Medicines & Healthcare products Regulatory Agency

Public Assessment Report

National Procedure

Wegovy 0.25 mg, FlexTouch solution for injection in pre-filled pen
Wegovy 0.5 mg, FlexTouch solution for injection in pre-filled pen
Wegovy 1 mg, FlexTouch solution for injection in pre-filled pen
Wegovy 1.7 mg, FlexTouch solution for injection in pre-filled pen
Wegovy 2.4 mg, FlexTouch solution for injection in pre-filled pen

semaglutide

PLGB 04668/0436-0440

Novo Nordisk A/S

LAY SUMMARY

Wegovy 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, and 2.4 mg FlexTouch solution for injection in pre-filled pen
semaglutide

This is a summary of the Public Assessment Report (PAR) for Wegovy 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, and 2.4 mg FlexTouch solution for injection in pre-filled pen. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Wegovy FlexTouch in this lay summary for ease of reading.

For practical information about using Wegovy FlexTouch, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Wegovy FlexTouch and what is it used for?
These applications are full-dossier applications. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

Wegovy FlexTouch is used for weight loss and weight maintenance in addition to diet and physical activity in adults, who have:
• a Body Mass Index (BMI) of 30 kg/m² or greater (with obesity) or
• a BMI of 27 kg/m² and less than 30 kg/m² (overweight) and weight-related health problems.

BMI is a measure of weight in relation to height.

Wegovy Flextouch is used together with diet and physical activity for weight management in adolescents ages 12 years and above, who have
• obesity
• body weight >60kg

Adolescent patients should only continue using Wegovy Flextouch if they have lost at least 5% of their BMI after 12 weeks on the 2.4 mg dose or maximum tolerated dose.

Risk reduction of serious heart issues in adults
Wegovy Flextouch is also used in addition to diet and physical activity to reduce the risk of serious heart issues (heart-related death, heart attacks, strokes) in adults with a history of heart disease (like a heart attack, stroke or poor blood flow to the limbs) and either obesity or overweight (BMI ≥27 kg/m2).

How does Wegovy FlexTouch work?
Wegovy FlexTouch is a medicine for weight loss and weight maintenance that contains the active substance semaglutide. It is similar to a natural hormone called glucagon-like peptide-1 (GLP-1) that is released from the intestine after a meal. Wegovy FlexTouch works by acting on receptors in the brain that control the appetite, causing the patient to feel fuller and less hungry and experience less craving for food. This will help the patient eat less food and reduce their body weight. Wegovy FlexTouch should be used with a reduced calorie meal plan and increased physical activity.

How is Wegovy FlexTouch used?

The pharmaceutical form of this medicine is a solution for injection in a pre-filled pen, and the route of administration is as an injection under the skin (subcutaneous injection). Wegovy FlexTouch should not be injected into a vein or muscle. This medicine should be used once weekly and, if possible, on the same day each week. Patients can inject themselves at any time of the day, regardless of meals.

Adults

The recommended dose is 2.4 mg once weekly**.** The treatment will start at a low dose which will be gradually increased over 16 weeks of treatment as follows:

- When the patient first starts using Wegovy, the starting dose is 0.25 mg once weekly.
- The patient's doctor will instruct the patient to gradually increase the dose every four weeks until the recommended dose of 2.4 mg once weekly is reached.
- Once the recommended dose of 2.4 mg is reached, it should not be increased further.

The patient will be told to follow the table below.

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
From week 17	2.4 mg

The patient's doctor will assess the treatment on a regular basis.

Adolescents (above 12 years of age)

For adolescents, the same dose escalation schedule as for adults should be applied (see above). The dose should be increased until 2.4 mg (maintenance dose) or maximum tolerated dose has been reached. Weekly doses higher than 2.4 mg are not recommended.

People with diabetes

Patients should tell a doctor if they have diabetes. A doctor may adjust the dose of diabetes medicines to prevent patients from getting low blood sugar.

Wegovy should not be mixed up with other medicines that patients inject (e.g. insulins).

Wegovy should not be used in combination with other medicines that contain GLP-1 receptor agonists (such as liraglutide, dulaglutide, exenatide or lixisenatide).

For further information on how Wegovy is used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Wegovy FlexTouch have been shown in studies?

Wegovy FlexTouch is a line extension of the existing products Wegovy 0.25 mg, 0.5 mg, 1 mg, 1.7 mg and 2.4 mg, solution for injection in pre-filled pen (PLGB 04668/0429-0433). Studies have shown that Wegovy is effective in helping people lose weight, with a significant proportion of them achieving at least a 5% weight reduction. The data submitted previously for Wegovy 0.25 mg, 0.5 mg, 1 mg, 1.7 mg and 2.4 mg, solution for injection in pre-filled pen and two new bioequivalence studies have been submitted to support the applications.

To support use in adolescents, a study was conducted involving 200 adolescents aged 12 to less than 18 years who were obese or overweight and had at least one weight-related health problem. The study found that after 68 weeks, BMI dropped by an average of 16% in those treated with Wegovy compared with an average increase of less than 1% in those who received placebo. Around 73% of those who received Wegovy lost at least 5% of their weight compared with around 18% of those who received placebo.

To support use for the reduction of risk of serious heart issues, a study was conducted to determine the effect of Wegovy relative to placebo on major adverse cardiovascular events (MACE) when added to current standard of care, which included management of cardiovascular risk factors and individualised healthy lifestyle counselling (including diet and physical activity). In this trial, 17,604 patients were randomised to Wegovy or placebo. The trial found that Wegovy significantly reduced the risk for first occurrence of MACE.

What are the possible side effects of Wegovy FlexTouch?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Wegovy FlexTouch is a line extension of the existing products Wegovy 0.25 mg, 0.5 mg, 1 mg, 1.7 mg and 2.4 mg, solution for injection in pre-filled pen, its benefits and possible side effects are taken as being the same as Wegovy 0.25, 0.5, 1, 1.7 and 2.4 mg, solution for injection in pre-filled pen.

Why was Wegovy FlexTouch approved?
It was concluded that, as Wegovy FlexTouch is a line extension of Wegovy 0.25, 0.5, 1, 1.7 and 2.4 mg solution for injection in pre-filled pen. Wegovy FlexTouch is proposed as an alternative presentation of the same five strengths, the indications and side effects observed with Wegovy 0.25, 0.5, 1, 1.7 and 2.4 mg solution for injection in pre-filled pen are applicable to Wegovy FlexTouch. Therefore, the MHRA decided that, as for Wegovy 0.25, 0.5, 1, 1.7 and 2.4 mg solution for injection in pre-filled pen, the benefits are greater than the risks and recommended that Wegovy FlexTouch can be approved for use.

What measures are being taken to ensure the safe and effective use of Wegovy FlexTouch?

As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Wegovy FlexTouch. The RMP details the important risks of Wegovy, how these risks can be minimised, any uncertainties about Wegovy (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Wegovy FlexTouch:

Summary of safety concerns GB/UK RMP

Summary Safety Concerns	
Important identified risks	Diabetic retinopathy complications (only for patients with T2D)
Important potential risks	Pancreatic Cancer Medullary Thyroid Cancer
Missing information	Pregnancy and lactation Patients with severe hepatic impairment Patient with history of major depression or other severe psychiatric disorders Concomitant use of other weight lowering drugs Off label use in patients who do not meet the criteria for treatment (weight management)

Abbreviations: T2D=Type 2 diabetes mellitus

Additional pharmacovigilance activities are in place for Wegovy FlexTouch, such as an observational study of the safety of Wegovy exposure in pregnant women and their offspring, a medullary thyroid carcinoma surveillance study, a study to assess the risk for pancreatic cancer and an additional study to assess the long-term effects of semaglutide treatment on development and progression of diabetic retinopathy.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Wegovy FlexTouch are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Wegovy FlexTouch

Marketing authorisation applications for Wegovy FlexTouch were granted in Great Britain (GB, consisting of England, Scotland and Wales) on 10 May 2022.

The full PAR for Wegovy 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, and 2.4 mg FlexTouch solution for injection in pre-filled pen follows this summary.

This summary was last updated in March 2025.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Wegovy 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, and 2.4 mg FlexTouch solution for injection in pre-filled pen (PLGB 04668/0436-0440) could be approved.

The products are approved for the following indications:
Weight management
Adults
Wegovy FlexTouch 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.

Adolescents (≥12 years)
Wegovy FlexTouch is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with

- obesity* and
- body weight above 60 kg.

Treatment with Wegovy FlexTouch should be discontinued and re-evaluated if adolescent patients have not reduced their BMI by at least 5% after 12 weeks on the 2.4 mg or maximum tolerated dose.
*Obesity (BMI ≥95th percentile) as defined on sex- and age-specific BMI growth charts (CDC.gov) (see Table 1).

