NATIONAL PHARMACEUTICAL REGULATORY AGENCY
MINISTRY OF HEALTH MALAYSIA

TECHNICAL EVALUATION SUMMARY

RODUCT NAME:

1. Wegovy 0.25 mg/0.5mL (0.25 mg/dose) Solution for injection in pre-filled pen (MAL23066004ACZ)
2. Wegovy 0.5mg/0.5mL (0.5mg/dose) Solution for injection in pre-filled pen (MAL23066005ACZ)
3. Wegovy 1mg/0.5mL (1mg/dose) Solution for injection in pre-filled pen (MAL23066006ACZ)
4. Wegovy 1.7mg/0.75 mL (1.7mg/dose) Solution for injection in pre-filled pen (MAL23066007ACZ)
5. Wegovy 2.4 mg/0.75mL (2.4mg/dose) Solution for injection in pre-filled pen (MAL23066008ACZ)

ACTIVE INGREDIENT:

1. Semaglutide 0.25 mg/0.5 mL
2. Semaglutide 0.5 mg/0.5 mL
3. Semaglutide 1 mg/0.5 mL
4. Semaglutide 1.7 mg/0.75 mL
5. Semaglutide 2.4 mg/0.75 mL

PRODUCT REGISTRATION HOLDER:

Novo Nordisk Pharma (Malaysia) Sdn. Bhd

PRODUCT MANUFACTURER:

DP Batch Releaser: Novo Nordisk Pharmaceutical Industries LP, United States of America (USA)

DP Manufacturer:

Catalent Belgium SA, Belgium

1. Semaglutide 0.25 mg/0.5 mL
2. Semaglutide 0.5 mg/0.5 mL
3. Semaglutide 1 mg/0.5 mL
4. Semaglutide 1.7 mg/0.75 mL
5. Semaglutide 2.4 mg/0.75 mL

Novo Nordisk A/S, Bagsvaerd, Denmark

1. Semaglutide 1.7 mg/0.75 mL
2. Semaglutide 2.4 mg/0.75 mL

APPROVAL DATE:

8 June 2023 (DCA 385)

1.0 BACKGROUND INFORMATION

1.1 Approved Indication

Wegovy is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of

- ≥30 kg/m^2 (obesity), or
- ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity e.g. dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease.

1.2 Approved Posology

The maintenance dose of semaglutide 2.4 mg once-weekly is reached by starting with a dose of 0.25 mg. To reduce the likelihood of gastrointestinal symptoms, the dose should be escalated over a 16-week period to a maintenance dose of 2.4 mg once weekly (see Table 1). In case of significant gastrointestinal symptoms, consider delaying dose escalation or lowering to the previous dose until symptoms have improved.

Table 1 Dose escalation schedule

Dose escalation	**Weekly dose**
Week 1–4	0.25 mg
Week 5–8	0.5 mg
Week 9–12	1 mg
Week 13–16	1.7 mg
Maintenance dose	2.4 mg

Weekly doses higher than 2.4 mg are not recommended.

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 hypoglycaemia.

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. If more doses are missed, reducing the starting dose for re-initiation should be considered.

Special populations

Elderly (≥65 years old)

No dose adjustment is required based on age. Therapeutic experience in patients ≥75 years of age is limited, and greater sensitivity of some older individuals cannot be excluded.

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/1.73m2) 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.

Paediatric population

The safety and efficacy of semaglutide in children and adolescents below 18 years have not yet been established. No data are available.

Method of administration

Subcutaneous use.

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

It is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed. It 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 3 days (>72 hours). After selecting a new dosing day, once-weekly dosing should be continued.

When administering Wegovy, the pen should be pressed firmly against the skin until the yellow bar has stopped moving. The injection takes about 5–10 seconds.

Patients should be advised to read the 'Instructions on how to use Wegovy pen on the other side of this leaflet carefully before administering the medicinal product.

1.3 Method of administration

Subcutaneous (SC)

1.4 Pharmacological Aspects

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 the homeostatic and hedonic contributions with executive function to regulate caloric intake, appetite, reward and food choice.

In addition, in clinical studies semaglutide have 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 hypoglycaemia, 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.

