**Unit: Technical Assessment Unit**

**Wegovy®**

**Administrative information:**

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| Trade name of the medicinal product: | **Wegovy 0.25 mg FlexTouch solution for injection in pre-filled pen**<br>**Wegovy 0.5 mg FlexTouch solution for injection in pre-filled pen**<br>**Wegovy 1 mg FlexTouch solution for injection in pre-filled pen**<br>**Wegovy 1.7 mg FlexTouch solution for injection in pre-filled pen**<br>**Wegovy 2.4 mg FlexTouch solution for injection in pre-filled pen** |
| INN (or common name) of the active substance(s): | **Semaglutide** |
| Manufacturer of the finished product | **Wegovy 0.25 mg&0.5 mg&1.7 mg&2.4mg**<br>- Novo Nordisk A/S, Brennum Park, 3400 Hillerod, Denmark - DENMARK;<br>- Novo Nordisk A/S, Novo Alle, DK-2880 Bagsvaerd- Denmark - DENMARK;<br>**Wegovy 1 mg**<br>- Novo Nordisk A/S, Novo Alle, DK-2880 Bagsvaerd- Denmark - DENMARK;<br>- Novo Nordisk A/S, Brennum Park, 3400 Hillerod, Denmark - DENMARK;<br>-Novo Nordisk Pharmaceutical Industries, LP 3612 Powhatan Road Clayton, NC 27527 USA - UNITED STATES OF AMERICA; |
| Marketing Authorization holder | Novo Nordisk A/S, Novo Alle, DK-2880 Bagsvaerd- Denmark - DENMARK; /<br>**Applicant:** Novo Nordisk scientific office, Egypt. |

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| Applied Indication(s): | - **Adults**<br>Wegovy is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of<br>• ≥30 kg/m2 (obesity), or<br>• ≥27 kg/m2 to <30 kg/m2 (overweight) in the presence of at least one weight-related comorbidity e.g. dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidemia, obstructive sleep apnea or cardiovascular disease.<br>**- Adolescents (≥12 years)**<br>Wegovy 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<br>• obesity* and<br>• body weight above 60 kg.<br>Treatment with Wegovy 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.<br>*Obesity (BMI ≥95th percentile) as defined on sex- and age-specific BMI growth charts<br>BMI cut-off points for obesity (≥95th percentile) by sex and age for pediatric patients aged 12 and older (CDC criteria)<br><br>**PIL:**<br>Wegovy® is used together with diet and physical activity for weight loss and to help keep the weight under control. It is used in adults, who have:<br>• a BMI of 30 kg/m² or greater (obesity) or |

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| | • a BMI of at least 27 kg/m² but less than 30 kg/m² (overweight) who have weight-related health problems (such as diabetes, high blood pressure, abnormal levels of fats in the blood, breathing problems during sleep called 'obstructive sleep apnea' or a history of heart attack, stroke or blood vessel problems).<br>BMI (Body Mass Index) is a measure of your weight in relation to your height.<br>-Wegovy® is used together with diet and physical activity for weight management in adolescents ages 12 years and above, who have: obesity and body weight >60 kg.<br>As an adolescent patient, you should only continue using Wegovy® if you have lost at least 5% of your BMI after 12 weeks on the 2.4 mg dose or maximum tolerated dose. Consult your doctor before you continue |
| Pharmaceutical form(s) and strength(s): | - **Solution for Subcutaneous injection in prefilled pen flex touch**<br>-Wegovy 0.25 mg FlexTouch solution for injection pre-filled pen<br>Each pre-filled pen contains 1 mg semaglutide* in 1.5 mL solution. One mL of solution contains 0.68 mg semaglutide*. One pre-filled pen contains 4 doses of 0.25 mg.<br>Wegovy 0.5 mg FlexTouch solution for injection pre-filled pen 1.5 mL:<br>Each pre-filled pen contains 2 mg semaglutide* in 1.5 mL solution. One mL of solution contains 1.34 mg semaglutide*. One pre-filled pen contains 4 doses of 0.5 mg.<br>Wegovy 1 mg FlexTouch solution for injection pre-filled pen |

