a sulfonylurea (1.2% of subjects, 0.03 events/patient year) or insulin (1.5% of subjects, 0.02 events/patient year). Few episodes (0.1% of subjects, 0.001 events/patient year) were observed with semaglutide in combination with oral antidiabetics other than sulfonylureas.
American Diabetes Association (ADA) classified hypoglycemia occurred in 11.3% (0.3 events/patient year) of patients when semaglutide 1 mg was added to SGLT2 inhibitor in SUSTAIN 9 compared to 2.0% (0.04 events/patient year) of placebo-treated patients. Severe hypoglycemia was reported in 0.7% (0.01 events/patient year) and 0% of patients, respectively. In a 40-week phase 3b trial in patients receiving semaglutide 1 mg and 2 mg, the majority of the hypoglycemic episodes (45 out of 49 episodes) occurred when semaglutide was used in combination with sulfonylurea or insulin. Overall, there was no increased risk of hypoglycemia with semaglutide 2 mg.

Gastrointestinal adverse reactions

Nausea occurred in 17% and 19.9% of patients when treated with semaglutide 0.5 mg and 1 mg, respectively, diarrhea in 12.2% and 13.3% and vomiting in 6.4% and 8.4%. Most events were mild to moderate in severity and of short duration. The events led to treatment discontinuation in 3.9% and 5% of patients. The events were most frequently reported during the first months on treatment.
Patients with low body weight may experience more gastrointestinal side effects when treated with semaglutide. In a 40-week phase 3b trial in patients receiving semaglutide 1 mg and 2 mg, nausea occurred in similar proportions of patients when treated with semaglutide 1 mg and 2 mg, respectively. Diarrhea and vomiting occurred in higher proportions of patients when treated with semaglutide 2 mg compared to semaglutide 1 mg. The gastrointestinal adverse reactions led to treatment discontinuation in similar proportions in the semaglutide 1 mg and 2 mg treatment groups.
In concomitant use with an SGLT2 inhibitor in SUSTAIN 9, constipation and gastro- esophageal reflux disease occurred in 6.7% and 4% respectively of patients treated with semaglutide 1 mg compared to no events for placebo-treated patients. The prevalence of these events did not decrease over time.

Acute pancreatitis

The frequency of adjudication-confirmed acute pancreatitis reported in phase 3a clinical trials was 0.3% for semaglutide and 0.2% for the comparator, respectively. In the 2-year cardiovascular outcomes trial the frequency of acute pancreatitis confirmed by adjudication was 0.5% for semaglutide and 0.6% for placebo.

Diabetic retinopathy complications

A 2-year clinical trial investigated 3 297 patients with type 2 diabetes, with high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose. In this trial, adjudicated events of diabetic retinopathy complications occurred in more patients treated with semaglutide (3%) compared to placebo (1.8%). This was observed in insulin-treated patients with known diabetic retinopathy. The treatment difference appeared early and persisted throughout the trial. Systematic evaluation of diabetic retinopathy complication was only performed in the cardiovascular outcomes trial. In clinical trials up to 1 year involving 4 807 patients with type 2 diabetes, adverse events related to diabetic retinopathy were reported in similar proportions of subjects treated with semaglutide (1.7%) and comparators (2.0%).

Injection site reactions

Injection site reactions (e.g. injection site rash, erythema) have been reported by 0.6% and 0.5% of patients receiving semaglutide 0.5 mg and 1 mg, respectively. These reactions have usually mild.

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 neutralizing antibodies or anti-semaglutide antibodies with endogenous GLP-1 neutralizing effect at end-of-trial.
In the clinical study conducted by Intas Pharmaceuticals, the incidence of anti-drug antibodies (ADAs) was low and comparable to the immunogenicity rates reported in published clinical data for semaglutide. The antibodies detected were predominantly low-titre and transient, with no evidence of neutralizing activity against semaglutide or endogenous GLP-1. Presence of ADAs was not associated with any clinically meaningful impact on pharmacokinetics, glycemic efficacy, safety outcomes, or hypersensitivity-related events. Overall, the immunogenicity profile observed in the Intas study is consistent with the established immunogenicity profile of semaglutide described in the literature and does not indicate any additional immunogenic risk.

Heart rate increase

Increased heart rate has been observed with GLP-1 receptor agonists. In the phase 3a trials, mean increases of 1 to 6 beats per minute (bpm) from a baseline of 72 to 76 bpm were observed in subjects treated with semaglutide. In a long-term trial in subjects with cardiovascular risk factors, 16% of semaglutide-treated subjects had an increase in heart rate of >10 bpm compared to 11% of subjects on placebo after 2 years of treatment.

4.9 Overdose

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 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, considering the long half-life of semaglutide of approximately 1 week.

5.0 Pharmacological Properties

5.1. 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 in glucose and appetite regulation, and in the cardiovascular system. Glucose and appetite effects are specifically mediated via GLP-1 receptors in the pancreas and the brain.
Semaglutide reduces blood glucose in a dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. During hypoglycemia, semaglutide diminishes insulin secretion and does not impair glucagon secretion.
Semaglutide reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite. In addition, semaglutide reduces the preference for high fat foods. GLP-1 receptors are also expressed in the heart, vasculature, immune system and kidneys.
Semaglutide had a beneficial effect on plasma lipids, lowered systolic blood pressure and reduced inflammation in clinical studies. In animal studies, semaglutide attenuates the development of atherosclerosis by preventing aortic plaque progression and reducing inflammation in the plaque.

5.2. Pharmacodynamics Properties

All pharmacodynamics evaluations were performed after 12 weeks of treatment (including dose escalation) at steady state with semaglutide 1 mg once weekly.

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 hypoglycemia, 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.

Clinical Efficacy and Safety

The following information provided from published clinical Trial
The SUSTAIN trials comprehensively evaluated the safety, efficacy, and cardiovascular benefits of semaglutide, a GLP-1 receptor agonist, in various populations of type 2 diabetes mellitus (T2DM) patients. These trials demonstrated significant reductions in glycated hemoglobin (HbA1c), body weight, and cardiovascular risk compared to standard care or other antihyperglycemic agents.

Efficacy in Drug-Naive and Oral Antidiabetic Users
SUSTAIN 1 included drug-naive T2DM patients, demonstrating HbA1c reductions of 1.5% and 1.6% for semaglutide 0.5 mg and 1.0 mg, respectively, compared to a negligible reduction (0.02%) with placebo. Weight loss was also notable, at 3.8–4.5 kg, reinforcing semaglutide's dual benefits of glycemic control and weight management.
In patients inadequately controlled on oral antidiabetics (OADs), SUSTAIN 2 compared semaglutide to sitagliptin, showing superior HbA1c reductions of 1.3–1.6% versus 0.5%. Weight reductions were 3.8–4.3 kg for semaglutide, significantly outperforming sitagliptin's 0.9 kg reduction.
SUSTAIN 3 highlighted semaglutide's advantages over exenatide ER, with greater HbA1c reductions (1.5% vs. 0.9%) and weight loss (5.6 kg vs. 1.9 kg).

Comparisons against Injectable and Oral Therapies
SUSTAIN 4 and 7 addressed populations on basal insulin or other injectable therapies. Semaglutide showed greater HbA1c and weight reductions compared to insulin glargine (1.6% vs. 0.8%; 6.4 kg vs. +1.2 kg) and dulaglutide (1.8% vs. 1.6%; 6.5 kg vs. 3.0 kg). Similarly, SUSTAIN 8 demonstrated semaglutide's superior glycemic control and weight loss compared to canagliflozin (1.5% vs. 1.0%; 5.3 kg vs. 4.2 kg).
SUSTAIN 10 compared semaglutide to liraglutide, showing superior HbA1c reductions (1.7% vs. 1.0%) and weight loss (5.8 kg vs. 3.8 kg). Ongoing trials like SUSTAIN 11 aim to explore oral formulations and broader populations.
The SUSTAIN program consistently demonstrated semaglutide's superiority in glycemic control and weight management compared to multiple agents, including placebo, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 analogs, and insulin. Its cardiovascular benefits further underscore its comprehensive role in modern diabetes management. Semaglutide's efficacy across diverse populations and therapeutic settings highlights its potential to redefine T2DM care.