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/m2 to <30 kg/m2) or obesity (BMI ≥ 30 kg/m2) 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 metabolised 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 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.

Paediatrics

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

2.0 SUMMARY REPORT

2.1 Quality

2.1.1 Active Substance

- Semaglutide is a recombinant long acting analogue of 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. It has a 94% homology to human GLP-1 and a long half-life suitable for once-weekly dosing.
- The drug substance semaglutide has been previously evaluated as it is the same drug substance as the currently registered products; Ozempic® 1.34 mg/ml (1 mg/dose) Solution for injection in pre-filled pen (MAL20026058AZ) and Ozempic® 1.34 mg/ml (0.25 mg, 0.5 mg/dose) Solution for injection in pre-filled pen (MAL20026057AZ). Therefore, no further evaluation of quality specifically on drug substance will be warranted

2.1.2 Finished Product

- The formulation and filling process of semaglutide drug products manufactured for clinical trials is comparable to the manufacturing process intended for market. The manufacturing process for drug product from Catalent Belgium SA and Novo Nordisk A/S Bagsværd is shown to be comparable.
- Drug product manufacturing process validations have been performed at Catalent Belgium SA and Novo Nordisk A/S Bagsværd and the validation results demonstrate that the established manufacturing process is capable of consistently produce semaglutide 0.5 mg/ml, 1.0 mg/ml, 2.0 mg/ml, 2.27 mg/ml and 3.2 mg/ml drug products in accordance with the specifications and acceptance criteria.
- Long term stability studies results support the proposed shelf life of 24 months. Long term stability studies results showed that semaglutide Drug Product assembled in single dose pen-injector and packed in carton is stable at 24 months when stored at 2°C – 8°C.

In addition, the results of the in-use stability studies support the proposed in-use period of 28 days below 30°C for semaglutide drug products.

- Semaglutide Drug Product 0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg solution for injection are clear and colourless solutions filled in a pre-fillable syringe, with a filling volume of 0.5 mL (0.25 mg, 0.5 mg and 1 mg) or 0.75 ml (1.7 mg and 2.4 mg), assembled in a pen-injector. It is intended for subcutaneous use.
- The primary packaging is a 1 mL glass syringe barrel with a staked needle, rigid needle shield and a rubber plunger. The prefilled syringe is assembled in a single dose, single use prefilled pen-injector.
- The product has passed the evaluation on analytical protocol and method validation in accordance with the ICH Q2 (R1) guidelines.
- Good Manufacturing Practice (GMP) compliance for Catalent Belgium SA, Belgium and Novo Nordisk A/S, Denmark was verified by Federal Agency for Medicines and Health Products, Belgium and Danish Medicine Agency, Denmark respectively. The final batch releaser for this product is Novo Nordisk Pharmaceutical Industries LP, Clayton, United States. The GMP compliance for this site was verified by United States Food and Drug Administration (USFDA).
- Endorsement letter for the single-dose pen injector (DV3396 Pen-injector) had been issued by Medical Device Authority (MDA). (Dated: 25 April 2022).

2.2 Non-clinical studies

- The non-clinical dossier was based on the Ozempic application for type 2 diabetes with changes made to the pharmacology section to include summary of body weight related effects of semaglutide occurring within the brain and update to the animal to human exposure ratio due to the higher clinical dose for weight management (2.4mg/week) compared to the clinical dose for type 2 diabetes (1mg/week). As such there is no new nonclinical safety studies conducted to support weight management indication.
- Two pharmacology reports specifically for weight management were provided. Both studies concluded that semaglutide crosses the blood brain barrier (BBB) and has direct access to specific brain regions involved with the homeostatic regulation of energy intake, the hypothalamus and the brain stem.