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| | Each pre-filled pen contains 4 mg semaglutide* in 3 mL solution. One mL of solution contains 1.34 mg semaglutide*. One pre-filled pen contains 4 doses of 1 mg.<br>Wegovy 1.7 mg FlexTouch solution for injection pre-filled pen<br>Each pre-filled pen contains 6.8 mg semaglutide* in 3 mL solution. One mL of solution contains 2.27 mg semaglutide*. One pre-filled pen contains 4 doses of 1.7 mg.<br>Wegovy 2.4 mg FlexTouch solution for injection pre-filled pen Each pre-filled pen contains 9.6 mg semaglutide* in 3 mL solution. One mL of solution contains 3.2 mg semaglutide*. One pre-filled pen contains 4 doses of 2.4 mg. |
| Route of administration | S.C |
| Type of registration (EMA/FDA – Local) | EMA approved |

## List of abbreviations

**ADA:** anti-drug-antibodies
**ADR:** adverse drug reaction
**AE:** adverse event
**BBB:** blood-brain barrier
**BE:** Bioequivalence
**BMI:** body mass index
**BW:** body weight
**cAMP:** Cyclic adenosine monophosphate
**CV:** cardiovascular
**CVD:** cardiovascular disease
**CVOT:** cardiovascular outcome trial
**DM:** Diabetes Mellitus
**DNA:** Deoxyribonucleic acid
**GI:** gastrointestinal
**GLP-1 RA:** glucagon-like peptide-1 receptor agonist

**GLP-1:** glucagon-like peptide-1
**GLP-1R:** glucagon-like peptide-1 receptor
**HF:** heart failure
**HFpEF:** heart failure with preserved ejection fraction
**HFpEF-DM:** heart failure with preserved ejection fraction-Diabetes Mellitus
**i.v:** intravenous
**IWQOL-Kids:** Impact of weight on quality of life-kids
**MACE:** major adverse cardiovascular event
**MI:** myocardial infarction
**NOAEL:** No Observed Adverse Effect Level
**NT-proBNP:** N-terminal-pro-brain natriuretic peptide
**OA:** Osteoarthritis
**OD:** once daily
**OW:** once weekly
**P:** p-value
**PD:** pharmacodynamics
**PK:** Pharmacokinetic
**popPK:** population pharmacokinetics
**PT:** preferred term
**S.c.:** subcutaneous(ly)
**SAE:** serious adverse event
**SC:** Subcutaneous
**SOC:** system organ class
**STEP 1:** NN9536-4373 (weight management)
**STEP 2:** NN9536-4374 (weight management
**STEP 3:** NN9536-4375 (weight management
**STEP 4:** NN9536-4376 (sustained weight)
**STEP:** Semaglutide Treatment Effect in Patient with obesity
**$t_{1/2}$:** elimination half-life
**T1D:** type 1 diabetes
**T2D:** type 2 diabetes
**T2DM:** type 2 diabetes mellitus
**Vs:** versus
**WM:** weight management
**WOMAC:** Western Ontario and McMaster Universities osteoarthritis 3.1 Index

**Dossier initial submission and evaluation process:**

**The file evaluated according to EDA Reliance Model & the company submitted data which are the followings: (For process B, A)**

1. **Quality module-3 from the CTD file for Process B.**

2. **Quality module-3 from the Ozempic CTD file for process A of Semaglutide API and the data received from the company**
3. **Unredacted EMA assessment**
4. **List of variations**

## 1. Introduction

- Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue for once-weekly subcutaneous (s.c.) administration in patients with obesity (≥30 kg/m2) or overweight (≥27 kg/m2 to <30 kg/m2) in the present of at least one weight-related comorbidity.
- Semaglutide has unique therapeutic potential for weight management, including weight loss and weight maintenance, due to its combined effects not only on body weight but also on glucose metabolism and other weight-related comorbidities.