Table 3: Overview of Efficacy Outcomes across SUSTAIN Trials Evaluating Semaglutide in Type 2 Diabetes Mellitus

Trial	Patient Population	Intervention	Comparator	Results (Primary and Secondary Outcomes)
SUSTAIN 1	Drug-naive patients with T2DM (n=388)	Semaglutide 0.5 mg and 1.0 mg	Placebo	- HbA1c reduction: 1.5% (0.5 mg) and 1.6% (1.0 mg) vs. 0.02% (placebo). - Percentage achieving HbA1c <7%: 72.2% (0.5 mg) and 75.3% (1.0 mg) vs. 25.6% (placebo). - Weight reduction: 3.8 kg (0.5 mg) and 4.5 kg (1.0 mg) vs. 0.0 kg (placebo).
SUSTAIN 2	Patients inadequately controlled on metformin ± other OADs (n=1231)	Semaglutide 0.5 mg and 1.0 mg	Sitagliptin 100 mg	- HbA1c reduction: 1.3% (0.5 mg) and 1.6% (1.0 mg) vs. 0.5% (sitagliptin). - Percentage achieving HbA1c <7%: 69% (0.5 mg) and 78% (1.0 mg) vs. 36% (sitagliptin). - Weight reduction: 3.8 kg (0.5 mg) and 4.3 kg (1.0 mg) vs. 0.9 kg (sitagliptin).
SUSTAIN 3	Patients inadequately controlled oral antidiabetics (n=813)	Semaglutide 1.0 mg	Exenatide ER 2.0 mg	- HbA1c reduction: 1.5% (semaglutide) vs. 0.9% (exenatide). - Percentage achieving HbA1c <7%: 67% (semaglutide) vs. 40% (exenatide). - Weight reduction: 5.6 kg (semaglutide) vs. 1.9 kg (exenatide).
SUSTAIN 4	Patients on basal insulin ± oral antidiabetics (n=1089)	Semaglutide 0.5 mg and 1.0 mg	Insulin glargine	- HbA1c reduction: 1.2% (0.5 mg) and 1.6% (1.0 mg) vs. 0.8% (glargine). - Percentage achieving HbA1c <7%: 62% (0.5 mg) and 73% (1.0 mg) vs. 38% (glargine). - Weight change: 4.8 kg (0.5 mg) and 6.4 kg (1.0 mg) vs. +1.2 kg (glargine).
SUSTAIN 5	Patients on basal insulin ± oral antidiabetics (n=397)	Semaglutide 0.5 mg and 1.0 mg	Placebo	- HbA1c reduction: 1.4% (0.5 mg) and 1.8% (1.0 mg) vs. 0.02% (placebo). - Percentage achieving HbA1c <7%: 64% (0.5 mg) and 76% (1.0 mg) vs. 13% (placebo). - Weight reduction: 3.5 kg (0.5 mg) and 6.4 kg (1.0 mg) vs. +0.1 kg (placebo).
SUSTAIN 6	High CV risk patients with T2DM (n=3297)	Semaglutide 0.5 mg and 1.0 mg	Placebo	- MACE: 26% relative risk reduction (HR 0.74; 95% CI 0.58–0.95). - HbA1c reduction: 1.1% (0.5 mg) and 1.4% (1.0 mg) vs. 0.4% (placebo). - Weight reduction: 3.6 kg (0.5 mg) and 4.3 kg (1.0 mg) vs. +0.7 kg (placebo).
SUSTAIN 7	Patients inadequately controlled on metformin (n=1201)	Semaglutide 0.5 mg and 1.0 mg	Dulaglutide 0.75 mg and 1.5 mg	- HbA1c reduction: 1.5% (0.5 mg) and 1.8% (1.0 mg) vs. 1.4% (dulaglutide 0.75 mg) and 1.6% (dulaglutide 1.5 mg). Weight reduction: 4.6 kg (0.5 mg) and 6.5 kg (1.0 mg) vs. 2.9 kg (dulaglutide 0.75 mg) and 3.0 kg (dulaglutide 1.5 mg).
SUSTAIN 8	Patients inadequately controlled on metformin (n=788)	Semaglutide 1.0 mg	Canagliflozin 300 mg	- HbA1c reduction: 1.5% (semaglutide) vs. 1.0% (canagliflozin). - Percentage achieving HbA1c <7%: 68% (semaglutide) vs. 44% (canagliflozin) - Weight reduction: 5.3 kg (semaglutide) vs. 4.2 kg (canagliflozin).
SUSTAIN 9	Real-world T2DM patients inadequately controlled on OADs (n=171)	Semaglutide 0.5 mg and 1.0 mg	Placebo	- HbA1c reduction: 1.3–1.5% (semaglutide) vs. 0.0% (placebo). - Weight reduction: 5.4 kg (semaglutide) vs. +0.1 kg (placebo).
SUSTAIN 10	Patients inadequately controlled on OADs (n=577)	Semaglutide 1.0 mg	Liraglutide 1.2 mg	- HbA1c reduction: 1.7% (semaglutide) vs. 1.0% (liraglutide). - Percentage achieving HbA1c <7%: 72% (semaglutide) vs. 57% (liraglutide). - Weight reduction: 5.8 kg (semaglutide) vs. 3.8 kg (liraglutide)

Across the SUSTAIN trials, semaglutide demonstrated a favorable tolerability profile, comparable to other GLP-1 receptor agonists. The most frequently reported adverse events were nausea, vomiting, and diarrhea. These events were predominantly mild to moderate in severity and transient in duration. The incidences of these GI-related adverse effects were dose- dependent, with higher frequencies observed during the treatment initiation phase. Over time, the occurrence and intensity of these events diminished in the majority of patients, indicating an adaptation to the therapy.
There was no significant increase in hypoglycemia risk except when semaglutide was combined with insulin or sulfonylureas. Additionally, concerns regarding diabetic retinopathy were noted in SUSTAIN 6, with a slightly higher incidence in patients with pre-existing retinopathy, warranting cautious use in such populations.
Overall, the SUSTAIN trials established semaglutide as having a manageable and acceptable safety profile.

The information provided below is based on phase III (Study 0130-24) clinical study conducted with Intas Semaglutide
In this prospective, randomized, open-label, parallel group, active-controlled, multicenter, Phase-III study conducted to establish the non-inferiority of Intas Semaglutide Subcutaneous Injection Against Innovator Semaglutide (Ozempic, Novo Nordisk) Subcutaneous Injection in adult participants with Type 2 Diabetes Mellitus who were inadequately controlled on metformin, in adjunct to diet and exercise, a total of 223 participants were randomly assigned in this study [112 in Test Arm and 111 in Reference Arm].

Primary Efficacy Endpoint:

The summary results for primary endpoint are presented below:

Change from Baseline to Week 24 in Glycosylated Haemoglobin (HbA1c).
Number of Participants, mean, LS mean, point estimate, p-value, and Confidence Interval for change from baseline to week 24 (EOS) HbA1c levels of Semaglutide-test vs. Semaglutide-reference are presented as below:

Table 4: Mean change from baseline to week 24 (EOS) HbA1c levels

	ITT set (N= 217) *				
Treatments	Mean	LS Mean	Semaglutide test Vs. Semaglutide-reference		
			Point Estimate	p-value	95% CI
Semaglutide-test (N=108)	-1.51	-1.50	0.16	0.3266	[-0.16, 0.47]
Semaglutide-reference (N=109)	-1.63	-1.65			

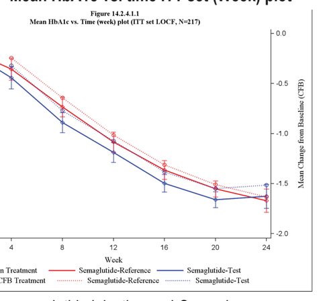
*LOCF

As shown in the table, the lower limit of the 95% CI was –0.16, which is above the predefined non-inferiority margin of –0.4. This demonstrates that the test product is non-inferior to the reference product.

In addition, the p-value of 0.3266 indicates no statistically significant difference between the Semaglutide-test and Semaglutide-reference products. Therefore, the Semaglutide-test product is concluded to be non-inferior to the Semaglutide-reference product.

Plot of mean HbA1c levels over weeks was provided as below for ITT set

Figure 1: Mean HbA1c vs. time ITT set (Week) plot



Overall, Intas semaglutide injection and Ozempic were comparable and no significant safety concerns were observed.

5.3. Pharmacokinetic Properties

The information below is derived from published clinical trial data
Compared to native GLP-1, semaglutide has a prolonged half-life of around 1 week making it suitable for one 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 stabilized against degradation by the DPP-4 enzyme.

Absorption

Maximum concentration was reached by 1 to 3 days post dose. Steady state exposure was achieved following 4–5 weeks of once weekly administration. In patients with type 2 diabetes, the mean steady state concentrations following subcutaneous administration of 0.5 mg and 1 mg semaglutide were approximately 16 nmol/L and 30 nmol/L, respectively. In the trial comparing semaglutide 1 mg and 2 mg, the mean steady state concentrations were 27 nmol/L and 54 nmol/L, respectively. 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%).

Biotransformation

Prior to excretion, semaglutide is extensively metabolized 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

In a trial with a single subcutaneous dose of radiolabeled semaglutide, it was found that the primary excretion routes of semaglutide-related material were via urine and faeces; approximately 2/3 of semaglutide-related material were excreted in urine and approximately 1/3 in faeces. Approximately 3% of the dose was excreted as intact semaglutide via urine. In patients with type 2 diabetes clearance of semaglutide was 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.

Special population

Elderly
Age had no effect on the pharmacokinetics of semaglutide based on data from phase 3a studies including patients of 20–86 years of age.

Gender, race and ethnicity
Gender, race (White, Black or African American, Asian) and ethnicity (Hispanic or Latino, non-Hispanic or -Latino) had no effect on the pharmacokinetics of semaglutide.

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.

Renal impairment
Renal impairment did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. This was shown with a single dose of 0.5 mg semaglutide for patients with different degrees of renal impairment (mild, moderate, severe or patients in dialysis) compared with subjects with normal renal function. This was also shown for subjects with type 2 diabetes and with renal impairment based on data from phase 3a studies, although the experience in patients with end-stage renal disease was limited.

Hepatic impairment
Hepatic impairment did not have any impact on the exposure of semaglutide. The pharmacokinetics of semaglutide were evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function in a trial with a single-dose of 0.5 mg semaglutide.

Pediatric population
Semaglutide has not been studied in pediatric patients.

6. Nonclinical Properties

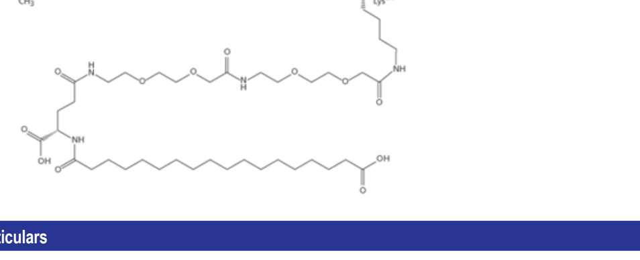
6.1. Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in CD-1 mice, subcutaneous doses of 0.3, 1 and 3 mg/kg/day [2-, 11-, and 30 fold the maximum recommended human dose (MRHD) of 2 mg/week, based on AUC] were administered to the males, and 0.1, 0.3 and 1 mg/kg/day (1-, 2-, and 7-fold MRHD) were administered to the females. A statistically significant increase in thyroid C-cell adenomas and a numerical increase in C-cell carcinomas were observed in males and females at clinically relevant exposures.
In a 2-year carcinogenicity study in Sprague Dawley rats, subcutaneous doses of 0.0025, 0.01, 0.025 and 0.1 mg/kg/day were administered (below quantification, 0.2-, 0.5-, and 3-fold the exposure at the MRHD). A statistically significant increase in thyroid C-cell adenomas was observed in males and females at all dose levels, and a statistically significant increase in thyroid C-cell carcinomas was observed in males at ≥0.01 mg/kg/day, at clinically relevant exposures.
Human relevance of thyroid C-cell tumors in rats is unknown and could not be determined by clinical studies or nonclinical studies.
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.

7. Description

Semaglutide Injection is a clear, colorless solution. Semaglutide Injection, for subcutaneous use, contains semaglutide, a human GLP-1 receptor agonist (or GLP-1 analogue). 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 $C_{187}H_{291}N_{45}O_{59}$ and the molecular weight is 4113.58 g/mol.



8. Pharmaceutical Particulars

8.1 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

8.2 Shelf-life

15 months
After first use: 6 weeks.

8.3 Packaging information

Semaglutide Injection 0.68mg/ml (1 mg/1.5 ml Prefilled Pen) Each pre-filled pen contains 1.5 ml of solution (delivering 4 doses of 0.25 mg) , 5 Pen Needles, 5 Alcohol Swabs.
Semaglutide Injection 1.34mg/ml (2 mg/1.5 ml Prefilled Pen): Each pre-filled pen contains 1.5 ml of solution (delivering 4 doses of 0.5 mg), 5 Pen Needles, 5 Alcohol Swabs.
Semaglutide Injection 1.34mg/ml (4 mg/3 ml Prefilled Pen): Each pre-filled pen contains 3 ml of solution (delivering 4 doses of 1 mg), 5 Pen Needles, 5 Alcohol Swabs.
Semaglutide Injection 2.68mg/ml (8 mg/3 ml Prefilled Pen): Each pre-filled pen contains 3 ml of solution (delivering 4 doses of 2 mg), 5 Pen Needles, 5 Alcohol Swabs.

8.4 Storage and handling instructions

Storage instructions
Before opening (before starting to use)
Store in a refrigerator (2°C to 8°C).
Keep away from the cooling element. Do not freeze

After first use store below 30°C or in refrigerator at 2 °C to 8 °C. The product may be stored for maximum 6 weeks after first dose.

Handling instructions
- The pen should not be used if it has been frozen
- Keep the pen cap on when the pen is not in use in order to protect it from light.
- Semaglutide Injection should not be used if it does not appear clear and colourless.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
- The patient should be advised to discard the injection needle in accordance with local requirements after each injection and store the pen without an injection needle attached. This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing.
- Always use a new needle for each injection.
- The pen is for use by one person only.

9. Patient Counselling Information

Patients should be counselled on the below-mentioned points.
Patients should not self initiate medication of the semaglutide injection without proper medical consultation.

Risk of Thyroid C-cell Tumors
Inform patients that semaglutide causes thyroid C-cell tumors in rodents and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia, or dyspnea) to their physician.
Pancreatitis
Inform patients of the potential risk for pancreatitis. Instruct patients to discontinue semaglutide promptly and contact their physician if pancreatitis is suspected (severe abdominal pain that may radiate to the back, and which may or may not be accompanied by vomiting).
Diabetic Retinopathy Complications
Inform patients to contact their physician if changes in vision are experienced during treatment with semaglutide.
Never Share a Semaglutide Pen between Patients
Advise patients that they must never share a semaglutide pen with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens.
Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin
Inform patients that the risk of hypoglycemia is increased when semaglutide is used with an insulin secretagogue (such as a sulfonylurea) or insulin. Educate patients on the signs and symptoms of hypoglycemia.
Acute Kidney Injury
Advice patients treated with semaglutide of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if acute kidney injury occurs.
Hypersensitivity Reactions
Inform patients that serious hypersensitivity reactions have been reported during post-marketing use of semaglutide. Advice patients on the symptoms of hypersensitivity reactions and instruct them to stop taking semaglutide and seek medical advice promptly if such symptoms occur.
Acute Gallbladder Disease
Inform patients of the potential risk for cholelithiasis or cholecystitis. Instruct patients to contact their physician if cholelithiasis or cholecystitis is suspected for appropriate clinical follow-up.
Pulmonary Aspiration during General Anesthesia or Deep Sedation
Inform patients that semaglutide may cause their stomach to empty more slowly which may lead to complications with anesthesia or deep sedation during planned surgeries or procedures. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking semaglutide.
Pregnancy
Advice a pregnant woman of the potential risk to a fetus. Advise women to inform their healthcare provider if they are pregnant or intend to become pregnant.
Missed doses
Inform patients if a dose is missed, it should be administered as soon as possible within 5 days after the missed dose. If more than 5 days have passed, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, inform patients to resume their regular once weekly dosing schedule.

10. Details of Manufacturer

Manufactured by:

INTAS PHARMACEUTICALS LTD.
Plot No. 85/87, Kailash Industrial Estate,
Village: Iyava, Taluka: Sanand, Dist.
Ahmedabad-382110.
For any safety and quality related concerns, please write to pv@intaspharma.com or report at our website www.intaspharma.com or call at our tollfree number: 1800 1200 124.

11. Details of Permission or License Number with Date

Mfg. Lic. No.: G/28/1546 Dated: 21-04-2026

12. Date of Revision

July, 2026

Note: Please refer specific prescribing information meant for use in Type 2 Diabetes mellitus management or Chronic weight management respectively as per the intended use.

FRONT SIDE

File Name : Semaglutide Multiple strengths India combipack PIL 6039731
Size : 900 x 450 mm (Front side) (Final Fold size - 150 x 50 mm)
Colour : CMYK
Date : 17^06^2026, 18^06^2026, 02^07^2026

PRESCRIBING INFORMATION

SEMAGLUTIDE INJECTION

1. Generic Name

- Semaglutide Injection 0.68mg/ml (1 mg/1.5 ml Prefilled Pen)
- Semaglutide Injection 1.34mg/ml (2 mg/1.5 ml Prefilled Pen)
- Semaglutide Injection 1.34mg/ml (4 mg/3 ml Prefilled Pen)
- Semaglutide Injection 2.27mg/ml (6.8 mg/3 ml Prefilled Pen)
- Semaglutide Injection 3.2mg/ml (9.6 mg/3 ml Prefilled Pen)

(For use in Chronic weight management - Please refer section 4.1 for details)

2. Qualitative and Quantitative Composition

Semaglutide Injection 0.68mg/ml (1 mg/1.5 ml Prefilled Pen)
Each 1 ml contains
Semaglutide……………………………..0.68mg
Phenol IP 5.50 mg
(As preservative)
Water for Injections IP q.s.
1.5 ml in prefilled pen capable of delivering 4 doses of 0.25 mg

Semaglutide Injection 1.34mg/ml (2 mg/1.5 ml Prefilled Pen)
Each 1 ml contains
Semaglutide……………………………..1.34mg
Phenol IP 5.50 mg
(As preservative)
Water for Injections IP q.s.
1.5 ml in prefilled pen capable of delivering 4 doses of 0.5 mg.

Semaglutide Injection 1.34mg/ml (4 mg/3 ml Prefilled Pen)
Each 1 ml contains
Semaglutide……………………………..1.34mg
Phenol IP 5.50 mg
(As preservative)
Water for Injections IP q.s.
3 ml in prefilled pen capable of delivering 4 doses of 1 mg.

Semaglutide Injection 2.27mg/ml (6.8 mg/3 ml Prefilled Pen)
Each 1 ml contains
Semaglutide……………………………..2.27mg
Phenol IP 5.50 mg
(As preservative)
Water for Injections IP q.s.
3 ml in prefilled pen capable of delivering 4 doses of 1.7 mg.

Semaglutide Injection 3.2mg/ml (9.6 mg/3 ml Prefilled Pen)
Each 1 ml contains
Semaglutide……………………………..3.2mg.
Phenol IP 5.50 mg
(As preservative)
Water for Injections IP q.s.
3 ml in prefilled pen capable of delivering 4 doses of 2.4 mg.

Each ml of solution also contains the following inactive ingredients: Disodium phosphate dihydrate, 1.42 mg; Propylene glycol, 14.0 mg; Phenol, 5.50 mg; and Water for injections. Hydrochloric acid or Sodium hydroxide may be added to adjust pH.

3. Dosage Form and Strengths

- Dosage Form: Solution for injection.
- Strengths:
  - Semaglutide Injection 0.68 mg/ml, 1 mg/1.5 ml Prefilled pen
  - Semaglutide Injection 1.34 mg/ml, 2 mg/1.5 ml prefilled pen
  - Semaglutide Injection 1.34 mg/ml, 4 mg/3 ml prefilled pen
  - Semaglutide Injection 2.27 mg/ml, 6.8 mg/3 ml Prefilled pen
  - Semaglutide Injection 3.2 mg/ml, 9.6 mg/3 ml Prefilled pen

4. Clinical Particulars

4.1 Therapeutic Indication

Weight Management

Semaglutide Injection is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of

- 30 kg/m^2 or greater (obesity) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

4.2 Posology and Method of Administration

Posology

Initial and Escalation Dose

Initiate semaglutide with a dosage of 0.25 mg injected subcutaneously once weekly. Follow the dosage initiation and escalation in Table 1 to reduce the risk of gastrointestinal adverse reactions.
If patients do not tolerate a dose during dosage escalation, consider delaying dosage escalation for 4 weeks.

Maintenance Dose

The maintenance dosage of semaglutide is either 2.4 mg (recommended) or 1.7 mg once weekly. Consider treatment response and tolerability when selecting the maintenance dosage.

Table 1. Recommended Dosage Escalation in Adults

Treatment	Weeks	Once weekly Subcutaneous Dosage
Initiation	1 through 4	0.25 mg
Escalation	5 through 8	0.5 mg
	9 through 12	1 mg
	13 through 16	1.7 mg
Maintenance	17 and onward	1.7 mg or 2.4 mg

Patients with type 2 diabetes

When initiating semaglutide in patients with type 2 diabetes, consider reducing the dose of concomitantly administered insulin or insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycemia.

Dosage Modifications for Adverse Reactions

- If patients do not tolerate the 2.4 mg once-weekly maintenance dosage, the maintenance dosage may be reduced to 1.7 mg once weekly.
- Discontinue Semaglutide Injection if the patient cannot tolerate the 1.7 mg once-weekly dosage.

Missed dose

If a dose is missed, it should be administered as soon as possible and within 5 days after the missed dose. If more than 5 days have passed, the missed dose should be skipped, and the next dose should be administered on the regularly scheduled day. In each case, patients can then resume their regular weekly dosing schedule. If more doses are missed, reducing the starting dose for re-initiation should be considered.

Special Population

Elderly (≥65 years old)

No dose adjustment is required based on age. Therapeutic experience in patients ≥85 years of age is limited.

Patients with renal impairment

No dose adjustment is required for patients with mild or moderate 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 severe renal impairment (eGFR <30 ml/min/1.73m^2) including patients with end-stage renal disease.

Patients with hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment. Experience with the use of semaglutide in patients with severe hepatic impairment is limited.
Semaglutide is not recommended for use in patients with severe hepatic impairment and should be used cautiously in patients with mild or moderate hepatic impairment.

Pediatric population

The safety and efficacy of semaglutide in children (below 18 years) have not been established.

Method of Administration

Subcutaneous use

Semaglutide is to be injected subcutaneously into the abdomen, in the thigh or in the upper arm. The injection site can be changed without dose adjustment. Semaglutide should not be administered intravenously or intramuscularly.
Semaglutide is to be administered once weekly at any time of the day, with or without meals.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- A personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

4.4 Special warnings and precautions for use

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.
Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the post-marketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans.
Patients with type 2 diabetes
Semaglutide should not be used as a substitute for insulin in patients with type 2 diabetes. Semaglutide should not be used in combination with other GLP-1 receptor agonist products. It has not been evaluated and an increased risk of adverse reactions related to overdose is considered likely.

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 diarrhea may cause dehydration which could cause a deterioration of renal function.

Acute 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.

Hypoglycemia in Patients with Type 2 Diabetes

Insulin and sulfonylurea are known to cause hypoglycemia. Patients treated with semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with a GLP-1 receptor agonist.

Diabetic Retinopathy Complications in Patients with Type 2 Diabetes

In patients with diabetic retinopathy treated with semaglutide, an increased risk of developing diabetic retinopathy complications has been observed. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. Patients with diabetic retinopathy using semaglutide should be monitored closely and treated according to clinical guidelines. There is no experience with semaglutide in patients with type 2 diabetes with uncontrolled or potentially unstable diabetic retinopathy. In these patients, treatment with semaglutide is not recommended.

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. 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 Reactions

Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported in patients treated with Semaglutide. If hypersensitivity reactions occur, discontinue use of Semaglutide; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity to Semaglutide.
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 semaglutide.

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. In placebo-controlled trials, cholelithiasis was reported in 1.5% and 0.4% of patients-treated with Semaglutide 0.5 mg and 1 mg, respectively. Cholelithiasis was not reported in placebo-treated patients.
Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with semaglutide. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin value may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. 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.

Suicidal Behavior and Ideation

Suicidal behavior and ideation have been reported in clinical trials with other weight management products. Monitor patients treated with semaglutide for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue semaglutide in patients who experience suicidal thoughts or behaviors. Avoid semaglutide in patients with a history of suicidal attempts or active suicidal ideation.

Heart Rate Increase

Treatment with semaglutide was associated with increases in resting heart rate. Mean increases in resting heart rate of 1 to 4 beats per minute (bpm) were observed in semaglutide treated adult patients compared to placebo in clinical trials. More adult patients treated with semaglutide compared with placebo had maximum changes from baseline at any visit of 10 to 19 bpm (41% versus 34%, respectively) and 20 bpm or more (26% versus 16%, respectively).
Monitor heart rate at regular intervals consistent with usual clinical practice. Instruct patients to inform their healthcare providers of palpitations or feelings of a racing heartbeat while at rest during semaglutide treatment. If patients experience a sustained increase in resting heart rate, discontinue semaglutide.

4.5 Drugs Interactions

Semaglutide delays gastric emptying and could potentially influence the absorption of concomitantly administered oral medicinal products. No clinically relevant effect on the rate of gastric emptying was observed with semaglutide 2.4 mg, probably due to a tolerance effect. Semaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption.

Paracetamol

Semaglutide delays the rate of gastric emptying as assessed by paracetamol pharmacokinetics during a standardized meal test. Paracetamol $AUC_{0-60min}$ and C_{max} were decreased by 27% and 23%, respectively, following concomitant use of semaglutide 1 mg. The total paracetamol exposure (AUC_{0-5h}) was not affected. No clinically relevant effect on paracetamol was observed with semaglutide. No dose adjustment of paracetamol is necessary when administered with semaglutide.

Oral contraceptives

Semaglutide is not anticipated to decrease the effectiveness of oral contraceptives. It did not change the overall exposure of ethinylestradiol and levonorgestrel to a clinically relevant degree, when an oral contraceptive combination medicinal product (0.03 mg ethinylestradiol/0.15 mg levonorgestrel) was co-administered with semaglutide. Exposure of ethinylestradiol was not affected; an increase of 20% was observed for levonorgestrel exposure at steady state. Cmax was not affected for any of the compounds.

Atorvastatin

Semaglutide did not change the overall exposure of atorvastatin following a single dose administration of atorvastatin (40 mg). Atorvastatin Cmax was decreased by 38%. This was assessed not to be clinically relevant.

Digoxin

Semaglutide did not change the overall exposure or Cmax of digoxin following a single dose of digoxin (0.5 mg).

Metformin

Semaglutide did not change the overall exposure or Cmax of metformin following dosing of 500 mg twice daily over 3.5 days.

Warfarin and other coumarin derivatives

Semaglutide did not change overall exposure or Cmax of R- and S-warfarin following a single dose of warfarin (25 mg), and the pharmacodynamic effects of warfarin as measured by the international normalised ratio (INR) were not affected in a clinically relevant manner. However, 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.

4.6 Use in special populations

Pregnant Women

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.

Lactating Women

In lactating rats, semaglutide was excreted in milk. A risk to a breast-fed child cannot be excluded. Semaglutide should not be used during breast-feeding.

Geriatric Patients

In the semaglutide clinical trials for weight reduction and long-term maintenance, 233 (9%) semaglutide-treated patients were aged 65 to 75 years and 23 (1%) semaglutide-treated patients were aged 75 years and older. In a cardiovascular outcomes trial, 2656 (30%) semaglutide- treated patients were aged 65 to 75 years and 703 (8%) semaglutide-treated patients were aged 75 years and older. No overall difference in effectiveness was observed between patients aged 65 years and older and younger adult patients. In the cardiovascular outcomes trial, patients aged 75 years and older reported more fractures of the hip and pelvis on semaglutide than on placebo. Patients aged 75 years and older (semaglutide-treated and placebo-treated) reported more serious adverse reactions overall compared to younger adult patients.

4.7 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 the dose escalation period. Driving or use of machines should be done cautiously if dizziness occurs.

Patients with type 2 diabetes

If semaglutide is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycemia while driving and using machines.

4.8 Undesirable Effects

Summary of safety profile

The information provided below is derived from the Phase III study conducted by Intas Pharmaceuticals with the Study code: 0131-24. The Safety profile of Intas semaglutide subcutaneous injection against Innovator semaglutide subcutaneous injection, Wegovy FlexTouch, was evaluated in a randomized, open-label, multicenter, active-controlled, parallel-group, phase III study in Overweight and Obese Adult Participants in Adjunct to Diet and Exercise.

In Study 0131-24, all the 231 randomized participants received at least one dose of study medication and were included in the safety set: 118 in Test Arm and 113 in Reference Arm.
The most frequently reported treatment emergent adverse events (TEAEs) during the study were Diarrhoea (14.3 % participants), Hyperchlorhydria (10.0 % participants), Nausea (10.0 % participants) and Vomiting (10.4 % participants).
In general, these reactions were mild or moderate in severity and of short duration. The clinical trial safety data generated by the Intas Pharmaceuticals demonstrated a safety profile comparable to that reported in published clinical studies, indicating concordance across data sources.

Table 2: List of adverse reactions based on System organ Class from study 0131-24

System Organ Class	Preferred Term as per MedDRA Version 28.0 and 28.1	Semaglutide-test N = 118 n (%) e	Semaglutide-Reference N = 113 n (%) e	Total N = 231 n (%) e
Blood and lymphatic system disorders	Anaemia	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
	Leukocytosis	1 (0.8) 1	2 (1.8) 2	3 (1.3) 3
	Leukopenia	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
	Thrombocytopenia	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
Gastrointestinal disorders	Abdominal discomfort	4 (3.4) 7	3 (2.7) 5	7 (3.0) 12
	Abdominal distension	1 (0.8) 1	1 (0.9) 2	2 (0.9) 3
	Abdominal pain	3 (2.5) 4	1 (0.9) 1	4 (1.7) 5
	Abdominal pain upper	2 (1.7) 3	2 (1.8) 2	4 (1.7) 5
	Constipation	2 (1.7) 5	7 (6.2) 8	9 (3.9) 13
	Diarrhoea	18 (15.3) 30	15 (13.3) 25	33 (14.3) 55
	Dyspepsia	3 (2.5) 7	7 (6.2) 12	10 (4.3) 19
	Eructation	0 (0.0) 0	3 (2.7) 6	3 (1.3) 6
	Flatulence	2 (1.7) 2	4 (3.5) 5	6 (2.6) 7
	Gastritis	1 (0.8) 4	1 (0.9) 1	2 (0.9) 5
	Gastrooesophageal reflux disease	1 (0.8) 1	0 (0.0) 0	1 (0.4) 1
	Hyperchlorhydria	10 (8.5) 14	13 (11.5) 36	23 (10.0) 50
	Nausea	9 (7.6) 31	14 (12.4) 16	23 (10.0) 47
	Vomiting	13 (11.0) 15	11 (9.7) 19	24 (10.4) 34
General disorders and administration site conditions	Asthenia	2 (1.7) 2	2 (1.8) 2	4 (1.7) 4
	Chest pain	1 (0.8) 1	0 (0.0) 0	1 (0.4) 1
	Injection site reaction	1 (0.8) 1	0 (0.0) 0	1 (0.4) 1
	Pain	2 (1.7) 3	0 (0.0) 0	2 (0.9) 3
	Pyrexia	3 (2.5) 3	4 (3.5) 5	7 (3.0) 8
Infections and infestations	Fungal infection	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
	Gastroenteritis	4 (3.4) 4	2 (1.8) 3	6 (2.6) 7
	Nasopharyngitis	2 (1.7) 3	1 (0.9) 3	3 (1.3) 6
	Upper respiratory tract infection	1 (0.8) 1	1 (0.9) 1	2 (0.9) 2
	Urinary tract infection	1 (0.8) 1	3 (2.7) 3	4 (1.7) 4
Injury, poisoning and procedural complications	Muscle rupture	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
Investigations	Alanine aminotransferase increased	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
	Aspartate aminotransferase increased	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
	Blood alkaline phosphatase increased	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
	Blood glucose increased	1 (0.8) 1	0 (0.0) 0	1 (0.4) 1
	Blood uric acid increased	1 (0.8) 1	0 (0.0) 0	1 (0.4) 1
	Neutrophil count increased	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
	Pancreatic enzymes increased	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
	Protein total increased	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
	Urobilinogen urine increased	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
Metabolism and nutrition disorders	Decreased appetite	0 (0.0) 0	3 (2.7) 4	3 (1.3) 4
	Dyslipidaemia	2 (1.7) 2	2 (1.8) 2	4 (1.7) 4
	Hypoglycaemia	1 (0.8) 2	0 (0.0) 0	1 (0.4) 2
	Impaired fasting glucose	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
Musculoskeletal and connective tissue disorders	Arthralgia	1 (0.8) 1	0 (0.0) 0	1 (0.4) 1
	Pain in extremity	1 (0.8) 1	0 (0.0) 0	1 (0.4) 1
Nervous system disorders	Dizziness	1 (0.8) 1	1 (0.9) 1	2 (0.9) 2
	Headache	5 (4.2) 5	5 (4.4) 8	10 (4.3) 13
Psychiatric disorders	Nervousness	1 (0.8) 1	0 (0.0) 0	1 (0.4) 1
Renal and urinary disorders	Albuminuria	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
	Crystalluria	1 (0.8) 1	0 (0.0) 0	1 (0.4) 1
Respiratory, thoracic and mediastinal disorders	Asphyxia	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
	Cough	2 (1.7) 2	1 (0.9) 3	3 (1.3) 5
	Oropharyngeal pain	2 (1.7) 2	0 (0.0) 0	2 (0.9) 2
	Rhinorrhoea	1 (0.8) 1	0 (0.0) 0	1 (0.4) 1
	Sneezing	1 (0.8) 1	0 (0.0) 0	1 (0.4) 1
Skin and subcutaneous tissue disorders	Alopecia	2 (1.7) 2	0 (0.0) 0	2 (0.9) 2
	Hyperhidrosis	0 (0.0) 0	1 (0.9) 1	1 (0.4) 1
	Pruritus	1 (0.8) 4	1 (0.9) 4	2 (0.9) 8
	Rash	1 (0.8) 1	0 (0.0) 0	1 (0.4) 1
	Urticaria	1 (0.8) 1	0 (0.0) 0	1 (0.4) 1
Total	Total	54 (45.8) 174	60 (53.1) 195	114 (49.4) 369

Safety Conclusion from study 0131-24

A total of 369 TEAEs (treatment emergent adverse events) were reported by 114 (49.4%) of the 231 participants during the conduct of study, of which 174 TEAEs were reported by 54 (45.8 %) of 118 participants from Test Arm-T and 195 TEAEs were reported by 60 (53.1 %) of 113 participants from Reference Arm-R.
Of the 369 TEAEs, 275 TEAEs were AESI (Adverse event of special interest) were reported in 98 (42.4%) participants; 130 AESI were reported by 49 (41.5%) participants in Test Arm (T) and 145 AESI were reported by 49 (43.4%) participants in Reference Arm (R).
Out of the 369 TEAEs, 350 TEAEs were mild, 18 TEAEs were moderate and 1 TEAE was severe in nature.
The causality assessment was judged as unlikely for 62 TEAEs, as probable/likely for 162 TEAEs, as certain for 2 TEAEs and as possible for 143 AEs.

Adverse reactions from published clinical trials

The data derived from four phase IIIa trials, 2650 adult patients were exposed to Semaglutide. The duration of the trials was 68 weeks. The most frequently reported adverse reactions were gastrointestinal disorders including nausea, diarrhea, constipation and vomiting.

Table 3: List of adverse events from published clinical trials

MedDRA system organ Class	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)	Not Known (No estimation)
Immune system disorders				Anaphylactic reaction	
Metabolism and nutrition disorders		Hypoglycemia in patients with type 2 diabetes[a]			
Nervous system disorders	Headache[b]	Dizziness[b] Dyspepsia[b,c] Dysaesthesia[a]			
Eye disorders		Diabetic retinopathy in patients with type 2 diabetes[a]			
Cardiac disorders			Hypotension Orthostatic hypotension Increased heart rate[a,c]		
Gastrointestinal disorders	Vomiting[a,b] Diarrhoea[a,b] Constipation[a,b] Nausea[a,b] Abdominal pain[b,c]	Gastritis[b,c] Gastrooesophageal reflux disease[b] Dyspepsia[b] Eructation[b] Flatulence[b] Abdominal distension[b]	Acute pancreatitis[a] Delayed gastric emptying		Intestinal Obstruction
Hepatobiliary disorders		Cholelithiasis[a]			
Skin and subcutaneous tissue disorders		Hair loss[a]			Angioedema
General disorders and administration site conditions	Fatigue[b,c]		Injection site reactions[c]		
Investigations			Increased lipase[c], Increased amylase[c]		

a) see description of selected adverse reactions below
b) mainly seen in the dose-escalation period
c) Grouped preferred terms

Gastrointestinal adverse reactions

Over the 68 weeks trial period, nausea occurred in 43.9% of patients when treated with semaglutide (16.1% for placebo), diarrhea in 29.7% (15.9% for placebo) and vomiting in 24.5% (6.3% for placebo). Most events were mild to moderate in severity and of short duration. Constipation occurred in 24.2% of patients treated with semaglutide (11.1% for placebo) and was mild to moderate in severity and of longer duration. In patients treated with semaglutide, median duration of nausea was 8 days, vomiting 2 days, diarrhoea 3 days, and constipation 47 days.
Patients with moderate renal impairment (eGFR ≥30 to <60 ml/min/1.73m2) may experience more gastrointestinal effects when treated with semaglutide.
The gastrointestinal events led to permanent treatment discontinuation in 4.3% of patients.

Acute pancreatitis

The frequency of adjudication-confirmed acute pancreatitis reported in phase 3a clinical trials was 0.2% for semaglutide and <0.1% for placebo, respectively. In SELECT, the cardiovascular outcomes trial, the frequency of acute pancreatitis confirmed by adjudication was 0.2% for semaglutide and 0.3% for placebo.

Acute gallstone disease/Cholelithiasis

Cholelithiasis was reported in 1.6% and led to cholecystitis in 0.6% of patients treated with semaglutide. Cholelithiasis and cholecystitis was reported in 1.1% and 0.3%, respectively, of patients treated with placebo.

Hair loss

Hair loss was reported in 2.5% of patients treated with semaglutide and in 1.0% of patients treated with placebo. The events were mainly of mild severity and most patients recovered while on continued treatment. Hair loss was reported more frequently in patients with a greater weight loss (≥20%).

Increased heart rate

In the phase 3a trials, a mean increase of 3 beats per minute (bpm) from a baseline mean of 72 bpm was observed in patients treated with semaglutide. The proportions of subjects with an increase in pulse from baseline ≥10 bpm at any time point during the on-treatment period were 67.0% in the semaglutide group vs. 50.1% in the placebo group.

Immunogenicity

The information provided below is from published clinical trial data

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 testing positive for anti-semaglutide antibodies at any time post- baseline was low (2.9%) and no patients had anti-semaglutide neutralizing antibodies or anti-semaglutide antibodies with endogenous GLP-1 neutralizing effect at end-of-trial. During treatment, high semaglutide concentrations might have lowered the sensitivity of the assays, hence the risk of false negatives cannot be excluded. However, in subjects testing positive for antibodies during and after treatment, the presence of antibodies was transient and with no apparent impact on efficacy and safety.
In the clinical study conducted by Intas Pharmaceuticals, the incidence of anti-drug antibodies (ADAs) was low and comparable to the immunogenicity rates reported in published clinical data for semaglutide. The antibodies detected were predominantly low-titre and transient, with no evidence of neutralizing activity against semaglutide or endogenous GLP-1. Presence of ADAs was not associated with any clinically meaningful impact on pharmacokinetics, glycemic efficacy, safety outcomes, or hypersensitivity-related events. Overall, the immunogenicity profile observed in the Intas study is consistent with the established immunogenicity profile of semaglutide described in the literature and does not indicate any additional immunogenic risk.

Hypoglycemia in patients with type 2 diabetes

In STEP 2, clinically significant hypoglycemia was observed in 6.2% (0.1 events/patient year) of subjects treated with semaglutide compared with 2.5% (0.03 events/patient year) of subjects treated with placebo. Hypoglycemia with semaglutide was seen both with and without concomitant use of sulfonylurea. One episode (0.2% of subjects, 0.002 events/patient year) was reported as severe in a subject not concomitantly treated with a sulfonylurea. The risk of hypoglycemia increased when semaglutide was used with sulfonylurea.
In STEP-HFpEF-DM, clinically significant hypoglycemia was observed in 4.2% of subjects in both the semaglutide and placebo groups when used in combination with sulfonylurea and/or insulin (0.065 events/patient year with semaglutide and 0.098 events/patient year with placebo).

Diabetic retinopathy in patients with type 2 diabetes

A 2-year clinical trial investigated semaglutide 0.5 mg and 1 mg vs. placebo in 3 297 patients with type 2 diabetes, with high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose. In this trial, adjudicated events of diabetic retinopathy complications occurred in more patients treated with semaglutide (3.0%) compared to placebo (1.8%). This was observed in insulin-treated patients with known diabetic retinopathy. The treatment difference appeared early and persisted throughout the trial. In STEP 2, retinal disorders were reported by 6.9% of patients treated with Semaglutide, 6.2% of patients treated with semaglutide 1 mg, and 4.2% of patients treated with placebo. The majority of events were reported as diabetic retinopathy (4.0%, 2.7%, and 2.7%, respectively) and non-proliferative retinopathy (0.7%, 0%, and 0%, respectively).

Dysaesthesia

Events related to a clinical picture of altered skin sensation such as paraesthesia, pain of skin, sensitive skin, dysaesthesia and burning skin sensation were reported in 2.1% of patients treated with semaglutide 2.4 mg and 1.2% of patients treated with placebo. The events were mild to moderate in severity and most patients recovered while on continued treatment.

Other special populations

In the SELECT and SUSTAIN 6 trials, in adults with established cardiovascular disease, the adverse reaction profile was similar to that seen in the weight management phase 3a trials.
In the HFpEF trials, in adults with obesity related heart failure with preserved ejection fraction (HFpEF), the adverse reaction profile was similar to that seen in the weight management phase 3a trials.

4.9 Overdose

Overdose with semaglutide may be associated with gastrointestinal disorders which could lead to dehydration. In the event of overdose the patient should be observed for clinical signs and appropriate supportive treatment initiated.

5. Pharmacological Properties

5.1. 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 regulator of appetite and calorie intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation.
Animal studies show that semaglutide works in the brain through the GLP-1 receptor. Semaglutide has direct effects on areas in the brain involved in homeostatic regulation of food intake in the hypothalamus and the brainstem. Semaglutide may affect the hedonic reward system through direct and indirect effects in brain areas including the septum, thalamus and amygdala.
Clinical studies show that semaglutide reduces energy intake, increases feelings of satiety, fullness and control of eating, reduces feelings of hunger, and frequency and intensity of cravings. In addition, semaglutide reduces the preference for high fat foods.
Semaglutide orchestrates homeostatic and hedonic contributions with executive function to regulate caloric intake, appetite, reward and food choice.
In addition, in clinical studies semaglutide has shown to reduce blood glucose in a glucose dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. During hypoglycemia, semaglutide diminishes insulin secretion and does not impair glucagon secretion.
GLP-1 receptors are also expressed in the heart, vasculature, immune system and kidneys. Semaglutide has a beneficial effect on plasma lipids, lowered systolic blood pressure and reduced inflammation in clinical studies. Furthermore, animal studies have shown that semaglutide attenuated the development of atherosclerosis and had an anti-inflammatory action in the cardiovascular system. The mechanism of action of semaglutide for cardiovascular risk reduction is likely multifactorial, in part driven by weight loss effects and effects on known cardiovascular risk factors (reduction in blood pressure, improvements in lipid profile and glucose metabolism, and anti-inflammatory effects as demonstrated by reductions in high-sensitivity C-reactive protein (hsCRP)). The exact mechanism of cardiovascular risk reduction has not been established.

5.2. Pharmacodynamics

Effects

Appetite, energy intake and food choice

Semaglutide reduces appetite by increasing feelings of fullness and satiety, while lowering hunger and prospective food consumption. In a phase 1 trial, energy intake during an ad libitum meal was 35% lower with semaglutide compared to placebo after 20 weeks of dosing. This was supported by improved control of eating, less food cravings and a relative lower preference for high fat food. Food cravings were further assessed in STEP 5 by a Control of Eating Questionnaire (CoEQ). At week 104, the estimated treatment difference both for control of cravings and craving of savory food significantly favored semaglutide, whereas no clear effect was seen for craving of sweet food.

Fasting and postprandial lipids

Semaglutide 1 mg compared to placebo lowered fasting triglyceride and very low density lipoproteins (VLDL) concentrations by 12% and 21%, respectively. The postprandial triglyceride and VLDL response to a high fat meal was reduced with >40%.

Clinical Efficacy and Safety

The information provided below is from the published clinical trial

The efficacy and safety of semaglutide for weight management in combination with a reduced calorie intake and increased physical activity were evaluated in four 68 weeks double-blinded randomized placebo-controlled phase 3a trials (STEP 1-4). A total of 4 684 adult patients (2652 randomized to treatment with semaglutide) were included in these trials. Furthermore, the two-year efficacy and safety of semaglutide compared to placebo were evaluated in a double- blinded randomized placebo-controlled phase 3b trial (STEP 5) including 304 patients (152 in treatment with semaglutide).
Treatment with semaglutide demonstrated superior, clinically meaningful, and sustained weight loss compared with placebo in patients with obesity (BMI ≥30 kg/m2), or overweight (BMI ≥27 kg/m2 to <30 kg/m2) and at least one weight-related comorbidity. Furthermore, across the trials, a higher proportion of patients achieved ≥5%, ≥10%, ≥15% and ≥20% weight loss with semaglutide compared with placebo. The reduction in body weight occurred irrespective of the presence of gastrointestinal symptoms such as nausea, vomiting or diarrhoea.
Treatment with semaglutide also showed statistically significant improvements in waist circumference, systolic blood pressure and physical functioning compared to placebo.
Efficacy was demonstrated regardless of age, sex, race, ethnicity, baseline body weight, BMI, presence of type 2 diabetes and level of renal function. Variations in efficacy existed within all subgroups. Relatively greater weight loss was observed in women and in patients without type 2 diabetes as well as in patients with a lower versus higher baseline body weight.

Table 4: Efficacy and Safety Outcomes of Semaglutide 2.4 mg Weekly in the STEP Clinical Trials for Obesity and Weight Management

Trial	Patient Population	Intervention	Comparator	Primary Endpoint	Secondary Endpoints
STEP 1	Adults with obesity or overweight with comorbidities (n=1,961)	Semaglutide 2.4 mg weekly + lifestyle	Placebo + lifestyle	- Weight loss: **−14.9%** (semaglutide) vs. **−2.4%** (placebo), p<0.001.	- ≥5% weight loss: **86.4%** (semaglutide) vs. **31.5%** (placebo). - Adverse events: **89.7%** (semaglutide) vs. 86.4%.
STEP 2	T2DM patients with obesity or overweight (n=1,210)	Semaglutide 2.4 mg and 1.0 mg weekly	Placebo	- Weight loss: **−9.6%** (2.4 mg), **−7.0%** (1.0mg) vs. **−3.4%** (placebo),p<0.001. - HbA1c: **−1.6%** vs. −0.4%.	- ≥10% weight loss: **45.6%** (semaglutide) vs. **10.3%** (placebo). - Nausea most common side effect.
STEP 3	Obesity or overweight patients with intensive behavioural therapy	Semaglutide 2.4 mg weekly	Placebo	- Weight loss: **−16.0%** (semaglutide) vs. **−5.7%** (placebo), p<0.001.	- ≥5% weight loss: **87.8%** vs. **48.5%**. - Higher adherence with semaglutide.
STEP 4	Adults with obesity: continuation of treatment	Semaglutide 2.4 mg weekly	Placebo	- Sustained weight loss: **−17.4%** (semaglutide continuation) vs. weight regain in placebo group.	- Maintenance of ≥5% weight loss: **82.7%** (semaglutide) vs. **34.8%** (placebo).
STEP 5	Obesity or overweight adults (2- year study, n=1,908)	Semaglutide 2.4 mg weekly	Placebo	- Weight loss over 2 years: **−15.2%** (semaglutide) vs. **−2.6%** (placebo), p<0.001.	- High adherence rate with once- weekly dosing. - Similar adverse events as STEP 1
STEP 8	Obesity or overweight adults with comorbidities	Semaglutide 2.4 mg weekly	Liraglutide 3.0 mg daily	- Weight loss: **−15.8%** (semaglutide) vs. **−6.4%** (liraglutide), p<0.001.	- Higher adherence with semaglutide due to weekly dosing.

The information provided below is based on Phase III Trial conducted by Intas Pharmaceutical

In this prospective, randomized, open-label, parallel group, active-controlled, multicenter, Phase-III study conducted to establish non-inferiority of Intas Semaglutide Subcutaneous Injection (Test) Against Innovator Semaglutide (Wegovy FlexTouch, Novo Nordisk) Subcutaneous Injection (Reference) in overweight and obese adult participants in adjunct to diet and exercise, a total of 231 participants were randomly assigned in this study [118 in Test Arm and 113 in Reference Arm].

Primary Efficacy Endpoint:

The summary results for primary endpoint are presented below:

Percent change in the body weight from baseline to Week 24.

Number of Participants, mean, LS mean, point estimate, p-value and Confidence Interval for change from baseline to week 24 (EOS) Body weight of Semaglutide-test vs. Semaglutide-reference for ITT set are presented as below

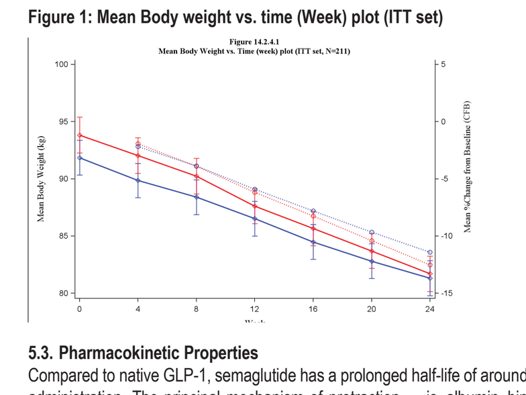
Table 5: Mean percentage change from baseline to week 24 (EOS) Body weight

ITT set (N= 211)					
Treatments	Mean	LS Mean	Semaglutide test Vs. Semaglutide-reference		
			Point Estimate	p-value	95% CI
Semaglutide-test (N=110)	-11.42	-11.39	1.17	0.0834	[0.16, 2.49]
Semaglutide-reference (N=101)	-12.54	-12.56			

As shown in the table, the lower limit of the 95% CI was 0.16 which is above the predefined non-inferiority margin of -4.5. This demonstrates that the test product is non-inferior to the reference product in ITT set.

In addition, the p-value of 0.0834 indicates no statistically significant difference between the Semaglutide-test and Semaglutide-reference products. Therefore, the Semaglutide-test product is concluded to be non-inferior to the Semaglutide-reference product.

Figure 1: Mean Body weight vs. time (Week) plot (ITT set)



5.3. Pharmacokinetic Properties

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 stabilized against degradation by the DPP-4 enzyme.

Absorption

The average semaglutide steady state concentration following s.c. administration of the semaglutide maintenance dose was approximately 75 nmol/L in patients with overweight (BMI ≥27 kg/m^2 to <30 kg/m^2) or obesity (BMI ≥30 kg/m^2) based on data from phase 3a trials, where 90% of patients had average concentrations between 51 nmol/L and 110 nmol/L. The steady state exposure of semaglutide increased proportionally with doses from 0.25 mg up to 2.4 mg once weekly. Steady state exposure was stable with time as assessed up to week 68.
Similar exposure was achieved with s.c. administration of semaglutide in the abdomen, thigh, or upper arm. The absolute bioavailability of semaglutide was 89%.

Distribution

The mean volume of distribution of semaglutide following S.C. administration in patients with overweight or obesity was approximately 12.4 L. Semaglutide is extensively bound to plasma albumin (>99%).

Metabolism/biotransformation

Prior to excretion, semaglutide is extensively metabolized through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid side chain. The enzyme neutral endopeptidase (NEP) was identified as one of the active metabolic enzymes.

Elimination

The primary excretion routes of semaglutide-related material are via the urine and faeces. Approximately 3% of the absorbed dose was excreted in the urine as intact semaglutide.
The clearance of semaglutide in patients with overweight (BMI ≥27 kg/m2 to <30 kg/m2) or obesity (BMI ≥30 kg/m2) was approximately 0.05 L/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for approximately 7 weeks after the last dose of 2.4 mg.

Special populations

Elderly

Age had no effect on the pharmacokinetics of semaglutide based on data from phase 3 trials including patients 18–86 years of age.

Gender, race and ethnicity

Gender, race (White, Black or African American, Asian) and ethnicity (Hispanic or Latino, non-Hispanic or -Latino) had no effect on the pharmacokinetics of semaglutide based on data from phase 3a trials.

Body weight

Body weight had an effect on the exposure of semaglutide. Higher body weight was associated with lower exposure; a 20% difference in body weight between individuals will result in an approximate 18% difference in exposure. The 2.4 mg weekly dose of semaglutide provided adequate systemic exposures over the body weight range of 54.4−245.6 kg evaluated for exposure response in the clinical trials.

Renal impairment

Renal impairment did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. This was shown with a single dose of 0.5 mg semaglutide for patients with different degrees of renal impairment (mild, moderate, severe or patients in dialysis) compared with patients with normal renal function. This was also shown for patients with overweight (BMI ≥27 kg/m2 to <30 kg/m2) or obesity (BMI ≥30 kg/m2) and mild to moderate renal impairment based on data from phase 3a trials.

Hepatic impairment

Hepatic impairment did not have any impact on the exposure of semaglutide. The pharmacokinetics of semaglutide were evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) and compared with patients with normal hepatic function in a study with a single dose of 0.5 mg semaglutide.

Prediabetes and diabetes

Prediabetes and diabetes did not have any clinically relevant effect on the exposure of semaglutide based on data from phase 3 trials.

Immunogenicity

Development of anti-semaglutide antibodies when treated with semaglutide occurred infrequently and the response did not appear to influence semaglutide pharmacokinetics.

6. Nonclinical Properties

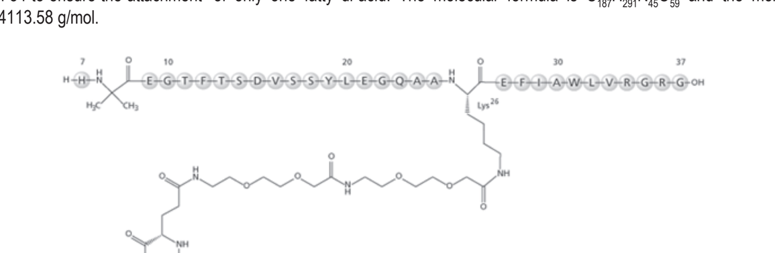
6.1. Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in CD-1 mice, subcutaneous doses of 0.3, 1 and 3 mg/kg/day (2-, 8-, and 22-fold the maximum recommended human dose [MRHD] of 2.4 mg/week, based on AUC) were administered to the males, and 0.1, 0.3 and 1 mg/kg/day (0.6-, 2-, and 5-fold MRHD) were administered to the females. A statistically significant increase in thyroid C-cell adenomas and a numerical increase in C-cell carcinomas were observed in males and females at all dose levels (greater than or equal to 0.6 times human exposure).
In a 2-year carcinogenicity study in Sprague Dawley rats, subcutaneous doses of 0.0025, 0.01, 0.025 and 0.1 mg/kg/day were administered (below quantification, 0.2-, 0.4-, and 2-fold the exposure at the MRHD). A statistically significant increase in thyroid C-cell adenomas was observed in males and females at all dose levels, and a statistically significant increase in thyroid C-cell carcinomas was observed in males at greater than or equal to 0.01 mg/kg/day, at clinically relevant exposures.
Human relevance of thyroid C-cell tumors in rats is unknown and could not be determined by clinical studies or nonclinical studies.
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 (0.04-, 0.1-, and 0.4-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 greater than or equal to 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.

7. Description

Semaglutide Injection is a clear, colorless solution. Semaglutide Injection, for subcutaneous use, contains semaglutide, a human GLP-1 receptor agonist (or GLP-1 analog). 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 $C_{187}H_{291}N_{45}O_{59}$ and the molecular weight is 4113.58 g/mol.



8. Pharmaceutical particulars

8.1. Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

8.2. Shelf-life

15 months
After first opening in use shelf-life is: 6 weeks

8.3. Packaging information

- Semaglutide Injection 0.68mg/ml (1 mg/1.5 ml Prefilled Pen): Each pre-filled pen contains 1.5 ml of solution (delivering 4 doses of 0.25 mg), 5 Pen Needles, 5 Alcohol Swabs.
- Semaglutide Injection 1.34mg/ml (2 mg/1.5 ml Prefilled Pen): Each pre-filled pen contains 1.5 ml of solution (delivering 4 doses of 0.5 mg), 5 Pen Needles, 5 Alcohol Swabs.
- Semaglutide Injection 1.34mg/ml (4 mg/3 ml Prefilled Pen): Each pre-filled pen contains 3 ml of solution (delivering 4 doses of 1 mg), 5 Pen Needles, 5 Alcohol Swabs.
- Semaglutide Injection 2.27mg/ml (6.8 mg/3 ml Prefilled Pen): Each pre-filled pen contains 3 ml of solution (delivering 4 doses of 1.7 mg), 5 Pen Needles, 5 Alcohol Swabs.
- Semaglutide Injection 3.2mg/ml (9.6 mg/3 ml Prefilled Pen) Each pre-filled pen contains 3 ml of solution (delivering 4 doses of 2.4 mg), 5 Pen Needles, 5 Alcohol Swabs.

8.4. Storage and handling instructions

Storage instructions

Before opening (before starting to use)
Store in a refrigerator (2°C to 8°C).
Keep away from the cooling element. Do not freeze.
After first use store below 30 °C or in refrigerator at 2 °C to 8 °C. The product may be stored for maximum 6 weeks after first dose.

Handling instructions

- The pen should not be used if it has been frozen
- Keep the pen cap on when the pen is not in use in order to protect it from light.
- Semaglutide Injection should not be used if it does not appear clear and colourless.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
- The patient should be advised to discard the injection needle in accordance with local requirements after each injection and store the pen without an injection needle attached. This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing.
- Always use a new needle for each injection.
- The pen is for use by one person only.

9. Patient Counselling Information

Patients should be counselled on below mentioned points

Risk of Thyroid C-cell Tumors

Inform patients that semaglutide causes thyroid C-cell tumors in rodents and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia, or dyspnea) to their physician.

Acute Pancreatitis

Inform patients of the potential risk for acute pancreatitis and its symptoms: severe abdominal pain that may radiate to the back, and which may or may not be accompanied by vomiting. Instruct patients to discontinue semaglutide promptly and contact their physician if pancreatitis is suspected.

Acute Gallbladder Disease

Inform patients of the risk of acute gallbladder disease. Advise patients that substantial or rapid weight loss can increase the risk of gallbladder disease, but that gallbladder disease may also occur in the absence of substantial or rapid weight loss. Instruct patients to contact their healthcare provider for appropriate clinical follow-up if gallbladder disease is suspected.

Hypoglycemia

Inform patients of the risk of hypoglycemia and educate patients on the signs and symptoms of hypoglycemia. Advise patients with diabetes mellitus on glycemic lowering therapy that they
may have an increased risk of hypoglycemia when using semaglutide and to report signs and/or symptoms of hypoglycemia to their healthcare provider.

Dehydration and Renal Impairment

Advice patients treated with semaglutide of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs.

Severe Gastrointestinal Adverse Reactions

Inform patients of the potential risk of severe gastrointestinal adverse reactions. Instruct patients to contact their healthcare provider if they have severe or persistent gastrointestinal symptoms.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions have been reported during postmarketing use of semaglutide, the active ingredient in semaglutide. Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking semaglutide and seek medical advice promptly if such symptoms occur.

Diabetic Retinopathy Complications in Patients with Type 2 Diabetes

Inform patients with type 2 diabetes to contact their physician if changes in vision are experienced during treatment with semaglutide.

Heart Rate Increase

Instruct patients to inform their healthcare providers of palpitations or feelings of a racing heartbeat while at rest during semaglutide treatment.

Suicidal Behavior and Ideation

Advise patients to report emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Inform patients that if they experience suicidal thoughts or behaviors, they should stop taking semaglutide.

Pulmonary Aspiration during General Anesthesia or Deep Sedation

Inform patients that semaglutide may cause their stomach to empty more slowly which may lead to complications with anesthesia or deep sedation during planned surgeries or procedures. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking semaglutide.

Pregnancy

Semaglutide may cause fetal harm. Advise patients to inform their healthcare provider of a known or suspected pregnancy.

10. Details of manufacturer

Manufactured by:
INTAS
INTAS PHARMACEUTICALS LTD.
Plot No.: 85/87, Kailash Industrial Estate, Village– Iyava,
Taluka: Sanand, Dist. Ahmedabad-382110
For any safety and quality related concerns, please write to pv@intaspharma.com or report at our website www.intaspharma.com or call at our tollfree number: 1800 1200 124.

11. Details of permission or license number with date

Mfg. Lic. No.: G/28/1546 Dated: 21-04-2026

12. Date of revision

July, 2026

Note: Please refer specific prescribing information meant for use in Type 2 Diabetes mellitus management or Chronic weight management respectively as per the intended use.

INP7522

91 8551 1 6039731

BACK SIDE

File Name : Semaglutide Multiple strengths India combipack PIL 6039731
Size : 900 x 450 mm (Front side) (Final Fold size - 150 x 50 mm)
Colour : CMYK
Date : 17^06^2026, 18^06^2026, 02^07^2026