Table 1 BMI cut-off points for obesity (≥95th percentile) by sex and age for paediatric patients aged 12 and older (CDC criteria)

Age (years)	BMI (kg/m2) at 95th Percentile	
	Males	Females
12	24.2	25.2
12.5	24.7	25.7
13	25.1	26.3
13.5	25.6	26.8
14	26.0	27.2
14.5	26.4	27.7
15	26.8	28.1
15.5	27.2	28.5
16	27.5	28.9
16.5	27.9	29.3
17	28.2	29.6
17.5	28.6	30.0

Cardiovascular Risk Reduction

Wegovy is indicated as an adjunct to a reduced-calorie diet and increased physical activity to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight (BMI ≥27 kg/m2).

The name of the active substance is glucagon-like peptide-1 (GLP-1) analogues.

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.

Semaglutide has direct effects on areas in the brain involved in homeostatic regulation of food intake in the hypothalamus and the brainstem, and direct and indirect effects on areas involved in hedonic regulation of food intake, including the septum, thalamus and amygdala.

In addition, in clinical studies semaglutide has shown to reduce blood glucose in a glucose-dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. During hypoglycaemia, semaglutide diminishes insulin secretion and does not impair glucagon secretion.

The exact mechanism of cardiovascular risk reduction has not been established.

These applications were approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), as full-dossier applications.

These applications are for line extensions of the existing products Wegovy 0.25, 0.5, 1, 1.7 and 2.4 mg, solution for injection in pre-filled pen (PLGB 04668/0429-0433), the data submitted previously for Wegovy 0.25, 0.5, 1, 1.7 and 2.4 mg solution for injection in pre-filled pen and two new bioequivalence studies have been submitted to support the applications.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation planMHRA-1000467-PIP01-22M01.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing authorisations for Wegovy 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, and 2.4 mg FlexTouch solution for injection in pre-filled pen were granted in Great Britain (GB, consisting of England, Scotland and Wales) on 10 May 2022.

II QUALITY ASPECTS

II.1 Introduction

These products consist of a solution for injection in a pre-filled pen. Each Wegovy 0.25 mg, 0.5 mg, 1 mg, 1.7 mg and 2.4 mg FlexTouch solution for injection in pre-filled pen contains 0.68 mg/mL, 1.34 mg/mL, 1.34 mg/mL, 2.27 mg/mL and 3.2 mg/mL of semaglutide, respectively.

In addition to semaglutide, these products also contain the excipients disodium phosphate, dihydrate, propylene glycol, phenol, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment), and water for injection.

The finished products are packaged in a 1.5 mL or 3 mL multidose glass cartridge (type I glass) closed at one end with a rubber plunger (type I/chlorobutyl) and at the other end with an aluminium cap containing a rubber disc (type I/bromobutyl/isoprene) insert. The cartridge is assembled into a pre-filled multidose disposable pen made of polypropylene polyoxymethylene, polycarbonate and acrylonitrile butadiene styrene.

The products are packaged in pack sizes of 1 multiple-dose pre-filled pen and 4 disposable NovoFine Plus needles.

The pen is designed for use with NovoFine Plus, NovoFine, or NovoTwist disposable needles up to 8 mm in length.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

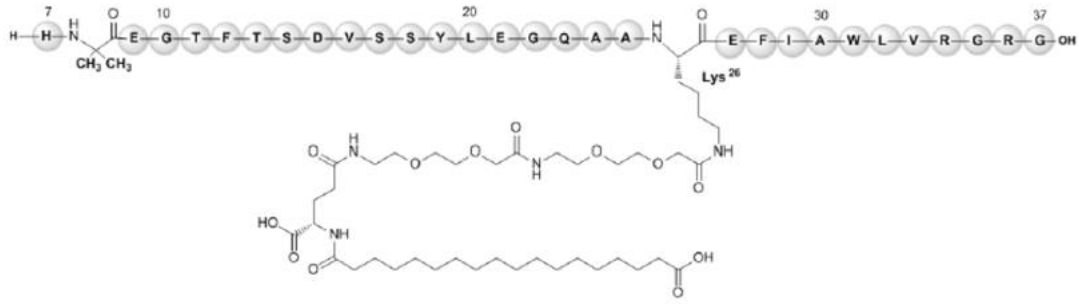
II.2 ACTIVE SUBSTANCE

rINN: semaglutide

Chemical Name: $N^{\epsilon 26}$[(22,40-dicarboxy-10,19,24-trioxo-3,6,12,15-tetraoxa-9,18,23-triazatetracontan-1-oyl)][Aib^{8},Arg^{34}]GLP-1-(7-37)peptide

Molecular Formula: $C_{187}H_{291}N_{45}O_{59}$

Chemical Structure:



Molecular Weight: 4113.6 g/mol

Appearance: White or almost white powder.

Solubility: Very slightly soluble in ethanol.

The active substance, semaglutide, is neither covered by a Certificate of Suitability nor a Drug Master File. Full information was provided in the dossier.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished products.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years and in-use shelf life of 6 weeks; with the storage conditions "Before first use: Store in a refrigerator (2°C to 8°C). Keep away from the cooling element. Do not freeze Wegovy and do not use it if it has been frozen.
After first use: Store below 30°C or, preferably, in a refrigerator (2°C to 8°C), do not freeze Wegovy and do not use it if it has been frozen. Keep the pen cap on when the pen is not in use in order to protect it from light", is acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As these applications are for a line extensions of the existing products Wegovy 0.25, 0.5, 1, 1.7 and 2.4 mg, solution for injection in pre-filled pen (PLGB 04668/0429-0433), the non-clinical data are identical to those submitted previously.

III.2 Pharmacology

No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
According to the European Medicines Agency's guideline "Guideline on the environmental risk assessment of medicinal products for human use" ERA studies are not required for substances like amino acids, peptides, proteins, carbohydrates and lipids since they are unlikely to result in significant risk to the environment.

On this basis it is concluded that the use of semaglutide is unlikely to result in significant risk to the environment and consequently, is exempt from submitting ERA studies.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
In support of the applications, the applicant has provided two single dose bioequivalence studies, as follows:

Study 4649
Comparison to demonstrate bioequivalence when a 0.25 mg dose of semaglutide was given in a pre-filled pen, using semaglutide drug product concentrations of 0.68 mg/mL and 1.0 mg/mL, respectively. A 1.0 mg/mL strength of the product was used in the original Phase III clinical studies.

Study 3687
Comparison to demonstrate bioequivalence when a 0.5 mg dose of semaglutide was given in a pre-filled pen using semaglutide drug product concentrations of 1 mg/mL, 3 mg/mL and 10 mg/mL, respectively.

All studies were conducted in line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics
In support of the applications, the following 2 bioequivalence studies were submitted:

Study 4649
The primary objective of this study was to demonstrate bioequivalence between single dose pen-injector administrations of 0.25 mg semaglutide with the two drug product concentrations 0.68 mg/mL and 1.0 mg/mL. This to ensure that semaglutide 0.68 mg/mL can be used for the 0.25 mg semaglutide dose.

This was a randomised, single-centre trial investigating the pharmacokinetic profiles of semaglutide after s.c. administration of 0.25 mg with different drug product concentrations, 0.68 mg/mL and 1.0 mg/mL, respectively. The trial was performed using a double-blind, two-period, cross-over, balanced design in healthy subjects.

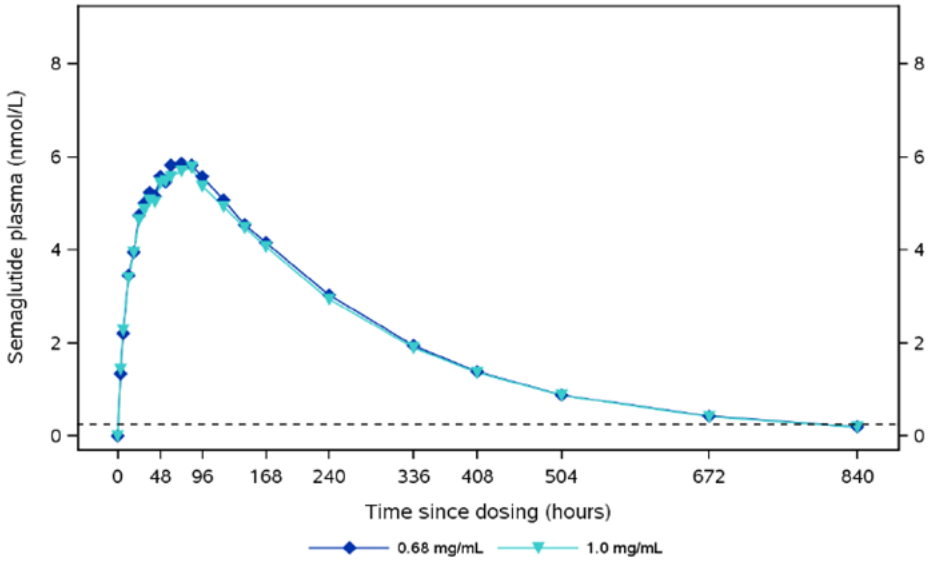
Subjects were randomised 1:1 into one of two treatment sequences. In treatment period 1, subjects received a single 0.25 mg dose of semaglutide with the 0.68 mg/mL or 1.0 mg/mL

drug product concentration followed by 5 weeks of serial PK sampling. This was followed by a washout period of 1-3 weeks. In treatment period 2, subjects again received a single 0.25 mg dose of semaglutide but from the other drug product concentration, which was followed by 5 weeks of serial PK sampling.