- Semaglutide for weight management will be provided in the PDS290 pen-injector with four drug product concentrations: 0.68 mg/mL, 1.34 mg/mL, 2.27 mg/mL and 3.2 mg/mL to deliver five doses: the escalation doses (0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg) and the maintenance dose (2.4 mg).

**About the semaglutide molecule**

- Semaglutide is classified as a GLP-1 receptor agonist (GLP-1 RA), and has a 94% homology to human GLP-1. Compared to native GLP-1, the semaglutide molecule has structural modifications to obtain a longer half-life. The modifications include: 1) modifying alanine in position 8 of the peptide backbone to 2-aminoisobutyric acid to increase stability against the DPP-4 enzyme, and changing lysine in position 34 to arginine to prevent acylation in this position; 2) adding a hydrophilic spacer between the lysine in position 26 and the gamma glutamate whereto the fatty acid is attached; and 3) a C18 fatty di-acid with a terminal acidic group. The spacer and the fatty acid both contribute to increased albumin binding which slows the degradation of semaglutide in plasma and decreases the renal clearance, which combined with the increased stability against theDPP-4 enzyme, prolong the half-life of semaglutide to approximately 1 week, thus enabling once-weekly s.c. administration.

## 2. <u>Quality aspects:</u>

- **Manufacturer(s):**
  - **Drug Substance**

**- The Active substance (Semaglutide) is manufactured at** Novo Nordisk A/S,Hallas Alle, 4400 Kalundborg- Denmark - DENMARK;

- **Drug product**

**- The Finished product of Wegovy 0.25 mg&0.5 mg&1.7 mg&2.4mg is manufactured at**

1- Novo Nordisk A/S, Brennum Park, 3400 Hillerod, Denmark - DENMARK;
2- Novo Nordisk A/S, Novo Alle, DK-2880 Bagsvaerd- Denmark - DENMARK;

**- The Finished product of Wegovy 1 mg is manufactured at**

1- Novo Nordisk A/S, Novo Alle, DK-2880 Bagsvaerd- Denmark - DENMARK;
2- Novo Nordisk A/S, Brennum Park, 3400 Hillerod, Denmark - DENMARK;
3- Novo Nordisk Pharmaceutical Industries, LP 3612 Powhatan Road Clayton, NC 27527 USA - UNITED STATES OF AMERICA;

- Manufacturing of both DS and DP are performed in accordance with cGMP regulations.

- **Stability**
  - **Drug substance:**

**- Approved Storage Conditions of the active substance:** −20°C ± 5°C
**-Approved shelf life for the active substance:** 48 months

  - **Drug product:**

**-Approved Storage Conditions of the finished product:**
**Finished product**:
-Store in a refrigerator (2- 8°C). Keep away from the cooling element.
-Do not freeze.
-After first use: 6 weeks. Store below 30°C or in a refrigerator (2°C to 8°C).
- Keep the pen cap on when the pen is not in use in order to protect it from light.
**-Approved shelf life for the finished product:** (**Before use** )36 months/ **After first use**: 6 weeks

### 3. Non –clinical aspect:

- Wegovy is an injectable medicine containing semaglutide, which is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) that binds to and activates the GLP-1 receptor. The GLP-1 RA drug class is associated with unique therapeutic potential for weight management, including weight loss and weight maintenance, due to its combined effects not only on body weight but also on glucose metabolism and other weight-related comorbidities.
Semaglutide is a GLP-1 analogue with 94% sequence homology to human GLP-1 and a long half-life suitable for once-weekly dosing.
Semaglutide is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*) and chemical modification. Semaglutide was originally evaluated as an adjunct to diet and exercise for the treatment of type 2 diabetes mellitus (T2DM).

