NONCLINICAL EVALUATION REPORT

Product:	Semaglutide (WEGOVY)		
Dose form & strength:	Solution for Injection; 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 2.27 mg/mL, 3.2 mg/mL	**Tox File No.:**	E18-318244
Sponsor:	Novo Nordisk Pharmaceuticals Pty Ltd	**TRIM Reference:**	D23-5203115
Submission No.:	PM-2022-04980-1-5	**Evaluator:**	s22
Submission Type:	Extension of indication	**Date:**	11 August 2023

This submission proposes to extend the indication for the use of WEGOVY (semaglutide) as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with

- obesity or
- overweight and with at least one weight-related comorbidity.

WEGOVY is currently approved for use as an adjunct to a reduced-calorie diet and increased physical activity for chronic 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.

The proposed dosing regimen for the new indication is identical to that approved for use in the adult patient group.

In population PK studies comparing adolescents and adults, exposure was inversely correlated with bodyweight and age caused on clinically relevant change in semaglutide exposure (Module 2.5 Clinical Overview). Exposure levels in adolescent subjects with obesity were comparable to exposure levels in adult subjects with obesity. From the model (Population PK study [STEP TEENS], page 29), in the adolescent population aged 12 to <18 years with bodyweight of 62–212 kg the geometric mean for C_{avg} was 74 nM and $AUC_{0\text{-}168h}$ was 12.4 µM·h. This is similar to the C_{avg} and $AUC_{0\text{–}168h}$ previously used to support the indication in adult patients (59.4 nM and 14.7 µM.h, respectively; PM-2021-00612-1-5 [D21-2820164]).

No new module 4 data were submitted in support of the extension of indication.

In previously evaluated juvenile animal studies (evaluated in submission PM-2018-02748-1-5 [D18-11164343]; 2 studies; identical doses), when rats were treated directly with semaglutide, delayed sexual maturation likely secondary to suppressed body weight gain was observed in both sexes. No adverse effects on development were observed at doses up to 600 µg/kg/day SC. At this

dose, semaglutide exposures achieved were moderate (ER_{AUC} 9) compared to the clinical AUC at the maximum clinical dose of 2.4 mg/week SC (see Table I below). These studies did not raise any safety concerns for the proposed patient group.

Table I. Relative exposure in juvenile animal toxicity studies

Species	Study duration [Study no.]	Dose (µg/kg/day SC)	AUC_{0-168h}^ (µM·h)	Exposure ratio#
Rat (SD)	Juvenile study 11 weeks Study 214479*	20	3.2	0.3
		130	25.3	2.0
		600	105	9
Human (Adolescence patients)	steady state [STEP TEENS]	[2.4 mg]	12.4	–

= animal:human plasma $AUC_{0-168\ h}$; ^ = data are for the sexes combined at the last sampling occasion; AUC_{0-24h} data from rodents were ×7. *Study 214479 was previously evaluated in submission PM-2018-02748-1-5

No nonclinical PI changes are proposed, and none are necessary.

Overall, there are no nonclinical objections to registration of WEGOVY for the proposed indication in adolescence.

Australian Government
Department of Health
Therapeutic Goods Administration

Nonclinical Evaluation Report

Semaglutide [WEGOVY®]

Submission No: PM-2021-00612-1-5
Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

27 October 2021

TGA Health Safety Regulation

NONCLINICAL EVALUATION REPORT

Submission type:	Extension of indications New indication, new strengths & new dosage delivery system
Sponsor:	Novo Nordisk Pharmaceuticals Pty Ltd
Generic name:	**Semaglutide**
Trade name:	**WEGOVY®**
Dose form and strength:	Solution for Injection; 0.5 mg/mL; 1.0 mg/mL; 2.0 mg/mL; 2.27 mg/mL; 3.2 mg/mL
Drug class:	GLP-1 receptor agonist
Submission No:	PM-2021-00612-1-5
Tox file No:	E18-318244
TRIM reference:	D21-2820164
Date authorised:	27 October 2021

Note: This evaluation report has been peer-reviewed and is authorised for release to the sponsor.

TABLE OF CONTENTS

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS 4

ASSESSMENT 5

PHARMACOLOGY 5

TOXICITY 6

PRODUCT INFORMATION 10

MAIN BODY OF REPORT 15

1. INTRODUCTION 15

1.1. EXISTING AND PROPOSED CLINICAL USE 15

1.2. CHEMISTRY AND FORMULATION 15

1.3. INTERNATIONAL REGULATORY STATUS 16

1.4. SCOPE OF NONCLINICAL DATA 16

2. PRIMARY PHARMACOLOGY 17

3. PHARMACOKINETICS 19

3.1.1. Plasma kinetics in human subjects 19

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

- Novo Nordisk Pharmaceuticals Pty Ltd has applied to extend the indications for semaglutide to be used as an adjunct to a reduced-calorie diet and increased physical activity for chronic 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. For the new indication, the Sponsor is proposing a new trade name (WEGOVY®), new strengths (up to 3.2 mg/mL), an increase in the maximum dose (from 1 mg/week, SC to 2.4 mg/week, SC) and a new dosage delivery system.
- The submitted Module 4 dossier was generally acceptable. No major deficiencies were identified.
- Two primary pharmacology studies were submitted. Semaglutide is a GLP-1 receptor agonist, which is a physiological regulator of appetite and caloric intake. The GLP-1 receptor is present in several areas of the brain involved in appetite regulation. Animal studies showed that semaglutide distributed to and activated neurons in brain regions involved in regulation of food intake, and therefore support the new indication.
- There are no new safety concerns associated with the higher systemic exposures expected with the higher strength formulation of semaglutide (as WEGOVY®), and overall no nonclinical objections to registration.
- The draft Product Information should be amended as directed on pages 10–14.