A summary of the pharmacokinetic data is presented below:

	0.68 mg/mL	1.0 mg/mL
Number of subjects	27	27
AUC, 0-inf (nmol*h/L)		
N	27	27
Mean (SD)	1788 (315)	1751 (315)
Geometric mean (CV)	1761 (18.3)	1723 (18.8)
Median	1739	1751
Min ; Max	1219 ; 2343	1153 ; 2423
Tmax (h)		
N	27	27
Mean (SD)	66.3 (19.5)	66.0 (21.5)
Geometric mean (CV)	63.1 (34.8)	62.2 (38.4)
Median	60.0	72.1
Min ; Max	30.0 ; 99.3	24.0 ; 120.3
thalf (h)		
N	27	27
Mean (SD)	154 (17)	154 (16)
Geometric mean (CV)	154 (11.0)	153 (10.4)
Harmonic mean	153	152
Median	155	150
Min ; Max	127 ; 195	126 ; 187
Cl/F (L/h)		
N	27	27
Mean (SD)	0.035 (0.007)	0.036 (0.007)
Geometric mean (CV)	0.035 (18.3)	0.035 (18.8)
Median	0.035	0.035
Min ; Max	0.026 ; 0.050	0.025 ; 0.053
Vz/F (L)		
N	27	27
Mean (SD)	7.8 (1.3)	7.9 (1.2)
Geometric mean (CV)	7.6 (16.8)	7.8 (15.5)
Median	7.8	7.6
Min ; Max	5.8 ; 11.0	6.0 ; 10.4

	No. of subjects in FAS	N	Estimate	90% CI	95% CI
AUC, 0-tz (nmol*h/L)					
Mean					
0.68 mg/mL	27	27	1676		[1655 ; 1697]
1.0 mg/mL	27	27	1638		[1617 ; 1658]
Treatment ratio					
0.68 mg/mL / 1.0 mg/mL			1.0232	[1.0082 ; 1.0385]	
Cmax (nmol/L)					
Mean					
0.68 mg/mL	27	27	6.2		[6.1 ; 6.4]
1.0 mg/mL	27	27	6.1		[6.0 ; 6.2]
Treatment ratio					
0.68 mg/mL / 1.0 mg/mL			1.0225	[1.0012 ; 1.0442]	



Following single doses, bioequivalence was demonstrated for AUC and Cmax between the 2 tested products [0.68 mg/ml and 1 mg/ml concentration of active] at the 0.25 mg dose. Tmax and the overall concentration versus time profile was also comparable between test products.

Study 3687

The objectives of this study were as follows:

Primary objective:
To assess if the total semaglutide exposure after single dose subcutaneous (s.c.) administration of three different strengths (1 mg/mL, 3 mg/mL, 10 mg/mL) of semaglutide when administered in equimolar doses fulfils the bioequivalence criteria.

Secondary objectives:
To assess and compare other pharmacokinetic properties of semaglutide in the three different strengths (1 mg/mL, 3 mg/mL, 10 mg/mL) when administered in equimolar doses
To assess the absolute bioavailability of semaglutide
To assess safety and tolerability of semaglutide

This was a randomised, single-centre, single-dose, two-period, incomplete cross-over trial in healthy subjects investigating if the total exposure after single s.c. injections with different strengths of semaglutide, 1 mg/mL, 3 mg/mL, and 10 mg/mL, fulfils the bioequivalence criteria and to assess the absolute bioavailability of semaglutide.

Subjects received 1 of the following 2 sequences:

Group A: 0.5 mg s.c semaglutide from two out of three possible strengths of semaglutide (1 mg/mL, 3 mg/mL, and 10 mg/mL)

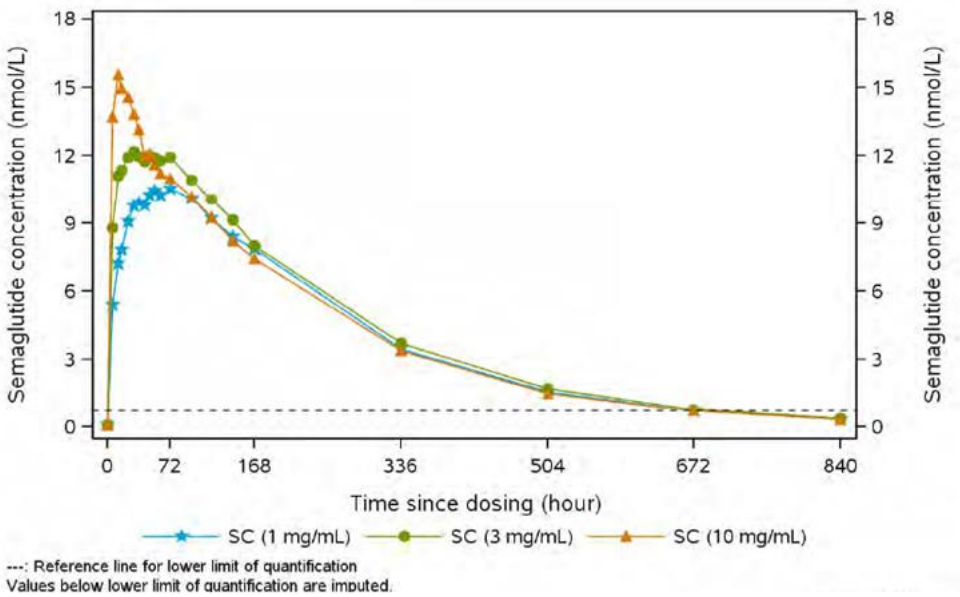
Group B: 0.5 mg s.c semaglutide (1 mg/mL) and 0.25 mg of i.v. semaglutide (1 mg/mL)

A summary of the pharmacokinetic data is presented below:

	Subcutaneous (1 mg/mL)	Subcutaneous (3 mg/mL)	Subcutaneous (10 mg/mL)
Number of subjects	20	18	20
AUC, 0-last (nmol*h/L)			
N	20	18	20
Geometric mean (CV)	2997 (22.6)	3278 (26.8)	3180 (22.7)
Min ; Max	1946 ; 4655	1832 ; 5050	2320 ; 5606
AUC, 0-168h (nmol*h/L)			
N	20	18	20
Geometric mean (CV)	1534 (22.4)	1733 (23.2)	1786 (19.4)
Min ; Max	984 ; 2427	989 ; 2569	1334 ; 2665
Cmax (nmol/L)			
N	20	18	20
Geometric mean (CV)	11.3 (24.0)	13.1 (25.9)	16.2 (22.7)
Min ; Max	7.3 ; 18.8	7.0 ; 21.6	11.1 ; 24.4
tmax (h)			
N	20	18	20
Median	60.0	41.9	12.0
Min ; Max	30.0 ; 96.3	16.1 ; 72.0	6.0 ; 48.0
t half (h)			
N	20	18	20
Geometric mean (CV)	147 (7.6)	152 (9.6)	149 (8.8)
Min ; Max	125 ; 168	130 ; 177	129 ; 179
CL/F (L/h)			
N	20	18	20
Geometric mean (CV)	0.037 (20.2)	0.034 (24.9)	0.035 (20.9)
Min ; Max	0.025 ; 0.055	0.023 ; 0.061	0.021 ; 0.048
Vz/F (L)			
N	20	18	20
Geometric mean (CV)	7.87 (23.1)	7.53 (21.2)	7.57 (18.4)
Min ; Max	4.86 ; 12.03	5.23 ; 11.49	5.36 ; 10.04
MRT (h)			
N	20	18	20
Geometric mean (CV)	230.4 (6.7)	227.0 (9.4)	214.1 (7.7)
Min ; Max	202.3 ; 265.3	193.5 ; 264.0	188.3 ; 256.3

	Number of subjects in full analysis set	N	Estimate	95% CI	90% CI
AUC0-inf,sema (nmol*h/L)					
Mean	32				
1 mg/mL		20	3416	[3146 ; 3709]	
3 mg/mL		18	3349	[3083 ; 3638]	
10 mg/mL		20	3506	[3229 ; 3806]	
Treatment ratio					
1 mg/mL / 3 mg/mL			1.02		[0.99 ; 1.05]
1 mg/mL / 10 mg/mL			0.97		[0.94 ; 1.01]
3 mg/mL / 10 mg/mL			0.96		[0.92 ; 0.99]

	Number of subjects in full analysis set	N	Estimate	95% CI	90% CI
Cmax,sema (nmol/L)					
Mean	32				
1 mg/mL		20	11.6	[10.5 ; 12.8]	
3 mg/mL		18	12.7	[11.5 ; 14.1]	
10 mg/mL		20	16.3	[14.8 ; 18.0]	
Treatment ratio					
1 mg/mL / 3 mg/mL			0.91		[0.84 ; 1.00]
1 mg/mL / 10 mg/mL			0.71		[0.65 ; 0.78]
3 mg/mL / 10 mg/mL			0.78		[0.72 ; 0.85]



Study 3687

At the same dose of 0.5 mg s.c semaglutide, tmax occurred earlier and the Cmax was higher as semaglutide concentration in the formulation increased. However, between 1 and 3 mg/ml, the ratio was within the standard bioequivalence acceptance range for both AUC and Cmax. This supports the proposed concentrations of 0.68, 1.34 and 2.27 mg/ml. A further analysis based on AUC0-t was in accordance with the analysis for AUC0-inf.

For the proposed 3.2 mg/ml concentration; when comparing 3 to 10 mg/ml bioequivalence was met for AUC, but not for Cmax (lower CI was 0.72). Even though the mechanism for this has not been clarified, it would be scientifically unreasonable to suggest a significant difference between 3 and 3.2 mg/ml. Based on linear interpolation the calculated CIs for 3 vs 3.2 mg were within the standard bioequivalence acceptance range for Cmax

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications. This would be unchanged from arrangements supporting the existing licences.

IV.4 Clinical efficacy

No new efficacy data were assessed in Study 3687 and Study 4649. As these applications are for a line extensions of the existing products Wegovy 0.25, 0.5, 1, 1.7 and 2.4 mg, solution for injection in pre-filled pen (PLGB 04668/0429-0433), the efficacy data is identical to those submitted previously.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence studies, no new safety data were submitted with these applications.

The safety data from the bioequivalence studies showed that the test and reference products were equally well tolerated.

In study 3687 there were two serious adverse events (SAEs) reported; one was a of volvulus in a subject who received s.c. semaglutide 1 mg/mL strength, which led to withdrawal of this subject from the trial (probably related, recovered). Another was a non-treatment emergent

SAE reported after the follow-up visit of period 2. Other than this, there were no serious or significant AEs.

Only 1 injection site reaction was reported, in study 4649. Therefore, no pattern of injection site AEs in relation to concentration of administered IMP can be inferred. In relation to the higher Cmax with the 10mg/ml concentration there was no associated difference in AEs.

The safety profile these products is considered to be the same as Wegovy 0.25 mg, 0.5 mg, 1 mg, 1.7 mg and 2.4 mg, solution for injection in pre-filled pen (PLGB 04668/0429-0433).

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, additional pharmacovigilance activities have been proposed (see table below for the risk minimisation measures and pharmacovigilance activities for all safety concerns):

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk Diabetic retinopathy complications (only for patients with T2D)	*Routine risk minimisation measures:* SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* Results from the trial NN9535-4352 (FOCUS; see Section 3.2.1) ongoing for semaglutide s.c. for T2D will also be relevant for the ongoing evaluation of the risk for semaglutide s.c. 2.4 mg for weight management in patients with T2D.
Important potential risk Pancreatic cancer	*Routine risk minimisation measures:* None *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* Results from study NN9535-4447 (see Section 3.2.3; Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide patients with T2D) will also be relevant for the ongoing evaluation of the risk for semaglutide s.c. 2.4 mg for weight management.

Important potential risk Medullary thyroid cancer	*Routine risk minimisation measures:* Nonclinical findings are presented in the SmPC Section 5.3 *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* Study MTC-22341 (Medullary Thyroid Carcinoma Surveillance Study: a Case-Series Registry; see Section 3.2.2)
Missing information: Pregnancy and lactation	*Routine risk minimisation measures:* SmPC Section 4.6 and PL Section 2. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None
Missing information: Patients with severe hepatic impairment	*Routine risk minimisation measures:* SmPC Sections 4.2 and 5.2. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None

Abbreviations: PL = package leaflet; SmPC = Summary of Product Characteristics; T2D = type 2 diabetes mellitus.

Safety concern	**Risk minimisation measures**
Missing information: Patients with history of major depression or other severe psychiatric disorders	*Routine risk minimisation measures:* None *Additional risk minimisation measures:* None
Missing information: Concomitant use of other weight lowering drugs	*Routine risk minimisation measures:* None *Additional risk minimisation measures:* None
Missing information: Off-label use in patients who do not meet the criteria for treatment (weight management)	*Routine risk minimisation measures:* The approved indication is described in Section 4.1 of the SmPC and Section 1 of the PL. *Other risk minimisation measures beyond the Product Information:* By the legal status of the product; prescription only. *Additional risk minimisation measures:* None

Additional pharmacovigilance activity in the UK population, UK patients to be added to the planned US pregnancy registry or pregnancy database study (required by the FDA for semaglutide s.c. 2.4 mg for weight management), results from which will be relevant for the evaluation of the missing information 'pregnancy and lactation'.

This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no non-clinical or clinical safety concerns have been identified. Clinical experience with semaglutide is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved GB versions of the SmPCs and PILs for these products are available on the MHRA website.

TABLE OF CONTENTS OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**
Type II	To extend the weight management indication with the adolescent population (12 to <18 years) for Wegovy. The paediatric indication is based on new data from clinical study NN9536-4451, investigating safety and efficacy of semaglutide on weight management in adolescent (ages 12 to <18 years) with overweight and at least one weight related comorbidity or with obesity. The submission is performed in compliance with a paediatric investigation plan. Sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated to the adolescent indication. Section 4.4 has also been updated to include a traceability statement as per QRD. Sections 1, 2 and 3 of the package leaflet have been updated to reflect this adolescent indication.	SmPC and PIL	12/06/2023	Granted	Y Annex I
Type II	1) To update section 5.1 of the SmPC in order to update the description of the pharmacodynamic effects and clinical efficacy and safety sections based on final results from the following study: Trial 4378 (STEP 5). Also, Section 4.1 of the SmPC has been updated to correct a typographical error. 2) To update section 5.1 of the SmPC in order to update the description of the pharmacodynamic effects and clinical efficacy and safety sections based on final results from the following study: Trial	SmPC and PIL	27/03/2023	Granted	Y Annex II

	4567 (STEP 8) 3) To update section 5.1 of the SmPC in order to update the description of the pharmacodynamic effects and clinical efficacy and safety sections based on final results from the following study: Trial 4373 extension (STEP 1 EXT).				
Type II	To extend the weight management indication with a risk reduction of major adverse cardiovascular events (MACE) (cardiovascular death, no-fatal myocardial infarction and non-fatal stroke) in adults with established cardiovascular disease (myocardial infarction, stroke, or peripheral arterial disease) and BMI ≥27 kg/m2. This is based on new data from clinical study EX9536-4388, a post-approval CVOT (cardiovascular outcomes trial) landmark study that was designed to demonstrate that semaglutide 2,4 mg lowers the incidence of major adverse cardiovascular (CV) events (MACE) vs placebo both added to CV standard of care in people with established CV disease (peripherial artery disease and/or prior MI and/or stroke) and overweight or obesity. Consequently, section 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 of the SmPC and PIL are updated.	SmPC and PIL	23/07/2024	Granted	Y Annex III
Type II	To update section 5.1 of the SmPC in order to include new data generated in patients with knee osteoarthritis (OA), based on final results from study NN9536-4578 (STEP 9); this is a phase 3b randomised, two-arm, double-blinded, multi-centre clinical trial comparing semaglutide s.c. 2.4 mg once-weekly with semaglutide placebo in subjects with moderate OA of one or both knees, pain due to knee OA, and obesity.	SmPC	22/11/2024		

Annex I

Reference: PLGB 04668/0436-0440 – 0004
Product:
Wegovy 0.25 mg, FlexTouch solution for injection in pre-filled pen
Wegovy 0.5 mg, FlexTouch solution for injection in pre-filled pen
Wegovy 1 mg, FlexTouch solution for injection in pre-filled pen
Wegovy 1.7 mg, FlexTouch solution for injection in pre-filled pen
Wegovy 2.4 mg, FlexTouch solution for injection in pre-filled pen

Type of Procedure: National

Submission category: Type II Variation

Reason
To extend the weight management indication with the adolescent population (12 to <18 years) for Wegovy. The paediatric indication is based on new data from clinical study NN9536-4451, investigating safety and efficacy of semaglutide on weight management in adolescent (ages 12 to <18 years) with overweight and at least one weight related comorbidity or with obesity. The submission is performed in compliance with a paediatric investigation plan.

Sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated to the adolescent indication. Section 4.4 has also been updated to include traceability statement as per QRD. Sections 1, 2 and3 of the package leaflet have been updated to reflect this adolescent indication. Additionally, the RMP has been updated.

This submission includes the CTR for trial NN956-4451 with the new data.

Supporting evidence
The MAH has submitted the results of study NN9536-4451 (STEP Teens trial), along with updated Summaries of Product Characteristics (SmPCs), Patient information leaflets (PILs) and an updated
RMP. An updated Clinical Overview and Clinical and Quality Expert Reports have also been provided.

Evaluation
The MAH proposes to extend the indications to include weight management in adolescents (12 to <18 years), based on the results of study NN9536-4451 (STEP Teens trial). Consequential changes are proposed to different parts of the SmPCs and the leaflets.

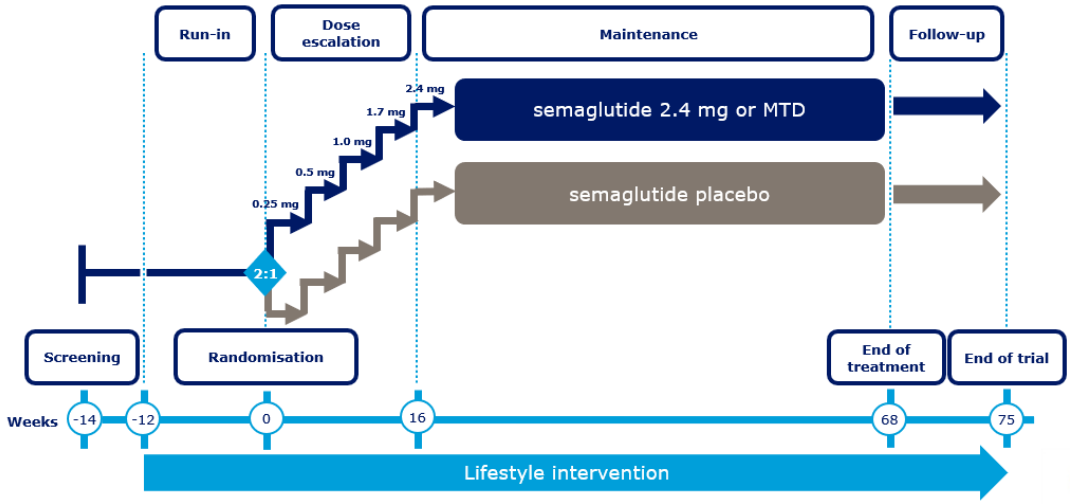
The adolescent indication (based on the same data) was approved by the US FDA in December 2022. A positive opinion on a parallel European Medicines Agency (EMA) centralised variation application was also issued by CHMP on 30 March 2023.

No new issues are raised from quality and non-clinical perspectives during this assessment.

A brief summary of the submitted clinical evidence and the pivotal study is provided below.

<u>Pivotal study</u>

The pivotal data come from the STEP Teens study, which was a multinational, randomised, double-blind, two-arm, placebo-controlled trial with a 68-week trial period comparing semaglutide s.c. 2.4 mg once weekly with placebo in pubertal adolescents, ages 12 to <18 years, with obesity or with overweight and ≥1 weight-related comorbidity. An overview of the trial design is shown below.



The study included male or female subjects, aged 12 to <18 years at the time of signing the informed consent and:
- BMI ≥95th percentile* OR ≥85th percentile* with ≥1 weight-related comorbidity (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or type 2 diabetes (T2D)
- History of at least one self-reported unsuccessful dietary effort to lose weight
- For subjects with T2D at screening: HbA1c ≤10.0% (86 mmol/mol) as measured by central laboratory at screening
* on gender and age-specific growth charts (CDC.gov).

The trial enrolled 201 subjects who were randomised 2:1 to receive either semaglutide 2.4 mg or placebo (see plan above).

The primary endpoint was the BMI (%) change from baseline (week 0) to week 68. A number of BMI/weight related measures, cardiovascular/metabolic parameters and patient-reported outcomes were included in the secondary endpoints.

Overall, the demographic and baseline characteristics were well-balanced between the semaglutide 2.4 mg and placebo groups, although baseline BMI and body weight were higher in the semaglutide 2.4 mg group.

The proportion of treatment completers (subjects on treatment at week 68) and trial completers (subjects who attended the end-of-trial visit) was similar between the semaglutide 2.4 mg and placebo groups. Permanent discontinuation of trial product due to adverse events (AEs) was reported by 4.5% of subjects with semaglutide 2.4 mg vs 6.0% with placebo.

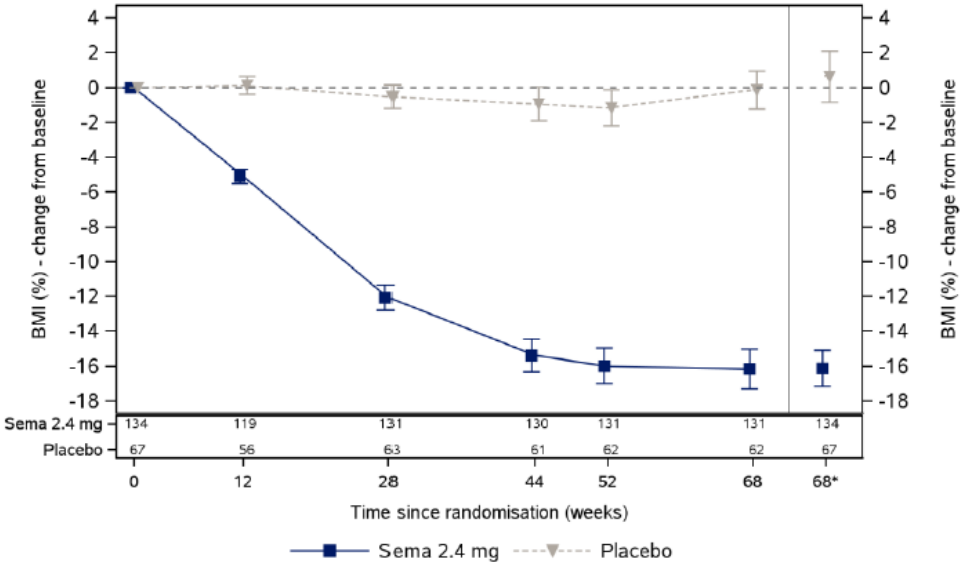
Efficacy
The results confirmed the superiority of semaglutide over placebo for both primary and confirmatory secondary endpoints.

The estimated change from baseline BMI (%) at week 68 was -16.14% with semaglutide and 0.61% with placebo. With semaglutide 72.5% of subjects achieved ≥5% weight loss vs 17.7% with placebo.

STEP Teens – key efficacy results – treatment policy estimand

Endpoint	Est.	95% CI	p-value	alpha	Hypothesis	Conclusion
Primary endpoint						
BMI (%) change from baseline to week 68						
Sema 2.4 mg - Placebo	-16.75	[-20.27; -13.23]	<.0001	0.05	Superiority	Confirmed
Confirmatory secondary endpoint						
Odds of achieving baseline body weight loss >=5% at week 68						
Sema 2.4 mg / Placebo	14.02	[6.34; 31.02]	<.0001	0.05	Superiority	Confirmed

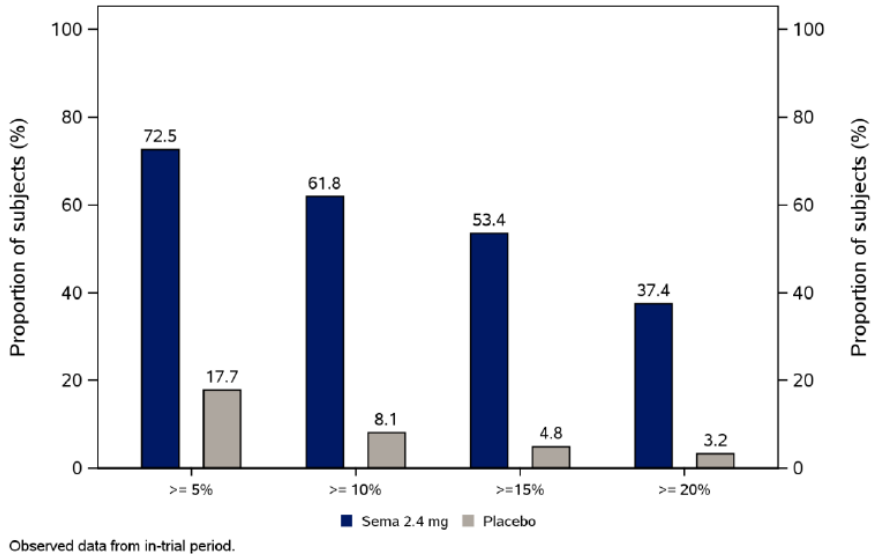
Est.: Estimate, alpha: Local significance level, CI: Confidence interval, p-value: Unadjusted two-sided p-value for test of no difference.



Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means are from the primary analysis. Numbers shown in the lower panel are subjects contributing to the mean.

Body weight reduction of ≥5% from baseline (week 0) to week 68 was a confirmatory secondary endpoint in STEP Teens. The superiority of semaglutide vs placebo was demonstrated in terms of the proportion of subjects achieving ≥5% body weight reduction from baseline to week 68, with odds ratios (ORs) in favour of semaglutide 2.4 mg. The proportions of subjects achieving ≥10%, ≥15% or ≥20% body weight reduction from baseline to week 68 were also greater with semaglutide 2.4 mg compared to placebo, with more than half of the subjects achieving a weight loss of at least 15%.

The proportion of subjects achieving body weight loss response criteria since baseline at week 68



Positive effects of semaglutide vs placebo were also seen in other secondary endpoints, including various metabolic and lipid parameters.

Safety
Of the 201 subjects randomised 2:1 to treatment, 200 were exposed to the trial product: 133 subjects in the semaglutide 2.4 mg group (181.8 patient-years exposure (PYE), 192.0 person-years of observation (PYO)); 67 subjects in the placebo group (90.4 PYE, 94.0 PYO). In total, 89.6% completed treatment and 97.5% of subjects completed the trial. Comparable proportions of subjects in both treatment groups completed treatment (89.6% for both treatment groups) and completed the trial (98.5% semaglutide 2.4 mg group; 95.5% placebo group).

The proportion of subjects with AEs, was comparable between the treatment groups (78.9% in semaglutide vs 82.1% in placebo). The rate of AEs reported, was higher with semaglutide than with placebo (435.7 events per 100 PYE in semaglutide vs 362.9 events per 100 PYE in placebo), driven primarily by gastro-intestinal (GI) AEs, which were most commonly reported.

GI disorders (a known class effect) were reported by a higher proportion of subjects, and at a higher rate, in the semaglutide group compared to placebo (61.7%, 211.8 events per 100 PYE vs 41.8%, 106.2 events per 100 PYE). Greater percentages of subjects reported events of nausea and vomiting in the semaglutide than in the placebo group. The majority of GI AEs were non-serious, mild or moderate in severity, and had a median duration of 2-3 days.

There were few (24) serious adverse events (SAEs) during the on-treatment period, 17 in the semaglutide group and 7 in the placebo group. Both the proportion of subjects with SAEs (11.3% vs 9.0%), and the rates of reporting SAEs (9.4 vs 7.7 events per 100 PYE) were comparable between semaglutide and placebo. Most of the events, in both treatment groups, were moderate in severity, and the subjects recovered. The SAEs in both groups were distributed, in low numbers, across several preferred terms (PTs), with no evident patterning. In the semaglutide 2.4 mg group, there was a small concentration (5 events in 4 subjects) of SAEs in the system organ class (SOC) Hepatobiliary disorders, primarily related to events of *cholelithiasis*. There were no deaths were reported in this trial.

In relation to AEs of special interest, a notable imbalance was observed in the reports of 'gall bladder disease'. Six events of acute gall bladder disease were reported in 5 subjects (3.8%) in the semaglutide 2.4 mg group, and 0% of patients treated with placebo, which is included in
the paediatric section of the label. It should be noted that the frequency is numerically higher than what has been observed in the adult studies - 3.8% in children and 1.6% in adults.

In general, the safety and tolerability data from STEP Teens appear comparable with the safety profile established in the adult clinical development programmes with semaglutide 2.4 mg and other GLP-1 analogues. As expected, the most frequently reported AEs with semaglutide 2.4 mg in adolescents were GI-related. The higher incidence of cholelithiasis is of concern; however, this is a well-known AE in populations with obesity, and rapid, significant weight loss is well-known and is already included in the product information.

Benefit:risk conclusions
The pivotal trial results showed a significant and clinically relevant effect of semaglutide on body weight management in adolescents. No major new safety issues were identified; the safety and tolerability data appear comparable with the safety profile established in the weight management clinical programmes in adults with semaglutide and other members of this class.

Overall, the benefit:risk of Wegovy in the studied adolescent population is considered positive.

It was noted that a considerable proportion of patients (27.5%) did not achieve a significant body weight loss. In order to prevent unnecessary long-term treatment in a group of patients who are unlikely to benefit from therapy, the product information states that treatment should be discontinued and re-evaluated if adolescent patients have not reduced their BMI by at least 5% after 12 weeks on the 2.4 mg or maximum tolerated dose.

Also, as only one subject in the trial was from the category of "overweight with comorbidities category" at baseline (all the rest were obese according to the inclusion criteria), the available data are insufficient to establish a positive benefit/risk in 'overweight' subjects and the indication for weight management is restricted to obese patients only.

Conclusion
There is still high need for effective weight management therapies, including for younger ages. The available data support a positive benefit:risk of Wegovy in the adolescent population.

The proposed changes are acceptable.

In accordance with legal requirements, the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website

Decision: Grant

Date: 12 June 2023

Annex II

Reference: PLGB 04668/0436-0440 - 0006
Product:
Wegovy 0.25 mg, FlexTouch solution for injection in pre-filled pen
Wegovy 0.5 mg, FlexTouch solution for injection in pre-filled pen
Wegovy 1 mg, FlexTouch solution for injection in pre-filled pen
Wegovy 1.7 mg, FlexTouch solution for injection in pre-filled pen
Wegovy 2.4 mg, FlexTouch solution for injection in pre-filled pen

Type of Procedure: National

Submission category: Type II Variation

Reason
1) To update section 5.1 of the SmPC in order to update the description of the pharmacodynamic effects and clinical efficacy and safety sections based on final results from the following study: Trial 4378 (STEP 5). Also, Section 4.1 of the SmPC has been updated to correct a typographical error.
2) To update section 5.1 of the SmPC in order to update the description of the pharmacodynamic effects and clinical efficacy and safety sections based on final results from the following study: Trial 4567 (STEP 8)
3) To update section 5.1 of the SmPC in order to update the description of the pharmacodynamic effects and clinical efficacy and safety sections based on final results from the following study: Trial 4373 extension (STEP 1 EXT).

Supporting evidence
The MAH has submitted the final study reports for Trial 4378, Trial 4576 and Trial 4373 Extension, along with an updated Clinical Overview.

Updated Summaries of Product Characteristics (SmPCs) and Patient information leaflets (PILs) have been submitted.
Evaluation
The proposed changes are the same as the ones previously approved for the rest of the Wegovy product range (Wegovy Solution for injection prefilled pen) as part of the type II variation (PLGB 04668/0429-0433 – 0003).

Conclusion
The proposed changes are acceptable.

In accordance with legal requirements, the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision: Grant

Date: 27 March 2023

Annex III

Reference:
PLGB 04668/0436 - 0016
PLGB 04668/0437-0440 - 0017

Product:
Wegovy 0.25 mg, FlexTouch solution for injection in pre-filled pen - PLGB 04668/0436
Wegovy 0.5 mg, FlexTouch solution for injection in pre-filled pen - PLGB 04668/0437
Wegovy 1 mg, FlexTouch solution for injection in pre-filled pen - PLGB 04668/0438
Wegovy 1.7 mg, FlexTouch solution for injection in pre-filled pen - PLGB 04668/0439
Wegovy 2.4 mg, FlexTouch solution for injection in pre-filled pen - PLGB 04668/0440

Type of Procedure: Reliance route
This variation is an International Recognition (IRP) application with the FDA as the Reference Regulator.

Submission category: Type II Variation

Reason
To extend the weight management indication with a risk reduction of major adverse cardiovascular events (MACE) (cardiovascular death, no-fatal myocardial infarction and non-fatal stroke) in adults with established cardiovascular disease (myocardial infarction, stroke, or peripheral arterial disease) and BMI ≥27 kg/m2. This is based on new data from clinical study EX9536-4388, a post-approval CVOT (cardiovascular outcomes trial) landmark study that was designed to demonstrate that semaglutide 2,4 mg lowers the incidence of major adverse cardiovascular (CV) events (MACE) vs placebo both added to CV standard of care in people with established CV disease (peripherial artery disease and/or prior MI and/or stroke) and overweight or obesity. Consequently, section 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 of the SmPC and PIL are updated.

Supporting evidence
The MAH has submitted the final clinical trial report for study EX9536-4388, along with an updated clinical overview that discusses the supporting clinical evidence considered by the FDA.

Updated Summaries of Product Characteristics (SmPCs) and Patient information leaflets (PILs) have been submitted.

Evaluation
The outcome of the RR assessment is fully endorsed.
A summary of the key clinical aspects is presented below; there were no new Quality or Non-clinical data. Also, no conditions were associated with the FDA approval and no conditions were proposed for the GB submission.

Clinical aspects
There were no updates in the clinical pharmacology dossier as part of this submission.
The pivotal efficacy and safety data come from a dedicated cardiovascular outcomes trial (CVOT), EX9536-4388, denoted SELECT, designed to demonstrate the superiority of

semaglutide s.c. 2.4 mg compared to placebo with regard to CV risk reduction, in adults with established CV disease and overweight or obesity without history of diabetes.

SELECT was a double-blind, randomised, placebo-controlled, event driven trial which included 17,604 subjects, with established cardiovascular disease; 67.6% of the subjects were enrolled in the trial based on history of prior myocardial infarction (MI) only, 17.8% were enrolled based on prior stroke only, 4.4% were enrolled based on history of peripheral arterial disease (PAD) only, and 8.2% fulfilled more than one of these qualifying criteria, and all subjects had a BMI ≥27 kg/m2. Subjects with a history of type 1 or 2 diabetes were excluded. The overall median time in-trial was 41.8 months. The study population consisted of 27.7% female and 72.3% male, with a mean age of 61.6 years, including 38.2% subjects ≥65 years (n=6,728) and 7.8% subjects ≥75 years (n=1,366). The mean BMI was 33.3 kg/m2 and mean body weight was 96.7 kg.

At baseline most subjects had cardiovascular related comorbidities including 24.3% with chronic heart failure, 81.8% with hypertension, 46.8% with inflammation (hsCRP ≥2 mg/L), 66.4% with HbA1c ≥5.7% indicative of pre-diabetes, as well as subjects with mild (48.7%), moderate (10.4%) or severe (0.4%) renal impairment. Also 92% of subjects were receiving cardiovascular medication (70.2% beta blockers, 45.0% angiotensin-converting enzyme (ACE) inhibitors, 29.5% angiotensin receptor blockers and 26.9% calcium-channel blockers, 90.1% of subjects were receiving lipid lowering agents (primarily statins 87.6%) and 86.2% of subjects were receiving anti-platelet agents.

Subjects were randomised to either semaglutide 2.4 mg (n=8,803) or placebo (n=8,801) in addition to standard-of-care.

The key design features of SELECT are present below:

Trial ID	EX9536-4388
Primary objective	To demonstrate that semaglutide s.c. 2.4 mg once weekly lowers the incidence of MACE vs placebo, both added to standard of care in subjects with established CV disease and overweight or obesity.
Primary endpoint	Time from randomisation to first occurrence of a composite MACE endpoint, defined as CV death, non-fatal MI, or non-fatal stroke.
Trial population	Multi-national; subjects ≥45 years with established CV disease and overweight or obesity (BMI ≥27 kg/m2), without history of T1D or T2D (HbA1c ≥6.5% or 48 mmol/mol).
Background treatment	Standard of care, e.g., management of CV risk factors including medical treatment and healthy lifestyle counselling.
Semaglutide treatment	Semaglutide s.c. 2.4 mg once weekly
Placebo treatment	Placebo s.c. once weekly
Randomisation ratio and blinding	1:1, double-blind
Duration of trial	Event-driven (minimum 1,225 first EAC-confirmed MACE)
Interim analysis	Prespecified interim test for superiority when 2/3 of the targeted number of primary endpoint events had been accrued.

Clinical efficacy

The trial was event driven and consequently the observation and treatment time varied between subjects depending on when they were recruited into the trial. Average time in-trial was similar across the two treatment groups and average time on-treatment was slightly

lower with semaglutide 2.4 mg than with placebo. The overall median time in-trial was 41.8 months and overall median on-treatment time was 38.2 months.

A total of 96.9% of subjects in the full analysis set (FAS) completed the trial. Vital status was available for 99.4% of the subjects in the trial. The amount of missing data was generally low in both treatment groups. A total of 543 randomised subjects (3.1%) did not complete the trial due to either withdrawal of consent or being LTFU and the number of non-completers was balanced between treatment groups.

Cardiovascular outcomes
The superiority of semaglutide 2.4 mg vs placebo was confirmed for the *primary endpoint* of time to first Event Adjudication Committee (EAC)-confirmed MACE, comprising CV death, non-fatal MI and non-fatal stroke (Figure 1).

• The primary analysis of time to first EAC-confirmed MACE resulted in an estimated HR of 0.80 [0.72; 0.90]$_{95\% CI}$ ($p<0.0001$) for semaglutide 2.4 mg relative to placebo. The absolute risk difference between semaglutide 2.4 mg and placebo at week 156 was -0.011 [-0.019; -0.004]$_{95\% CI}$. Each of the components of MACE contributed to the superior MACE reduction and the components (CV death, non-fatal MI and non-fatal stroke) had HRs below 1.0 favouring semaglutide (Figure 2)
• The results of the primary analysis of MACE were supported by all prespecified sensitivity analyses and consistent results were seen across all subpopulations investigated.

Superiority of semaglutide 2.4 mg vs placebo was not confirmed for the confirmatory secondary endpoint of time to EAC-confirmed CV death, and hence, due to the testing hierarchy, the confirmatory secondary endpoints of time to first EAC-confirmed composite HF outcome, and EAC-confirmed all-cause death were not tested for superiority.

Time to first event analyses of *other* CV composite endpoints provided results consistent with the primary analysis:

- EAC-confirmed expanded MACE endpoint (comprising CV death, non-fatal MI, non-fatal stroke, coronary revascularisation, or unstable angina pectoris requiring hospitalisation): HR 0.80 [0.73; 0.87]$_{95\% CI}$
- Expanded MACE (3-component MACE, unstable angina requiring hospitalisation or coronary revascularisation): Estimated HR 0.80 [0.73; 0.87]$_{95\% CI}$
- EAC-confirmed composite heart failure outcome (comprising ‘heart failure requiring hospitalisation or urgent heart failure visit’ and ‘CV death’): HR 0.82 [0.71; 0.96]$_{95\% CI}$

The results for time to first EAC-confirmed *modified* MACE (comprising all-cause death, non-fatal MI and non-fatal stroke) with a HR of 0.80 [0.72; 0.88]$_{95\% CI}$ were in line with the results for the primary analysis. Thus, the addition of the non-CV related deaths to the MACE endpoint led to the same conclusion as for the primary analysis.

Time to event analyses of the individual *mortality* endpoints provided results consistent with the primary analysis:

- EAC-confirmed all-cause death: HR 0.81 [0.71; 0.93]$_{95\% CI}$
- EAC-confirmed CV death: HR 0.85 [0.71; 1.01]$_{95\% CI}$

Figure 1. Cumulative incidence plot of time to first EAC-confirmed MACE (CV death, non-fatal MI, or non-fatal stroke)

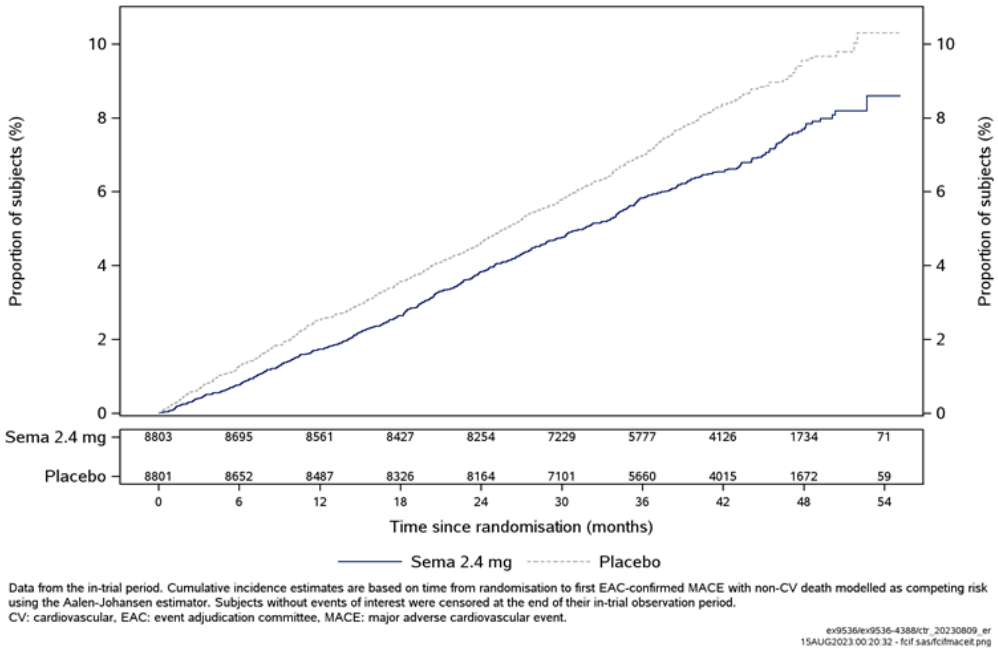
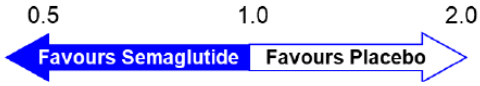