-The pharmacological mechanism of GLP-1 RA is well described, with blood glucose lowering and body fat loss mediated by lowered intake of calories. The primary pharmacological target tissues for GLP-1RA are the pancreas (beta-cells), the gastrointestinal system and the brain.
-The GLP-1R is a G protein-coupled receptor, and the cellular action of GLP-1 is mediated through the G-protein and subsequent activation of adenylate cyclase, leading to increased cAMP accumulation.
-The principal mechanism of protraction is albumin binding, which results in decreased renal clearance and protection from metabolic degradation.

- **Pharmacology (PD, safety pharmacology & PK studies):**

-The pharmacological mechanism of GLP-1 RA is well described, with blood glucose lowering and body fat loss mediated by lowered intake of calories. The primary pharmacological target tissues for GLP-1RA are the pancreas (beta-cells), the gastrointestinal system and the brain.
-The GLP-1R is a G protein-coupled receptor, and the cellular action of GLP-1 is mediated through the G-protein and subsequent activation of adenylate cyclase, leading to increased cAMP accumulation.
-It was confirmed that semaglutide crosses the BBB and that its effects include central homeostatic mechanisms involving the hypothalamus and brain stem.
-Semaglutide induced cFos activation in several brain regions in the mouse brain including areas that are known to be involved in the regulation of food intake and body weight. The brain areas include both directly targeted areas involved in homeostatic appetite regulation and secondarily activated areas known to be involved in both homeostatic and hedonic appetite regulation.
-As GLP- 1 receptor agonists including semaglutide stimulate insulin secretion and slow digestion, mechanisms other than the above central effects of semaglutide may also contribute to semaglutide-induced weight loss. These mechanisms of action may be a matter of future investigation.
-The principal mechanism of protraction is albumin binding, which results in decreased renal clearance and protection from metabolic degradation.

- **Toxicology:**

- Since the present application is intended for a new indication and a new dosage, no new studies have been submitted. There are no new safety concerns associated with the higher systemic exposures expected with the higher strength formulation of semaglutide (as Wegovy) no adverse changes were observed. As previously observed during evaluating Ozempic SC Injection 2 mg, the NOAEL for repeat dose toxicity (0.6 mg/kg/day) in rats is more than 10-fold the exposure at the maximum recommended human dose of 2.4 mg/week.
-It is worth mentioning that previous toxicology data submitted indicate that long-acting GLP-1 receptor agonists cause dose-related and treatment-duration-dependent thyroid C-cell tumors (adenomas or carcinomas) in rodents.

**Overall conclusion:** Taking into account of the results of studies for the initial approval of Ozempic SC Injection 2 mg, early evaluated, as well as two new pharmacodynamic studies, semaglutide is considered to have a pharmacological effect of weight loss. Therefore, Wegovy is approvable from the preclinical point of view.

## 4. Clinical aspect:

- Novo Nordisk has developed semaglutide s.c. 2.4 mg once weekly as a novel weight management therapy. Collectively, there is **a clear unmet medical need** for a convenient, efficacious and safe weight lowering drug with beneficial effects on obesity-related comorbidities.

➢ **Clinical Pharmacology (PK & PD):**

- **Steady-state pharmacokinetics (PK)** was as expected from the Ozempic® programme with an elimination half-life (t½) of approximately one week, supporting the once-weekly dosing of semaglutide 2.4 mg.
- **Exposure** of semaglutide **increased in** a **dose-proportional manner** up to 2.4 mg once weekly. As expected, **body weight was the most important covariate** resulting in lower exposure with higher body weight and vice versa. Other investigated covariates (sex, age, race, ethnicity, renal function, injection site and glycemic status) had a minor or no influence on semaglutide exposure.
- The proportion of subjects reporting **gastrointestinal adverse events**, in particular nausea or vomiting, increased to a minor extent with increasing semaglutide exposure and appeared to plateau so that it was almost constant over the studied exposure range for semaglutide 2.4 mg.
- Therefore, based on these data all subjects should be dosed with the proposed **maintenance dose of semaglutide 2.4 mg**, irrespective of body weight or any other covariate investigated.
- The **comparable PK characteristics** and results of **the population PK analysis** of semaglutide 2.4 mg and semaglutide 1.0 mg from phase 3a trials provide the justification for referring to the clinical pharmacology characteristics of semaglutide as described in the Ozempic® programme.
- **Overall, the clinical pharmacology characteristics of semaglutide s.c. at doses up to 2.4 mg support the use of semaglutide 2.4 mg as a weight management therapy.**