2.3 Efficacy

- The clinical development programme for weight management consists of 8 completed clinical trials as listed below:

a. 3 clinical pharmacology trials

b. 1 phase 2 dose finding trial

c. 4 phase 3a therapeutic confirmatory trials (Semaglutide Treatment Effect in People [STEP] trials)

- The efficacy and safety of semaglutide SC 2.4 mg once weekly for weight management as an adjunct to a reduced-calorie diet and increased physical activity (STEP 1, 2 and 4) or intensive behavioral therapy (IBT) (STEP 3) were studied in four pivotal phase 3a 68-week randomized, double-blind, placebo-controlled trials which included a total of 2652 subjects randomized to semaglutide 2.4 mg and 1530 randomized to placebo. In STEP 1, 2 and 4, standard lifestyle intervention was included according to clinical guidelines.
- The four phase 3a trials (STEP 1–4) all included subjects with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 to <30kg/ m^2) and at least one weight-related comorbidity. STEP 2 included subjects with overweight or obesity (BMI ≥27kg/m^2) and Type 2 diabetes mellitus (T2D) (HbA_{1c} 7–10%). STEP 3 evaluated semaglutide 2.4 mg when combined with IBT consisting of a very restrictive diet plan, increased physical activity and behavioral counselling.
- Dose-escalation was used to mitigate gastrointestinal side effects, based on experience from the development programme for Ozempic and from the GLP-1 RA drug class in general.
- All four trials had a treatment duration of 68 weeks with an additional 7 weeks of follow-up off treatment. In STEP 1–3, the 68 weeks of treatment included 16 weeks of dose escalation period during which the dose was gradually increased to the maintenance dose of 2.4 mg once weekly and 52 weeks on maintenance dose. The semaglutide 1.0 mg treatment arm in STEP 2 included 8 weeks of dose escalation and 60 weeks on 1.0 mg. In STEP 4, semaglutide was escalated during a 20-week run-in period, and patients who reached semaglutide 2.4 mg after the run-in period were randomized to either continued treatment with semaglutide or placebo for 48 weeks.
- The primary objective of the four phase 3a trials (STEP 1–4) was to compare the effect of semaglutide s.c. 2.4 mg once weekly vs placebo in subjects overweight or obesity (and T2D in STEP 2) on body weight, either as an adjunct to a reduced-calorie diet and increased physical activity (STEP 1, 2 and 4) or to IBT (STEP 3).
- Primary endpoint for all four trials were change from baseline to week 68 in body weight (%) [STEP 1-4] and subjects who achieve ≥ 5% body weight reduction from week 0 at week 68 [STEP 1-3].

Summary of pivotal clinical studies conducted are as follows:

Study Type & Design (N)	Objective (s) of the Study	Results of Primary Endpoint
STEP 1 – weight management Phase 3a, randomized, double-blind, placebo-controlled, two-armed, parallel group, multicentre trial ***Wilding, J. PH, et al.*** Once-weekly semaglutide in adults with overweight or obesity**. New England Journal of Medicine (2021).** Ratio: 2:1 N= 1306 to semaglutide N= 655 to placebo	To compare the effect of semaglutide s.c. 2.4 mg once weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in subjects with overweight or obesity on body weight.	**<u>Co-primary endpoints</u>** • At week 68, the estimated change in mean body weight from baseline to week 68 was −14.85% with semaglutide 2.4 mg and −2.41% with placebo with an estimated treatment difference of -12.4% [95%CI: (-13.4 to -11.5; p< 0.0001)] • Semaglutide treated participants were more likely to lose 5% or more of baseline body weight at week 68 than those who received placebo (p< 0.0001) with 86.4% in the semaglutide group vs 31.5% in the placebo group. **Conclusion:** In adults with overweight or obesity, superiority of semaglutide 2.4 mg versus placebo was confirmed for both co-primary endpoints from baseline to week 68
STEP 2 – weight management in type 2 diabetes Phase 3a, randomized, double-blind, double dummy, placebo-controlled, multicentre trial ***M. Davies, et al.*** Semaglutide 2· 4 mg once a week in adults	To compare the effect of semaglutide SC 2.4mg once weekly versus placebo as an adjunct to a reduced calorie diet and increased physical activity in subjects with overweight or obesity and T2D on body weight.	**<u>Co-primary endpoints</u>** • Change in mean body weight from baseline to week 68 was -9.6% with semaglutide 2.4mg vs -3.4% with placebo. Estimated treatment difference (ETD) for semaglutide 2.4mg versus placebo was -6.2 percentage point (95% CI -7.3 to -5.2; p< 0.0001). • At week 68, patients treated with semaglutide 2.4mg (68.8%) demonstrated a greater weight loss of ≥5% compared to placebo (28.5%) and compared to semaglutide 1.0 mg (57.1%).