Figure 2. Time to first MACE, components and modified MACE

	HR [95% CI]	Subjects with events/analysed Sema; Placebo
Primary analysis (3-component MACE)	0.80 [0.72; 0.90]	569/8803; 701/8801
CV death	0.85 [0.71; 1.01]	223/8803; 262/8801
Non-fatal myocardial infarction	0.72 [0.61; 0.85]	234/8803; 322/8801
Non-fatal stroke	0.93 [0.74; 1.15]	154/8803; 165/8801
Fatal or non-fatal myocardial infarction [a]	0.72 [0.61; 0.85]	243/8803; 334/8801
Fatal or non-fatal stroke [a]	0.89 [0.72; 1.11]	160/8803; 178/8801
Modified 3-component MACE	0.80 [0.72; 0.88]	710/8803; 877/8801
All-cause death	0.81 [0.71; 0.93]	375/8803; 458/8801
Non-fatal myocardial infarction	0.72 [0.61; 0.85]	234/8803; 322/8801
Non-fatal stroke	0.93 [0.74; 1.15]	154/8803; 165/8801



Kidney outcomes

The risk of deterioration in kidney function was lower with semaglutide 2.4 mg than with placebo: HR 0.78 [0.63; 0.96]$_{95\%\ CI}$

Cardiometabolic risk factors

Treatment with semaglutide 2.4 mg was associated with persistent beneficial effect on cardiometabolic risk factors including blood pressure, lipids, hsCRP, body weight, waist circumference, and HbA1c.

The risk of developing T2D (HbA1c ≥6.5%) during the trial was lower for the semaglutide 2.4 mg group vs placebo (HR 0.27 [0.24; 0.31]$_{95\%\ CI}$). A sustained reduction in hsCRP levels from baseline to week 104 was observed with semaglutide 2.4 mg vs placebo with a relative

reduction of 38%. As expected, the estimated change in heart rate was higher for the semaglutide 2.4 mg group vs placebo (ETD 3.10 bpm [2.80; 3.39]95% CI).

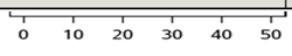
Clinical safety

The safety profile of semaglutide 2.4 mg in people with established CV disease and overweight or obesity, including subjects above 75 years-of-age, was similar and consistent with the known safety profile of semaglutide. In general, no unexpected safety or tolerability concerns were identified with semaglutide 2.4 mg when added to standard of care, based on the long-term safety data from SELECT. The types, frequencies and rates of AEs were in line with the well-known safety profile of semaglutide.

For most of the predefined safety focus areas (Figure 3) there were little or no differences between semaglutide 2.4 mg and placebo, including similar proportion of subjects in each treatment group reporting AEs of acute renal failure, malignant neoplasms, pancreatitis, COVID-19 and SAEs of gastrointestinal disorders. The proportion of subjects reporting SAEs of Cardiac disorders (SOC) was lower with semaglutide 2.4 mg than with placebo. The proportion of subjects reporting AEs of gallbladder-related disorders was higher with semaglutide 2.4 mg than placebo, mainly driven by an imbalance in cholelithiasis (PT).

Figure 3. Overview of events based on pre-defined MedDRA searches for each safety focus area

Predefined MedDRA Search	Sema 2.4 mg (N=8803)				Placebo (N=8801)			
	N	(%)	E	R	N	(%)	E	R
COVID-19	2108	(23.95)	2323	8.86	2150	(24.43)	2365	9.08
Cardiac disorders (SAEs)	1008	(11.45)	1414	4.83	1184	(13.45)	1800	6.18
Malignant tumours	422	(4.79)	517	1.77	418	(4.75)	505	1.73
Gastrointestinal disorders (SAEs)	342	(3.89)	455	1.55	323	(3.67)	403	1.38
Gallbladder-related disorders	246	(2.79)	300	1.02	203	(2.31)	246	0.85
Acute renal failure	171	(1.94)	193	0.66	200	(2.27)	222	0.76
Rare events (SAE)	136	(1.54)	150	0.51	139	(1.58)	150	0.52
Medication errors	54	(0.61)	63	0.22	70	(0.80)	83	0.29
Eye disorders (SAEs)	41	(0.47)	49	0.17	41	(0.47)	51	0.18
Hepatic disorders (SAEs)	36	(0.41)	45	0.15	35	(0.40)	47	0.16
Pancreatitis	29	(0.33)	33	0.11	30	(0.34)	33	0.11
Allergic reactions (SAEs)	26	(0.30)	27	0.09	24	(0.27)	24	0.08
Appendicitis (SAEs)	25	(0.28)	25	0.09	25	(0.28)	27	0.09
Abuse and misuse	10	(0.11)	11	0.04	12	(0.14)	17	0.06
Suicide / self-injury (SAEs)	10	(0.11)	12	0.04	10	(0.11)	12	0.04
Hypoglycaemia (SAEs)	3	(0.03)	3	0.01	1	(0.01)	1	<.01
Suspected transmission* (SAE)	0	-	-	-	1	0.01	1	<.01



Semaglutide 2.4 mg
Placebo

N: number of subjects with event(s), %: proportion of subjects with event(s), E: number of events, R: events per 100 patient years of observation, Sema: semaglutide, * Suspected transmission* of an infectious agent via trial product (SAE)

Benefit risk assessment

The pivotal SELECT trial achieved its objectives showing a significant and clinically relevant risk reduction of 20% in MACE with semaglutide 2.4 mg compared to placebo in patients with established CV disease and overweight or obesity without history of diabetes.

The results were consistent across different analyses and semaglutide also led to clinically meaningful improvements in cardiometabolic risk factors including lowering of blood pressure, improved lipid profile, reduction in inflammation, marked weight loss and improved glucose metabolism. The safety and tolerability findings were generally in line with the known safety profile of semaglutide, although some new safety information is proposed to be included in the SmPC in line with the updated FDA label.

As mentioned, SELECT included non-diabetic patients. However, CVOTs such as SUSTAIN 6 and PIONEER 6 with semaglutide in diabetic patients (with a large proportion being overweight or obese) have also provided evidence of beneficial effects. Therefore, overall it is reasonable to not specifically mention non-diabetic patients in the indication. This information is instead included in section 5.1 of the SmPC

Overall, based on the SELECT results and the submitted information on the RR review, it is agreed that the benefit:risk for the proposed use of semaglutide 2.4 mg in this new indication is positive and the outcome of the RR assessment is fully endorsed. No major UK-specific regulatory issues have been identified.

Information on paediatric requirements
In accordance with the Human Medicines Regulations 2012, a PIP (MHRA-101270-PIP01-23) was previously submitted and agreed. A product-specific waiver (all subsets paediatric population from birth to less than 18> years of age) for the prevention of cardiovascular events in patients with atherosclerosis has been granted.

Conclusion
The benefit:risk is considered positive.
The proposed changes are acceptable.

In accordance with legal requirements, the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision: Grant

Date: 23 July 2024

Annex IV

Reference: PLGB 04668/0436-0440 - 0023
Product:
Wegovy 0.25 mg, FlexTouch solution for injection in pre-filled pen
Wegovy 0.5 mg, FlexTouch solution for injection in pre-filled pen
Wegovy 1 mg, FlexTouch solution for injection in pre-filled pen
Wegovy 1.7 mg, FlexTouch solution for injection in pre-filled pen
Wegovy 2.4 mg, FlexTouch solution for injection in pre-filled pen

Type of Procedure: Reliance route
This variation is an International Recognition (IRP) application with the EMA as a Reference regulator

Submission category: Type II Variation

Reason
To update section 5.1 of the SmPC in order to include new data generated in patients with knee osteoarthritis (OA), based on final results from study NN9536-4578 (STEP 9); this is a phase 3b randomised, two-arm, double-blinded, multi-centre clinical trial comparing semaglutide s.c. 2.4 mg once-weekly with semaglutide placebo in subjects with moderate OA of one or both knees, pain due to knee OA, and obesity.

Supporting evidence
The MAH has submitted the complete clinical trial report for study NN9536-4578 (STEP 9, along with addenda to the clinical overview and clinical summary.
Updated Summaries of Product Characteristics (SmPCs) and Patient information leaflets (PILs) have been submitted.

Evaluation
This application was approved under International Recognition procedure (IRP). The Reference Regulator (RR) was the European Medicines Agency (EMA), with the procedure number (EMEA/H/C/005422/II/0021).

For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the reference regulator, please refer to the public assessment report on the relevant competent authority's website.

Conclusion
The proposed changes are acceptable.
In accordance with legal requirements, the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision: Grant

Date: 22 November 2024