ASSESSMENT

Novo Nordisk Pharmaceuticals Pty Ltd has applied to extend the indication of recombinant human glucagon-like peptide-1 (GLP-1) analogue semaglutide (under trade name WEGOVY®) to be used for chronic weight management. Semaglutide is currently approved (as OZEMPIC®) as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus and for the prevention of cardiovascular events in adults with type 2 diabetes mellitus and high cardiovascular risk. The new submission also concerns increased strength of semaglutide (up to 3.2 mg/mL solution for injection), an increase in the maximum weekly dose (from 1 mg to 2.4 mg) and use of a new dosage delivery system (single use prefilled pen with pre-assembled needle).

The proposed dosing regimen for WEGOVY® involves a fixed dose escalation regimen to reduce the likelihood of gastrointestinal symptoms, with an initiation dose of 0.25 mg once weekly from week 1–4. Thereafter, the dose is increased to 0.5 mg (week 5–8), 1 mg (week 9–12) and 1.7 mg (week 13–16) once weekly. After at least 16 weeks, the dose may be increased to 2.4 mg once weekly for additional glycaemic control. Treatment is expected to be ongoing.

The Sponsor indicated that nonclinical studies conducted to support the approval of OZEMPIC® for the Type 2 Diabetes (T2D) indication are also sufficient to support the new indication of weight management. In addition to these, the Sponsor also submitted two new pharmacology studies in mice that further explored the effects of semaglutide in the brain in relation to its effects on body weight.

Pharmacology

Primary pharmacology

GLP-1 is an intestinally-derived peptide hormone that is secreted after ingestion of glucose or a mixed meal. GLP-1 receptor agonists, such as semaglutide, are expected to lower post-prandial glucose levels *via* retardation of gastric emptying, a stimulation of insulin biosynthesis and secretion by pancreatic β cells and inhibition of glucagon secretion from pancreatic α cells[1]. Published studies indicate GLP-1 receptor agonists may have beneficial effects on cardiovascular outcomes[2] and have an appetite suppressant action[3].

Semaglutide has been previously shown to reduce bodyweight gain and food consumption in mice, normal and obese rats, and minipigs (see NER for OZEMPIC® D18-11164343).The two new pharmacology studies that were provided in this submission examined the *ex vivo* effects of semaglutide on neuronal activity and distribution in mouse brain.

In mice dosed with fluorescently-labelled semaglutide (0.5 mg/kg/day, SC for 5 weeks), semaglutide was detected in brain regions expressing the GLP-1 receptor, including several of the circumventricular organs (CVO) devoid of a blood brain barrier (area postrema (AP), the median eminence (ME) and subfornical organ (SFO)). Semaglutide was also measured in brain regions protected by the blood brain barrier in the brain stem (AP, the nucleus of the solitary tract (NTS) and the dorsal motor nucleus of the vagus nerve (DMX)), the hypothalamus (arcuate hypothalamic nucleus (ARH), ME, dorsomedial hypothalamic nucleus (DMH), and the paraventricular nucleus

[1] Meier, J.J. (2012) GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat. Rev. Endocrinol.* **8:** 728–742.

[2] Marso S.P., Holst A.G. and Vilsbøll T. (2017) Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N. Engl. J. Med.* **376:** 891–892.

[3] Friedrichsen M., Breitschaft A., Tadayon S., Wizert A. and Skovgaard D. (2021) The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity. *Diabetes. Obes. Metab.* **23:** 754–762.

(PVH)), and in the septum (triangular nucleus of septum (TRS), the caudal part of the lateral septal nucleus (LS), and the septofimbrial nucleus (SF)). These areas have been shown to express GLP-1 receptors in mouse and Rhesus monkey brains[4] [5], and stimulation of receptors in the LS has been associated with modification of dopamine-related reward pathways[6], suggesting that semaglutide has access to select GLP-1R populations in brain regions associated with homeostatic and reward related regulation of food intake.

In the second study peripheral administration of semaglutide to diet-induced obese mice (0.1 mg/kg, SC) activated neurons (measured by monitoring cFos expression) in several sites that express GLP-1 receptors (accessed from the periphery such as in the CVO and the brain stem), while acute administration with semaglutide activated neurons in the parabrachial nucleus (PB) and the midline group of the dorsal thalamus (MTN). PB and MTN are regions important for homeostatic and hedonic aspects of food intake and, which were not directly accessible to semaglutide. Semaglutide also activated neurons in brain regions that are part of the circuits to and from the PB and MTN (the bed nuclei of the stria terminalis (BST) and the central amygdala (CeA)).

Overall, the primary pharmacology studies showed that semaglutide can access and target areas of the brain associated with food intake and reward-processes, and therefore support the proposed indication for chronic weight management, including weight loss and weight maintenance, in adults.