with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. **The Lancet 397.10278 (2021): 971-984.** Ratio: 1:1:1 N= 404 to semaglutide 2.4mg N= 403 to semaglutide 1.0mg N= 403 to placebo		**Conclusion:** In adults with overweight or obesity, and type 2 diabetes, superiority of semaglutide 2.4mg administered once weekly was demonstrated in both primary endpoint of changes in body weight and body weight loss of ≥ 5% at week 68.
STEP 3 - Weight management with intensive behavioural therapy (IBT) Phase 3a, randomised, double-blind, placebo-controlled, two-armed, parallel group, multicentre trial ***Wadden, Thomas A., et al***. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. ***Jama*** **325.14 (2021): 1403-1413.** Ratio: 2:1	To compare the effect of semaglutide s.c. 2.4 mg once-weekly versus placebo as an adjunct to IBT in subjects with overweight or obesity, on body weight.	**<u>Co-primary endpoints</u>** • At week 68, the estimated mean weight change from baseline was −16.0% with semaglutide vs –5.7% with placebo, both combined with intensive behavioral therapy and meal replacements (difference, −10.3 percentage points [95% CI, −12.0 to −8.6]; *P* < .001). • Semaglutide-treated participants were significantly more likely to have lost at least 5% of baseline body weight at week 68 vs placebo (*P* < .001) with 86.6% of participants in the semaglutide group vs 47.6% in the placebo group. **Conclusion:** In adults with overweight or obesity, used as an adjunct to intensive behavioral therapy and initial low-calorie diet, superiority of semaglutide 2.4 mg versus placebo was

N= 407 to semaglutide N= 204 to placebo		confirmed for both primary endpoints (change in body weight (%) from baseline to week 68 and subjects who achieved ≥5% weight loss from baseline to week 68).
STEP 4 – sustained weight management Phase 3a, placebo-controlled, two-armed, double-blind, multinational, multicentre, randomised withdrawal trial. ***Rubino, D., et al.*** Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. ***Jama* 325.14 (2021): 1414-1425.** Ratio: 2:1 N= 535 to semaglutide N= 268 to placebo	Efficacy-related: randomisation (week 20) to week 68: To compare the effect of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo as an adjunct to reduced-calorie diet and increased physical activity in subjects with overweight or obesity who have reached target dose of semaglutide during the run-in period, on body weight.	**<u>Primary endpoint:</u>** • The estimated mean weight change from week 20 to week 68 was −7.9% with continued semaglutide vs +6.9% in participants switched to placebo (difference, −14.8 [95% CI, −16.0 to −13.5] percentage points; P < .001. **Conclusion:** Among adults with overweight or obesity who completed a 20-week run-in period with subcutaneous semaglutide, superiority of semaglutide 2.4 mg versus placebo was confirmed for the primary endpoint (change in body weight (%) from baseline (week 20) to week 68), resulted in continued weight loss over the following 48 weeks.

2.4 Safety

- The safety and tolerability profile of semaglutide 2.4 mg was overall similar to that of approved GLP-1 RAs, including semaglutide SC (Ozempic) and oral semaglutide (Rybelsus) for type 2 diabetes (T2D). No new safety concerns have been identified.
- The most frequent adverse reactions were (as expected) gastrointestinal disorders, including nausea, diarrhea, constipation, abdominal pain and vomiting. Dose-

escalation regimens were used for mitigation and most of the events were non-serious, mild or moderate in severity and gradually decreased over time.

- A higher proportion of subjects with T2D treated with semaglutide 2.4 mg reported hypoglycemic episodes (increased when semaglutide was used with a sulfonylurea) and retinal disorders in line with what was observed in the Ozempic. This information has been added to the package insert of Wegovy.
- 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.

3.0 CONCLUSION

Drug Control Authority (DCA) on the 385th meeting on 8th June 2023 has decided to approve the registration of this product with the following indication:

Wegovy is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of

- ≥30 kg/m^2 (obesity), or
- ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity e.g. dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease.