Applicant/PHCR:	Ranbaxy Pharmaceuticals (Pty) Ltd
Product proprietary name:	**Semagard**
Dosage form and strength:	Solution for injection, 2 mg / 1,5 mL and 4 mg / 3 mL (1,34 mg / mL) Semaglutide
Date of submission:	30 June 2026

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

WARNING: RISK OF THYROID C-CELL TUMOURS

- In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumours at clinically relevant exposures. It is unknown whether **SEMAGARD** causes thyroid C-cell tumours, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumours has not been reported [see **section 4.4**].
- **SEMAGARD** is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) [see **section 4.3**]. Counsel patients regarding the potential risk for MTC with the use of **SEMAGARD** and inform them of symptoms of thyroid tumours (e.g. a mass in the neck, dysphagia, dyspnoea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with **SEMAGARD** [see **section 4.4**].

1. NAME OF THE MEDICINE

SEMAGARD (solution for injection).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 1,34 mg of semaglutide (a human glucagon-like peptide-1 (GLP-1) receptor agonist) of synthetic origin, preserved with 5,50 mg/ml (0,55 % *m/v*) phenol.

Contains propylene glycol 14 mg/ml

SEMAGARD 0,25 mg and 0,5 mg / dose pen:

Each pre-filled pen contains 2 mg semaglutide in 1,5 ml solution

SEMAGARD 1 mg/dose pen:

Each pre-filled pen contains 4 mg semaglutide in 3 ml solution

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection (injection).

A clear, colourless solution, free from visible particulate matter, isotonic solution. **SEMAGARD** has a pH of approximately 7.4.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SEMAGARD is indicated for:

- 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.
- as combination therapy with oral anti-diabetic medicines (metformin, thiazoledinediones, sulphonylurea), basal insulin with or without metformin and pre-mix insulin.

4.2 Posology and method of administration

Posology

Semaglutide starting dose is 0,25 mg 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 glycaemic control.

Semaglutide dose 0,25 mg is not a therapeutic dose.
Semaglutide can be used as monotherapy or as combination therapy with one or more antidiabetic medicines. **See section 4.1** for further information.

When semaglutide is added to existing metformin and/or thiazolidinedione therapy, the current dose of metformin and/or thiazolidinedione can be continued unchanged.

When semaglutide is added to existing sodium-glucose co-transporter 2 (SGLT2) inhibitor therapy, the current dose of SGLT2 inhibitor can be continued unchanged.

When semaglutide is added to existing therapy of a sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia (**see section 4.4**).

The use of semaglutide does not require blood glucose self-monitoring. Self-monitoring should be performed when semaglutide is used together with metformin, sulfonylurea or insulin in order to allow adjustment of the dose of these medicines.

Special populations

Elderly (≥ 65 years old):

No dose adjustment is required based on age.

Gender and Ethnicity:

No dose adjustment is required based on gender, age, race or ethnicity.

Patients with renal impairment:

No dose adjustment is required for patients with renal impairment. The reported experience with the use of semaglutide in patients with end-stage renal impairment is limited. Caution should be exercised when treating these patients with semaglutide.

Patients with hepatic impairment:

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

Children and adolescents:

Safety and efficacy of semaglutide in children and adolescents below 18 years have not been reported.

Method of administration

Semaglutide is to be administered once weekly at any time of the day, with or without meals.

Semaglutide is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed without dose adjustment.

Semaglutide should not be administered intravenously or intramuscularly.

The day of weekly administration can be changed if necessary as long as the time between two doses is at least 2 days (> 48 hours).

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.

4.3 Contraindications

- Hypersensitivity to semaglutide or to any of the excipients listed under **section 6.1**.
- A personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) (see **section 4.4**).
- Pregnancy and lactation. Women who may become pregnant should use effective contraception while taking semaglutide (see **section 4.6**).

4.4 Special warnings and precautions for use

SEMAGARD should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Diabetic ketoacidosis has been reported in insulin-dependent patients whom had rapid discontinuation or dose reduction of insulin when treatment with a GLP-1 receptor agonist is started.

SEMAGARD is not a substitute for insulin.

Aspiration in association with general anaesthesia or deep sedation

Cases of pulmonary aspiration have been reported in patients receiving GLP-1 receptor agonists undergoing general anaesthesia or deep sedation. Therefore, the increased risk of residual gastric content due to delayed gastric emptying (see section 4.8) should be considered prior to performing procedures with general anaesthesia or deep sedation.

Gastrointestinal effects and dehydration

SEMAGARD may be associated with gastrointestinal adverse reactions. This should be considered when treating patients with impaired renal function as nausea, vomiting, and diarrhoea, may cause dehydration which could cause a deterioration of renal function. Patients treated with semaglutide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Acute pancreatitis

Acute pancreatitis has been reported with the use of **SEMAGARD**. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, **SEMAGARD** should be discontinued; if confirmed, **SEMAGARD** should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.

Hypoglycaemia

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

Diabetic retinopathy

In patients with diabetic retinopathy treated with insulin and **SEMAGARD**, an increased risk of developing diabetic retinopathy complications has been reported (see **section 4.8**). Caution should be exercised when using **SEMAGARD** in patients with diabetic retinopathy treated with insulin.

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Long-term glycaemic control decreases the risk of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for worsening and treated according to clinical guidelines.

There is no reported experience with semaglutide 2 mg use in patients with type 2 diabetes with uncontrolled or potentially unstable diabetic retinopathy and semaglutide 2 mg is therefore not recommended in these patients.

Heart failure

There is no report of therapeutic experience in patients with congestive heart failure New York Heart Association (NYHA) class IV.

Risk of Thyroid C-cell Tumours

SEMAGARD has been reported to cause a dose dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumours (adenomas and carcinomas) in mice and rats after lifetime exposure at clinically relevant plasma exposures. It is unknown whether **SEMAGARD** causes thyroid C-cell tumours, including medullary thyroid carcinoma (MTC), in humans as human relevance of **SEMAGARD**-induced rodent thyroid C-cell tumours 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.

SEMAGARD is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of **SEMAGARD** and inform them of symptoms of thyroid tumours e.g. mass in the neck, dysphagia, dyspnoea, persistent hoarseness). 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.

Hypersensitivity

Serious hypersensitivity reactions (e.g. anaphylaxis, angioedema) have been reported with GLP-1 receptor agonists such as **SEMAGARD**. If hypersensitivity reactions occur, discontinue use of **SEMAGARD**; treat promptly per standard of care and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity to **SEMAGARD** (see **section 4.3**).

Non-arteritic anterior ischaemic optic neuropathy (NAION)

Data from epidemiological studies indicates an increased risk for non-arteritic anterior ischaemic optic neuropathy (NAION) during treatment with semaglutide. There is no identified time interval for when NAION may develop following treatment start. A sudden loss of vision should lead to

ophthalmological examination and treatment with semaglutide should be discontinued if NAION is confirmed (see **section 4.8**).

Patients with gastroparesis

Semaglutide treated patients with gastroparesis may experience more serious or severe gastrointestinal adverse events. Semaglutide should be used with caution in these patients, and semaglutide is not recommended if gastroparesis is severe (see **section 4.8**).

Contains dibasic sodium phosphate and sodium hydroxide.

This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

Contains propylene glycol

This medicine contains 14 mg/ml of propylene glycol, which is equivalent to 21 mg/pen in the 2 mg/1,5 ml and 42 mg/pen in the 4 mg/3 mL strength.

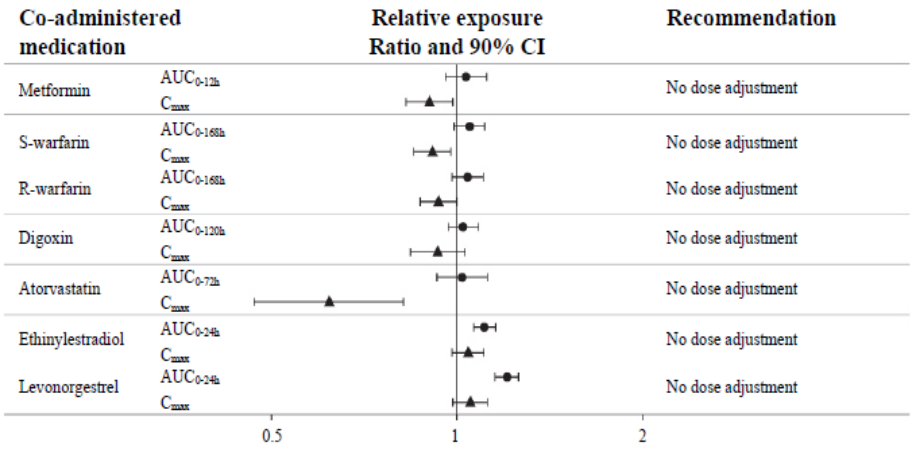
Propylene glycol in this medicine can have the same effects as drinking alcohol and may increase the likelihood of side effects. Use only if recommended by a doctor. Your doctor may carry out extra checks while you are taking this medicine.

4.5 Interaction with other medicines and other forms of interaction

In vitro studies have reported very low potential for semaglutide to inhibit or induce CYP enzymes, and to inhibit drug transporters.

The delay of gastric emptying with semaglutide may influence the absorption of concomitantly administered oral medicines. The potential effect of semaglutide on the absorption of co-administered oral medicines have been reported at semaglutide 1 mg steady state exposure.

No clinically relevant interaction with semaglutide (*Figure 1*) was observed based on the evaluated medicines. Therefore, no dose adjustment is required when co-administered with semaglutide.



Relative exposure in terms of AUC and C_{max} for each medication when given with semaglutide compared to without semaglutide. Metformin and oral contraceptive drug ethinylestradiol/levonorgestrel) were assessed at steady state. Warfarin (S-warfarin/R-warfarin), digoxin and atorvastatin were assessed after a single dose.

Abbreviations: AUC: area under the curve. C_{max}: maximum concentration. CI: confidence interval.

Figure 1 Impact of semaglutide on the exposure of co-administered oral medications

Paracetamol

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

Oral contraceptives

Reportedly, 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 medicine (0,03 mg ethinylestradiol/0,15 mg levonorgestrel) was co-administered with semaglutide. Exposure of ethinylestradiol was not affected; an increase of 20 % was reported for levonorgestrel exposure at steady state. C_{max} has been reported to be not affected for any of the compounds.

Atorvastatin

Semaglutide had been reported to not change the overall exposure of atorvastatin following a single dose administration of atorvastatin (40 mg). Atorvastatin C_{max} has been reported to decrease by 38 %. This was assessed not to be clinically relevant.

Digoxin

Semaglutide had been reported to not change the overall exposure or C_{max} of digoxin following a single dose of digoxin (0,5 mg).

Metformin

Semaglutide had been reported to not change the overall exposure or C_{max} of metformin following dosing of 500 mg twice daily over 3,5 days.

Warfarin and other coumarin derivatives

Semaglutide had been reported to not change the overall exposure or C_{max} 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, upon initiation of semaglutide treatment in patients on warfarin or other coumarin derivatives, frequent monitoring of INR is recommended.

4.6 Fertility, pregnancy and lactation

Semaglutide is contraindicated during pregnancy and lactation (see **section 4.3**).

Pregnancy

Studies in animals have reported reproductive toxicity (see **section 5.3**). Semaglutide should not be used during pregnancy. The safety of semaglutide in pregnant women has not been reported.

Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life.

Women who may become pregnant should use effective contraception while taking semaglutide and for 2 months after stopping the medicine.

Lactation

It is unknown whether semaglutide is excreted in human milk. In lactating rats, semaglutide has been reported to be excreted in milk. Women on treatment with semaglutide should not breastfeed their infants.

Fertility

The effect of semaglutide on fertility in humans is not reported. Semaglutide did not affect male fertility in rats. In female rats, an increase in oestrous length and a small reduction in number of ovulations were reported at doses associated with maternal body weight loss (see **section 5.3**).

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 hypoglycaemia while driving and using machines (see **section 4.4**).

4.8 Undesirable effects

a) Summary of safety profile

The most frequently reported adverse reactions with semaglutide were gastrointestinal disorders, including nausea, diarrhoea and vomiting.

In general, these reactions were mild or moderate in severity and of short duration.

b) Tabulated list of adverse reactions

Table 1 lists adverse reactions reported in patients with type 2 diabetes (further described in section Description of selected adverse reactions).

Table 1: Side effects reported for semaglutide

System organ class	Frequent	Less Frequent	Unknown
Immune-system disorders		Hypersensitivity[c], Anaphylactic reaction	
Metabolism and nutrition disorders	Hypoglycaemia[a] when used with insulin or sulfonylurea, Hypoglycaemia[a] when used with other oral antidiabetic drugs, Decreased appetite		
Nervous system disorders	Dizziness, Headache	Dysgeusia	Dysaesthesia[d]

Eye disorders	Diabetic retinopathy complications[b]	Non- arteritic anterior ischaemic optic neuropathy (NAION)	
Cardiac disorders		Increased heart rate	
Gastrointestinal disorders	Nausea, Diarrhoea, Vomiting, Abdominal pain, Abdominal distension, Constipation, Dyspepsia, Gastritis, Gastro-oesophageal reflux disease, Eructation, Flatulence,	Acute pancreatitis, Delayed gastric emptying	Intestinal obstruction[d].
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]Hypoglycaemia 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: need for retinal photocoagulation, need for treatment with intravitreal agents, vitreous haemorrhage, onset of diabetes-related blindness. Frequency based on reported cardiovascular outcomes trial.

[c]Grouped term covering adverse events related to hypersensitivity such as rash and urticaria

[d]From post-marketing reports.

Description of selected adverse reactions

Hypoglycaemia

One episode of severe hypoglycaemia was reported when semaglutide was used as monotherapy. Severe hypoglycaemia was primarily reported 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 severe episodes (0,1 % of subjects, 0,001 events/patient year) were reported with semaglutide in combination with oral antidiabetics other than sulfonylureas.

Hypoglycaemia has been reported in 11,3 % (0,3 events/patient year) of patients when semaglutide 1 mg was added to SGLT2 inhibitor compared to 2,0 % (0,04 events/patient year) of placebo-treated patients. Severe hypoglycaemia has been reported in 0,7 % (0,01 events/patient year) and 0 % of patients, respectively.

The majority of the hypoglycaemic episodes has been reported when semaglutide 1 mg and 2 mg was used in combination with sulfonylurea or insulin. Overall, there was no reported increased risk of hypoglycaemia with semaglutide 2 mg.

Gastrointestinal adverse reactions

Nausea has been reported in 17,0 % and 19,9 % patients when treated with semaglutide 0,5 mg and 1 mg respectively, diarrhoea 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 5,9 % of subjects. 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.

Nausea has been reported to occur in similar proportions of patients when treated with semaglutide 1 mg and 2 mg. Diarrhoea and vomiting has been reported 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, constipation and gastro-oesophageal reflux disease has been reported in 6,7 % and 4 % of patients, respectively treated with semaglutide 1 mg compared to no events for placebo-treated patients. The prevalence of these events did not decrease over time.

Patients with gastroparesis may experience more serious or severe gastrointestinal effects when treated with semaglutide.

Diabetic retinopathy complications

In patients with type 2 diabetes and high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose, adjudicated events of diabetic retinopathy has been reported in more patients treated with semaglutide (3,0 %) compared to placebo (1,8 %). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline. In patients that did not have a documented history of diabetic retinopathy, the number of events were similar for semaglutide and placebo. In 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 %).

Non-arteritic anterior ischaemic optic neuropathy (NAION)

Results from several large epidemiological studies suggest that exposure to semaglutide in adults with type 2 diabetes is associated with an approximately two-fold increase in the relative risk of developing NAION, corresponding to approximately one additional case per 10000 person-years of treatment.

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 reported by adjudication was 0,5 % for semaglutide and 0,6 % for placebo (see **section 4.4**).

Discontinuation due to an adverse event

The incidence of discontinuation of treatment due to adverse events was 6,1 % and 8,7 % for patients treated with 0,5 mg and 1 mg of semaglutide versus 1,5 % for placebo. The most frequent adverse events leading to discontinuation were gastrointestinal.

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 been 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 neutralising antibodies or anti-semaglutide antibodies with endogenous GLP-1 neutralising effect at end-of-trial.

Heart rate increase

Increased heart rate has been reported with GLP-1 receptor agonists. In the reported study, mean increases of 1 to 6 beats per minute (bpm) from a baseline of 72 to 76 bpm have been reported 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Suspected adverse reactions can also be reported directly to the HCR via email: pharmacovigilance.africasme@sunpharma.com or tel: +27(0) 12 643 2000

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 commonly reported adverse reaction was nausea. All patients recovered without complications.

There is no specific antidote for overdose with semaglutide. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A

prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of semaglutide of approximately 1 week (see **section 5.2**).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 21.13 Hormones, antihormones and oral hypoglycaemics - other

Pharmacotherapeutic group: Drugs used in diabetes, Glucagon-like peptide-1 (GLP-1) analogues;

ATC code: A10BJ06.

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.

Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner.

Semaglutide reduces body weight and body fat mass through lowered energy intake. The mechanism involves an overall reduced appetite, which includes increased satiety and reduced hunger.

5.2 Pharmacokinetic properties

Semaglutide has pharmacokinetic properties compatible with once weekly administration, with an elimination half-life of approximately 1 week.

Absorption

Maximum concentration was reached 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 s.c. administration of 0,5 mg and 1 mg semaglutide were approximately 16 nmol/L and 30 nmol/L, respectively.

Semaglutide exposure increased in a dose proportional manner for doses of 0,5 mg and 1 mg.

Similar exposure was achieved with s.c. administration of semaglutide in the abdomen, thigh, or upper arm. Absolute bioavailability of s.c semaglutide was 89 %.

Distribution

The mean volume of distribution of semaglutide following s.c. administration in patients with type 2 diabetes was approximately 12,5 L. Semaglutide was extensively bound to plasma albumin (> 99 %).

Metabolism/biotransformation

Semaglutide is metabolised through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid side chain.

Elimination

The primary excretion routes of semaglutide related material were via the urine (53 %) and faeces (18,6 %). Approximately 3% of the dose was excreted as intact semaglutide via urine.

Clearance of semaglutide in patients with type 2 diabetes 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 populations

No dose adjustment of semaglutide is needed based on age, gender, race, ethnicity, body weight, or renal or hepatic impairment.

Renal impairment:

Renal impairment did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. The reported experience in patients with end-stage renal disease was limited.

Hepatic impairment:

Hepatic impairment did not have any impact on the exposure 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.

Paediatrics:

Semaglutide has not been reported to be studied in paediatric patients.

5.3 Preclinical safety data

The reported preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeated dose toxicity or genotoxicity.

Non-lethal thyroid C-cell tumours reported in rodents are a class effect for GLP-1 receptor agonists. In 2-year reported carcinogenicity studies in rats and mice, semaglutide caused thyroid C-cell tumours at clinically relevant exposures. No other treatment-related tumours were reported. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. The relevance for humans is considered to be low, but cannot be completely excluded.

In reported fertility studies in rats, semaglutide did not affect mating performance or male fertility. In female rats, an increase in oestrous cycle length and a small reduction in corpora lutea (ovulations) were reported at doses associated with maternal body weight loss.

In reported embryo-foetal development studies in rats, semaglutide caused embryotoxicity below clinically relevant exposures. Semaglutide caused marked reductions in maternal body weight and reductions in embryonic survival and growth. In foetuses, major skeletal and visceral malformations were reported, including effects on long bones, ribs, vertebrae, tail, blood vessels and brain ventricles. Mechanistic evaluations indicated that the embryotoxicity involved a GLP-1 receptor mediated impairment of the nutrient supply to the embryo across the rat yolk sac. Due to species differences in yolk sac anatomy and function, and due to lack of GLP-1 receptor expression in the yolk sac of non-human primates, this mechanism is considered unlikely to be of relevance to humans. However, a direct effect of semaglutide on the foetus cannot be excluded.

In reported developmental toxicity studies in rabbits and cynomolgus monkeys, increased pregnancy loss and slightly increased incidence of foetal abnormalities were reported at clinically relevant exposures. The findings coincided with marked maternal body weight loss of up to 16 %. Whether these effects are related to the decreased maternal food consumption as a direct GLP-1 effect is unknown.

Postnatal growth and development were reported in cynomolgus monkeys. Infants were slightly smaller at delivery, but recovered during the lactation period.

In juvenile rats, semaglutide caused delayed sexual maturation in both males and females. These delays had no impact upon fertility and reproductive capacity of either sex, or on the ability of the females to maintain pregnancy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Dibasic Sodium Phosphate
- Hydrochloric Acid
- Phenol
- Propylene Glycol
- Sodium Hydroxide
- Water for Injection

SEMAGARD contains less than 1 mmol sodium (23 mg ($^{m}/_{v}$)) per dose, i.e. essentially 'sodium-free'.

6.2 Incompatibilities

Substances added to **SEMAGARD** may cause degradation of semaglutide. **SEMAGARD** must not be mixed with other medicines, e.g. infusion fluids.

6.3 Shelf life

24 months when stored in a refrigerator (2 °C to 8 °C).

In-use shelf life: 56 days when stored at room temperature (15 °C to 30 °C)

6.4 Special precautions for storage

Prior to first use, **SEMAGARD** should be stored in a refrigerator between 2 ºC to 8 ºC.

Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze **SEMAGARD** and do not use **SEMAGARD** if it has been frozen.

After first use of **SEMAGARD**, the pen can be stored for 56 days at controlled room temperature (15 °C to 30 °C) or in a refrigerator (2 °C to 8 °C). Do not freeze. Keep the pen cap on when not in use.

SEMAGARD should be protected from excessive heat and sunlight

6.5 Nature and contents of container

3 mL colourless USP type I glass cartridges with a 10 mm grey bromobutyl rubber plunger stopper and a combination seal (cream inner and gray outer).

One filled and sealed cartridge of **SEMAGARD**, 2 mg /1,5mL and 4 mg/ 3mL (1,34 mg/mL), packed in one transparent cartridge holder and assembled with the help of body subassembly (blue body with grey button and white dose knob) and blue cap for pen injector.

Pack sizes:

SEMAGARD 0,25 mg, 0,5 mg / dose pen:

1 x 1,5 ml pre-filled pen including 6 disposable needles.

SEMAGARD 1 mg/dose pen:

1 x 3 ml pre-filled pen including 4 disposable needles.

6.6 Special precautions for disposal and other handling

The patient should be advised to discard the injection needle 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. Needles and other waste material should be disposed of in accordance with local requirements. The pen is for use by one person only. **SEMAGARD** should not be used if it does not appear clear and colourless or almost colourless.

7. HOLDER OF CERTIFICATE OF REGISTRATION

RANBAXY PHARMACEUTICALS (PTY) LTD

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South Africa

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8. REGISTRATION NUMBER(S)

61/21.13/0768

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

30 June 2026

10. DATE OF REVISION OF THE TEXT

30 June 2026

Applicant/PHCR:	Ranbaxy Pharmaceuticals (Pty) Ltd
Product proprietary name:	**Semagard**
Dosage form and strength:	Solution for injection, 2 mg / 1,5 mL and 4 mg / 3 mL (1,34 mg / mL) Semaglutide
Date of submission:	30 June 2026