Toxicity

Repeat dose toxicity

Previously assessed repeat-dose toxicity studies of up to 13, 26 and 52 weeks duration were conducted in mice, rats and monkeys, respectively, using the clinical route (subcutaneous injection). Semaglutide exposures achieved in these studies were moderate to high multiples of the clinical AUC at the maximum clinical dose of 2.4 mg/week SC (7.4–55 times the clinical AUC; see Table I).

Semaglutide was generally well-tolerated in all repeat-dose studies. Transient effects on activity, body weight and food consumption (all species) were observed, which are relevant to the pharmacological actions of semaglutide.

Other notable findings included:

- ↑ incidence of proliferative lesions in thyroids of mice and rats seen at low relative exposures (**1.2×** and **0.14×** the clinical AUC at 2.4 mg/week SC, respectively), which were likely rodent specific, as GLP-1 receptor expression is ↑ in thyroids of rodents *cf*. humans, and mechanism for tumour development is present in rodent but not human thyroid.

- Minimal to moderate dilatation and/or hypertrophy of Brunner's glands in the duodenum were also seen in rodents at low systemic exposures (**1.2×** and **0.14×** the clinical AUC at 2.4 mg/week SC, respectively), but not in monkeys treated for 52 weeks (up to **7.4×** the clinical AUC), and therefore the toxicological significance is uncertain but likely to be minimal.

[4] Jensen C.B., Pyke C., Rasch M.G., Dahl A.B., Knudsen L.B. and Secher A. (2018) Characterization of the Glucagonlike Peptide-1 Receptor in Male Mouse Brain Using a Novel Antibody and In Situ Hybridization. *Endocrinology* **159:** 665–675.

[5] Heppner K.M., Kirigiti M., Secher A., Paulsen S.J., Buckingham R., Pyke C. *et al.* (2015) Expression and distribution of glucagon-like peptide-1 receptor mRNA, protein and binding in the male nonhuman primate (Macaca mulatta) brain. *Endocrinology* **156:** 255–267.

[6] Harasta A.E., Power J.M., von Jonquieres G., Karl T., Drucker D.J., Housley G.D. *et al.* (2015) Septal Glucagon-Like Peptide 1 Receptor Expression Determines Suppression of Cocaine-Induced Behavior. *Neuropsychopharmacology* **40:** 1969–1978.

- Uterine luminal dilatation seen in female rats at doses that achieved systemic exposures **8.6×** the clinical AUC at 2.4 mg/week SC was likely a secondary effect of lower body weight gain related to altered oestrus cycling.

- ECG abnormalities (bigeminal rhythm. sinus tachycardia, chronic left bundle block) observed in one female monkey (360 µg/kg SC, Q2W; **7.4×** the clinical AUC) from the 52 week study, were likely an isolated finding as there were no correlative cardiac lesions post-mortem.

Although exposure margins associated with these toxicity findings are lower at the higher clinical dose, none of these raise new concerns of toxicities.

Table I. Relative exposure in previously evaluated repeat-dose toxicity and carcinogenicity studies[7]

Species	Study duration [Study no.]	Dose (µg/kg SC)	AUC_{0-168h}^ (µM·h)	Exposure ratio#
Mouse (CD-1)	13 weeks [Study 200663]	1000	79.8	5.4
		3000	268	18
		10000	815	55
	104 weeks Carcinogenicity [Study 207362]	100	17.4 (♀ only)	1.2
		300	21.6	1.5
		1000	80.0	5.4
		3000	277 (♂ only)	19
Rat (SD)	13 weeks [Study 206662]	4	0.511	0.04
		82	8.44	0.6
		784	65.8	4.5
	26 weeks [Study 207377]	30	6.31	0.4
		130	27.0	1.8
		600	127	8.6
	104 weeks Carcinogenicity [Study 207363][a]	10	2.05	0.14
		25	4.49	0.3
		100	26.7	1.8
Monkey (Cynomolgus)	13 weeks Study 206450	4	1.61	0.11
		86	25.3	1.7
		977/467§	130	8.8
	12 months [Study 207288]	10	2.92	0.2
		60	18.5	1.25
		360	109	7.4
Human (Overweight to obese subjects)	steady state [Trial NN9535-4590]	[2.4 mg]	14.7	–

= animal:human plasma AUC_{0-168h}; Human AUC value for 2.4 mg was from Trial NN9535-4590 (2.7.2. Summary of Clinical Pharmacology Studies); ^ = data are for the sexes combined at the last sampling occasion unless otherwise indicated; AUC_{0-24h} data from rodents were ×7, AUC_{0-72h} data from monkeys were ×2; ; § = ♀ switched to lower dose wk 4; ♂, wk 5.

[7] Nonclinical Evaluation Report for semaglutide (OZEMPIC®) (D18-11164343)

Reproductive toxicity

Previously evaluated reproductive toxicity studies covered all stages of reproduction and development (fertility, early embryonic development, embryofetal development, and pre-/postnatal development). Studies were conducted by the SC route and used daily dosing in rats and rabbits and dosing every three days in monkeys. A dose escalation period was included in the rat and monkey studies. Exposures achieved in rats and rabbits were subclinical, but limited by pharmacological effects on body weight. Exposures in monkeys were subclinical to low in the pivotal embryofetal development study and in the pre-/postnatal study (see Table II).

Main treatment-related findings:

- Fertility:
    - no effect on fertility in male rats (NOAEL 828 µg/kg/day SC in the pilot study; **4.5×** the clinical AUC at 2.4 mg/week SC);
    - abnormal oestrus cycling & ↓ corpora lutea seen in females (NOEL 10 µg/kg/day; **0.03×** the clinical AUC), was likely secondary to effects on body weight and an effect seen with another GLP-1 agonist**Error! Bookmark not defined.**;
- Embryofetal development:
    - Embryofetal lethality & toxicity, e.g. embryonic death, ↓ live fetuses/infants, ↑ developmental abnormalities (NOAELs: rats 10 µg/kg/day SC or **0.03×** the clinical AUC; rabbits 1 µg/kg/day SC or **0.01×** the clinical AUC; monkeys 15 µg/kg SC every 3 days or **0.2×** the clinical AUC)
- Postnatal development:
    - ↓ infant body weights in monkeys (at maternal exposures of 150 µg/kg SC every 3 days or 2× the clinical AUC), which normalised by day 91
    - Delayed sexual maturation in rats of both sexes seen at all dose levels which was likely secondary to lower body weight gain (at 20–600 µg/kg/day, SC or **0.22–7×** the clinical AUC). No other adverse effects on development were observed.

Table II. Relative exposure in previously evaluated reproductive toxicity studies[7]

Species	Study [Study no.]	Dose (µg/kg SC)	AUC_{0-168h} (µM·h)	Exposure ratio#
Rat (SD)	Fertility/ embryofetal development [Study 207361]	10	0.5	0.03
		30	1.5	0.1
		90	4.1	0.3
Rabbit (NZW)	Embryofetal development [Study 207360]	1	0.14	0.01
		2.5	1.5	0.1
		7.5	10.7	0.7
Monkey (Cynomolgus)	Embryofetal development [Study 208486]	15	4.0	0.3
		75	20.8	1.4
		15	60.0	4.1
	Embryofetal+pre/post-natal development [Study 210061]	15§	2.6	0.2
		75§	13.4	0.9
		150§	28.8	2
Human (Overweight to obese subjects)	steady state [Trial NN9535-4590]	[2.4 mg]	14.7	–

= animal:human plasma AUC_{0-168h}; Human AUC value for 2.4 mg was from Trial NN9535-4590 (2.7.2. Summary of Clinical Pharmacology Studies); ^ = data are for the sexes combined at the last sampling occasion unless otherwise indicated; AUC_{0-24h} data from rodents were ×7, AUC_{0-72h} data from monkeys were ×2. § Mothers were not dosed during lactation.

Pregnancy classification

The sponsor is maintaining a **Pregnancy Category D**, which is considered appropriate, given the embryofetal lethality and toxicity (including malformations) previously observed at subclinical to low exposure margins in three species.

Local tolerance

In the original submission, injection site reactions to semaglutide in repeat dose toxicity studies were generally well-tolerated and were minimal to slight in severity. Although no new studies were submitted to support the higher strength semaglutide formulation *cf*. Ozempic® (i.e. 2.0–3.2 mg/mL *cf*. 1.34 mg/mL, respectively), the Sponsor referred to previously evaluated local tolerance studies conducted in rabbits and pigs where there were no notable local effects at the site of semaglutide administration. In rabbits, intramuscular, intraarterial and intravenous injections of semaglutide of up to 1.35 mg/mL were well tolerated with mild changes that were comparable to vehicle. Similarly subcutaneous injections of semaglutide at 10 mg/mL were well-tolerated in pigs, with injection site reactions comparable to saline vehicle-treated areas. Although the formulation that was used varied from the one proposed for WEGOVY®, the removal of propylene glycol and phenol from the WEGOVY® formulation is unlikely to negatively affect its tolerability. Injection site reactions have been observed with clinical use of semaglutide.

PRODUCT INFORMATION

The following comments refer to the draft Product Information document (Wegovy-pi-v0.3-annotated) accompanying the sponsor's letter of application dated 24 September 2021. Where changes are suggested, text proposed to be inserted is underlined and text to be deleted is shown struck-through. The Sponsor has proposed a separate Product Information document for WEGOVY® based on the existing OZEMPIC® Product Information document.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The text should be revised to more closely match that used in the existing PI for OZEMPIC®:

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

~~As with other GLP-1 receptor agonists, semaglutide may delay~~ The delay of gastric emptying with semaglutide may ~~and could potentially~~ influence the absorption of concomitantly administered oral medicinal products, therefore semaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption."

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The exposure margins should be included to more closely match the text used in the existing PI for OZEMPIC®:

"The effect of semaglutide on fertility in humans is unknown. Semaglutide did not affect male fertility in rats at daily SC doses of 828 µg/kg, resulting in exposures approximately 4.5 times the clinical AUC. In female rats, an increase in oestrous length and a small reduction in number of ovulations were observed at doses associated with maternal body weight loss (≥30 µg/kg/day SC, resulting in subclinical exposures)."

Use in pregnancy

The sponsor proposes Pregnancy Category D and the following statement (the text second paragraph onwards appears erroneously under the "genotoxicity" heading:

"*Studies in animals have shown reproductive toxicity (see section 5.3 Preclinical safety data). There are limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. Women of childbearing potential are recommended to use contraception when treated with semaglutide. 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 (see section 5.2 Pharmacokinetic properties)*."

(from section 5.3)

"In 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 observed, 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.

In developmental toxicity studies in rabbits and cynomolgus monkeys, increased pregnancy loss and slightly increased incidence of foetal abnormalities were observed 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 evaluated in cynomolgus monkeys. Infants were slightly smaller at delivery but recovered during the lactation period."

As outlined in the assessment, the proposed Pregnancy Category D is considered appropriate for this product based on the embryofetal lethality and toxicity seen in three species, rats, rabbits and monkeys. As the submitted embryofetal development studies and mechanistic studies did not confirm a species-specific effect for these adverse embryofetal development effects, the role of GLP-1 receptor expression on the yolk sac to the adverse effects should be phrased appropriately. Findings from the rabbit embryofetal development studies should be included. The changes in the text are recommended to more closely match the text used in the existing PI for OZEMPIC®:

"~~Studies in animals have shown reproductive toxicity (see section 5.3 Preclinical safety data). There are limited data from the use of semaglutide in pregnant women. Therefore, s~~Semaglutide should not be used during pregnancy. Women of childbearing potential are recommended to use contraception when treated with semaglutide. 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 (see section 5.2 Pharmacokinetic properties).

Studies in animals have shown reproductive toxicity ~~(see section 5.3 Preclinical safety data)~~ when semaglutide was administered during organogenesis. In pregnant rats, embryofetal toxicity (lethality, impaired growth and an increased incidence of fetal abnormalities) was observed at subclinical plasma exposures. Mechanistic studies suggest a direct GLP-1 receptor mediated role of semaglutide on some of the effects in rats (species specific). In pregnant rabbits, pharmacologically mediated reductions in maternal body weight gain and food consumption were observed at all dose levels. Early pregnancy losses and increased incidences of minor visceral (kidney, liver) and skeletal (sternebra) fetal abnormalities were observed at ≥0.0025 mg/kg/day, at clinically relevant exposures. In pregnant cynomolgus monkeys, pharmacologically mediated, marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with the occurrence of sporadic abnormalities (vertebra, sternebra, ribs) and with an increase in early pregnancy losses at ≥0.075 mg/kg twice weekly (>1.4- fold clinical exposure at 2.4 mg/week). Exposures at the NOAEL in all species were subclinical and a direct effect of semaglutide on the fetus cannot be excluded."

Use in lactation

The proposed text is acceptable.

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The text below is generally acceptable and supported by submitted or published data. Minor changes are recommended to specify pharmacological actions that are relevant to the indication (i.e. glucose and appetite regulation).Data referring to clinical studies require comments from the Clinical Evaluator.

"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 and has multiple actions in glucose and ~~of~~ appetite regulation. ~~and caloric intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation.~~ The glucose and appetite effects are specifically mediated via GLP-1 receptors in the pancreas and the brain.

Compared to native GLP-1, semaglutide has a prolonged half-life of around 1 week making it suitable for once weekly s.c. administration. The principal mechanism of protraction is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilised against degradation by the DPP-4 enzyme.

Clinical studies show that semaglutide reduces energy intake, increases feelings of satiety, fulness and control of eating, and reduces feelings of hunger, and frequency and intensity of cravings.

Animal studies show that semaglutide works in the brain through the GLP-1 receptor. Semaglutide have direct effects on areas in the brain involved in homeostatic regulation of food intake in the hypothalamus and the brainstem. Semaglutide affects the hedonic reward system through direct and indirect effects in brain areas including the septum, thalamus and amygdala. Semaglutide has shown an effect to change food intake in animals away from more rewarding high fat, sweet items.

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

~~Furthermore, animal studies have shown that semaglutide attenuated the development of atherosclerosis and had an anti-inflammatory action in the cardiovascular system.~~"

5.2 PHARMACOKINETIC PROPERTIES

Distribution

The following statement is supported by submitted nonclinical data. The remaining statement requires clinical comment.

"Semaglutide was extensively bound to plasma albumin (>99%)."

Metabolism

The following statement is supported by submitted nonclinical data.

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

Excretion

The following statement is supported by submitted nonclinical data.

"The primary excretion routes of semaglutide related material were via the urine and faeces."

5.3 PRECLINICAL SAFETY DATA

The following text should be deleted because it is not completely correct:

"~~Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity or genotoxicity.~~"

Genotoxicity

The sponsor has proposed the following text:

"In 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 observed, 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.

In developmental toxicity studies in rabbits and cynomolgus monkeys, increased pregnancy loss and slightly increased incidence of foetal abnormalities were observed 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 evaluated in cynomolgus monkeys. Infants were slightly smaller at delivery but recovered during the lactation period."

None of this information relates to genotoxicity and should be deleted with the relevant information placed in the "**Effects on fertility**", "**Use in pregnancy**" and "**Use in lactation**" sections.

The following text is recommended as an alternative:

"Semaglutide was not mutagenic in the bacterial reverse mutation assay, and was not clastogenic *in vitro* (cytogenetic assay in human lymphocytes), or *in vivo* (rat bone marrow micronucleus test)."

Carcinogenicity

The text proposed by the sponsor is generally acceptable. The exposure margins should be included. Thus, the following changes are recommended:

"Non-lethal thyroid C-cell tumours observed in rodents are a class effect for GLP-1 receptor agonists. In 2-year carcinogenicity studies in rats and mice, semaglutide caused thyroid C-cell tumours at clinically relevant exposures (at ≥ 1.2× the clinical AUC in mice [based on the plasma AUC at the maximum recommended human dose of 2.4 mg/week and subclinical exposures in rats; a no effect level was not established in either species). No other treatment-related tumours were observed. 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."

Juvenile toxicity

The proposed text is acceptable.

MAIN BODY OF REPORT

1. INTRODUCTION

Novo Nordisk Pharmaceuticals Pty Ltd has applied to extend the indication of recombinant human glucagon-like peptide-1 (GLP-1) analogue semaglutide (as WEGOVY®) to be used for chronic weight management. This submission relates to change in strength (up to 3.2 mg/mL), an increase in the maximum weekly dose (from 1 mg to 2.4 mg) and a new dosage delivery system (solution for injection in pre-filled pens).

1.1. EXISTING AND PROPOSED CLINICAL USE

Semaglutide (registered as OZEMPIC®) is currently approved to be used as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus and for the prevention of cardiovascular events in adults with type 2 diabetes mellitus and high cardiovascular risk, as an adjunct to standard treatment of cardiovascular risk factors. Patients are required to follow a fixed dose escalation regimen, with an initiation dose of 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 may be increased to 1.0 mg once weekly for additional glycaemic control. The maximum recommended dose is 1.0 mg once weekly. OZEMPIC® is provided in a pre-filled multidose disposable pen, which contains semaglutide in a 1.5 mL or 3 mL cartridge.

WEGOVY® is proposed to be used as an adjunct to a reduced-calorie diet and increased physical activity for chronic 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. The proposed dosing regimen involves a fixed dose escalation regimen to reduce the likelihood of gastrointestinal symptoms, with an initiation dose of 0.25 mg once weekly from week 1–4. Thereafter, the dose should be increased to 0.5 mg (week 5–8), 1 mg (week 9–12) and 1.7 mg (week 13–16) once weekly. After at least 16 weeks, the dose may be increased to 2.4 mg once weekly for additional glycaemic control. Treatment is expected to be ongoing. The proposed presentation is a solution for injection in pre-filled pen with pre-assembled needle.

1.2. CHEMISTRY AND FORMULATION

The formulation of WEGOVY® solutions for injection is shown in **Error! Reference source not found.**. A comparison with the currently registered OZEMPIC® solution is shown. In addition the amounts, differences in the composition of the new formulation *cf.* the old formulation includes the use of sodium chloride as a tonicity agent instead of propylene glycol, and the removal of phenol (preservative).

Table 1.1. Product formulation

Ingredient	Function	Quantity (mg) per mL		
		WEGOVY®		OZEMPIC®
Semaglutide	Active ingredient	WEGOVY® 0.25 mg [a]	0.5	1.34
		WEGOVY® 0.5 mg [a]	1.0	
		WEGOVY® 1.0 mg [a]	2.0	
		WEGOVY® 1.7 mg [b]	2.27	
		WEGOVY® 2.4 mg [b]	3.2	
Disodium phosphate, dehydrate	Buffer	1.42		1.42
Propylene glycol	Tonicity agent	—		14
Phenol	Preservative	—		5.5
Sodium chloride	Tonicity agent	8.25		—
Hydrochloric acid	pH adjustment	q.s. [c]		
Sodium hydroxide	pH adjustment	q.s. [c]		
Water for injection	Solvent	To make 1.0 mL		

[a] Semaglutide 0.5 mg/ml, 1.0 mg/ml and 2.0 mg/ml in single dose pen-injector for semaglutide supplied as 0.5 mL volume;

[b] Semaglutide 2.27 mg/ml and 3.2 mg/ml in single dose pen-injector for semaglutide supplied as 0.75 mL volume;

[c] To reach pH 7.4

1.3. INTERNATIONAL REGULATORY STATUS

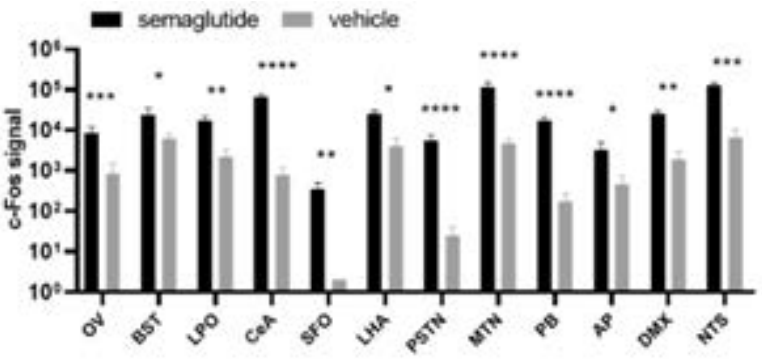
A similar application has been made in the USA (04 December 2020), the EU (4 January 2021), Canada (8 December 2020) and in the UK (5 January 2021). Semaglutide under the tradename WEGOVY® was approved in the USA on 4 June 2020, for an indication comparable to the proposed indication in the current application.

1.4. SCOPE OF NONCLINICAL DATA

Nonclinical studies conducted for semaglutide to support the Type 2 Diabetes indication also support the indication for weight management. Two new pharmacology studies in mice, investigating the effects of semaglutide in the brain were submitted and are evaluated in this report for WEGOVY® to further support the understanding of mode of action n in weight management.

2. PRIMARY PHARMACOLOGY

The following additional studies were submitted:

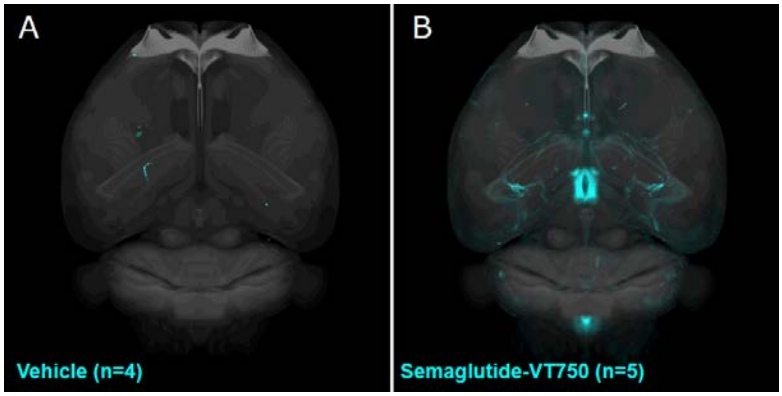
Study details	Main findings
Study 321410 **Mouse** (C57BL/6J, Diet induced obese ♂) *n*= 8/group Semaglutide 0, 0.1 mg/kg SC for 4 hours Examinations: Brain – Immunohistochemistry for cFos (proto-oncogene expressed within some neurons following depolarization) microscopy (LSFM). Follow up by co-staining for cFos (selected brain regions) and calcitonin gene-related peptide (CGRP)	• c-Fos expression was used as a marker for neuronal activity. • Activation of cFos was seen in regions of mouse brain following semaglutide administration. • cFos activity was observed in several brain areas: brain stem in the area postrema (AP) and the nucleus of the solitary tract (NTS). • Increased cFos activity was also observed in the central amygdala nucleus (CeA), the parabrachial nucleus (PB) and the midline group of the dorsal thalamus (MTN). Effects of semaglutide on cFos induction in different brain areas is shown below.  *p<0.05, **p<0.01, ***p<0.001, ****p<0.00001 *cf.* vehicle OV: Vascular organ of the lamina terminalis, BST: Bed nuclei of the stria terminalis, LPO: Lateral preoptic area, CeA: Central amygdala nucleus, SFO: Subfornical organ, LHA: Lateral hypothalamic area, PSTN: Parasubthalamic nucleus, MTN: Midline group of the dorsal thalamus, PB: Parabrachial nucleus, AP: Area postrema, DMX: Dorsal motor nucleus of the vagus nerve, NTS: Nucleus of the solitary tract • Subset of cFos positive cells were identified as CGRP positive cells within the Parabrachial nucleus (PB).

Study 321411
Mouse (C57BL/6J, ♂)
n= 5 (test), 4 (vehicle)
0, 0.5 mg/kg total (Semaglutide VT750 – fluorescently labelled) SC daily for 5 weeks

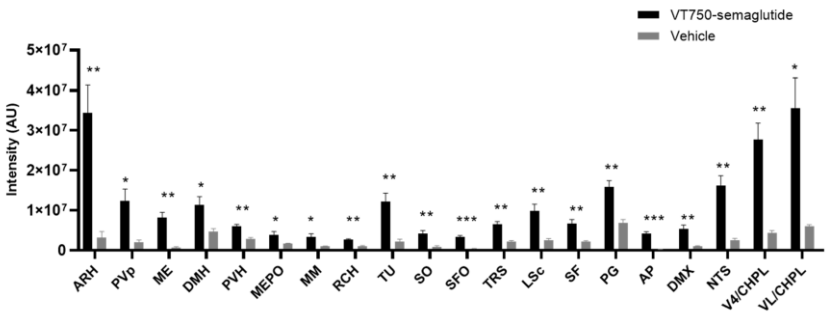
Group	Day	Dose (mg/kg)
Vehicle	1-5	–
Semaglutide VT750	1	0.04
	2	0.07
	3-5	0.15

Examinations:
Whole brain by scanning with a laser sheet to determine the distribution of the fluorescently labelled peptide

Distribution of semaglutide-VT750 in the mouse brain was observed following peripheral administration (SC) of semaglutide VT750 as shown below.



- Strong fluorescent signal was observed in the meninges and the choroid plexus (CHPL)
- Strong signal was observed in the brain regions devoid of a blood brain barrier: circumventricular organs (CVO's –), including the area postrema (AP) and the median eminence (ME)
- Signal was observed in brain regions protected by the blood-brain barrier: hypothalamus including the arcuate hypothalamic nucleus (ARH) and the brainstem including the nucleus of the solitary tract (NTS)
- Semaglutide-VT750 was observed in the septum (caudal part of the lateral septal nucleus (LSc)
- Steady-state distribution of semaglutide-VT750 in mouse brain is shown below with average intensity of total fluorescence signal in all brain regions that showed 2-fold enrichment and were significant



*p<0.5, **p<0.01, ***p<0.001 *cf.* vehicle

ARH – Arcuate hypothalamic nucleus, PVp – Arcuate nucleus, posterior part, ME – Median eminence, DMH – Dorsomedial hypothalamic nucleus, PVH – Paraventricular nucleus of the hypothalamus, MEPO – Median preoptic nucleus, MM – Medial mammillary nucleus, RCH – Retrochiasmatic area, TU – Tuberal nucleus, SO – Supraoptic nucleus, SFO – Subfornical organ, TRS – Triangular nucleus of septum, LSc – Caudal part of the lateral septal nucleus, SF – Septofimbrial nucleus, PG – Pontine gray, AP – Area postrema, DMX – Dorsal motor nucleus of the vagus nerve, NTS – Nucleus of the solitary tract, V4/CHPL – Choroid plexus, VL/CHPL – Choroid plexus.

3. PHARMACOKINETICS

3.1.1. Plasma kinetics in human subjects

The steady-state exposure of semaglutide 2.4 mg for weight management was evaluated by standard PK endpoints in Bioequivalence study (Trial 4590) in overweight or obese individuals. Steady-state PK endpoints for semaglutide 2.4 mg are shown in Table 3-1 below.

Table 3-1. Pharmacokinetic parameters in humans

Study details	Dose (mg)	C_{max} (nM)	C_{avg} (nM)**	Vss/F (L)	t_{max} (h)	$AUC_{0-168\,h}$ (nM·h)*	$t_{½}$ (h)
Bioequivalence study – Trial 4590 ****NN9536 Phase 3a Meta Analysis Modelling report** Overweight or obese individuals NN9536-4373 and overweight or obese individuals with T2D NN9536-4374	2.4	119	59.4	9.8	24	14698	155 (~1 week)

* AUC value is for a dosing interval (168 h) at steady-state.

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

NONCLINICAL EVALUATION REPORT

Product:	Semaglutide (WEGOVY)		
Dose form & strength:	Solution for Injection; 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 2.27 mg/mL, 3.2 mg/mL	**Tox File No.:**	E18-318244
Sponsor:	Novo Nordisk Pharmaceuticals Pty Ltd	**TRIM Reference:**	D23-5203115
Submission No.:	PM-2022-04980-1-5		
Submission Type:	Extension of indication	**Date:**	11 August 2023

This submission proposes to extend the indication for the use of WEGOVY (semaglutide) as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with

- obesity or
- overweight and with at least one weight-related comorbidity.

WEGOVY is currently approved for use as an adjunct to a reduced-calorie diet and increased physical activity for chronic 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.

The proposed dosing regimen for the new indication is identical to that approved for use in the adult patient group.

In population PK studies comparing adolescents and adults, exposure was inversely correlated with bodyweight and age caused on clinically relevant change in semaglutide exposure (Module 2.5 Clinical Overview). Exposure levels in adolescent subjects with obesity were comparable to exposure levels in adult subjects with obesity. From the model (Population PK study [STEP TEENS], page 29), in the adolescent population aged 12 to <18 years with bodyweight of 62–212 kg the geometric mean for C_{avg} was 74 nM and $AUC_{0\text{-}168h}$ was 12.4 µM·h. This is similar to the C_{avg} and $AUC_{0\text{–}168h}$ previously used to support the indication in adult patients (59.4 nM and 14.7 µM.h, respectively; PM-2021-00612-1-5 [redacted]).

No new module 4 data were submitted in support of the extension of indication.

In previously evaluated juvenile animal studies (evaluated in submission PM-2018-02748-1-5 [redacted]; 2 studies; identical doses), when rats were treated directly with semaglutide, delayed sexual maturation likely secondary to suppressed body weight gain was observed in both sexes. No adverse effects on development were observed at doses up to 600 µg/kg/day SC. At this dose,

semaglutide exposures achieved were moderate (ER_{AUC} 9) compared to the clinical AUC at the maximum clinical dose of 2.4 mg/week SC (see Table I below). These studies did not raise any safety concerns for the proposed patient group.

Table I. Relative exposure in juvenile animal toxicity studies

Species	Study duration [Study no.]	Dose (µg/kg/day SC)	AUC_{0-168h}^ (µM·h)	Exposure ratio#
Rat (SD)	Juvenile study 11 weeks Study 214479*	20	3.2	0.3
		130	25.3	2.0
		600	105	9
Human (Adolescence patients)	steady state [STEP TEENS]	[2.4 mg]	12.4	–

= animal:human plasma $AUC_{0-168\,h}$; ^ = data are for the sexes combined at the last sampling occasion; AUC_{0-24h} data from rodents were ×7. *Study 214479 was previously evaluated in submission PM-2018-02748-1-5

No nonclinical PI changes are proposed, and none are necessary.

Overall, there are no nonclinical objections to registration of WEGOVY for the proposed indication in adolescence.