- The results from **the bioequivalence trials NN9536-4649 and NN9535-3687** support the change in drug product concentrations between:

- the semaglutide drug product concentrations to-be-marketed using the PDS290 pen-injector (0.68 mg/mL for the escalation dose of semaglutide 0.25 mg, 1.34 mg/mL and 2.27 mg/mL for the escalation doses of semaglutide 0.5 mg, 1 mg and 1.7 mg, and 3.2 mg/mL for the maintenance dose of semaglutide 2.4 mg) and
- the semaglutide drug product concentrations administered during the phase 3a trials using the PDS290 pen-injector (1.0 mg/mL and 3.0 mg/mL).

- Population PK analysis (comparing the adolescent subjects in STEP Teens to the adult subjects in STEP 1) showed that exposure was inversely correlated with body weight in adolescents. This is in line with adult data. No clear differences were observed between adolescents and adults based on the presented exposure-response data (BMI) or exposure-safety data (nausea and vomiting). Age caused no clinically relevant change in semaglutide exposure.

➢ **Clinical Efficacy:**

- **Semaglutide 2.4 mg once weekly with dose escalation every 4 weeks** was the proposed maintenance dose for the phase 3a **weight management development programme** as it resulted in similar $C_{max}$ at steady state as that obtained by the once-daily 0.4 mg semaglutide dose in the dose-finding phase 2 trial (4153), and also projected lower proportions of subjects reporting gastrointestinal AEs by approximately 2% and the proportion of subjects discontinuing due to gastrointestinal AEs. The exposure-response relationship showed a consistent increase in effects with increasing exposure. Consequently, it is considered the most efficacious dose with no unexpected safety signals to the existing semaglutide safety profile, and is therefore **the recommended clinical dose for weight management.**

- The **phase 3a clinical development programme** confirmed that semaglutide s.c. 2.4 mg once weekly led to a substantial and clinically meaningful weight loss and improved physical functioning in subjects with overweight or obesity. Furthermore, treatment with semaglutide 2.4 mg improved physical functioning, and had beneficial effects on glucose metabolism, as well as on blood pressure, lipid profile and other cardiovascular risk markers. **Superiority of semaglutide 2.4 mg** was demonstrated for the primary endpoint change from baseline to week 68 in body weight (%) in all four phase 3a trials (STEP 1-4 trials).

- A dose-dependent decrease in body weight from baseline to week 68 was observed and semaglutide 2.4 mg was superior to placebo in providing marked reduction in body weight (%), achieving a clinically relevant weight loss of ≥5%, and improving weight-related endpoints in subjects with overweight or obesity with and without T2D.

- **For long-term weight management and ≥20% weight loss**, results from STEP 5 demonstrated the sustained weight loss effect of semaglutide 2.4 mg following 2 years of treatment. Furthermore, data from STEP 8 demonstrated a greater proportion of patients achieving a weight loss of at least 20% (included as a confirmatory endpoint in STEP 8) with semaglutide 2.4 mg compared with liraglutide 3.0 mg (Saxenda®), currently one of the most effective weight loss pharmacotherapies on the market. This is further supported by the results from the STEP 1ext, demonstrating the effects of treatment discontinuation after 68 weeks of treatment with semaglutide 2.4 mg versus placebo, showing weight regain after end of treatment with semaglutide 2.4 mg. **Superiority of semaglutide 2.4 mg** versus placebo was demonstrated in STEP 5 and of semaglutide 2.4 mg versus liraglutide 3.0 mg in STEP 8 for change in body weight (%) from baseline to week 68 (STEP 8) or week 104 (STEP 5).

- **For Adolescents,** in STEP Teens trial, treatment with semaglutide 2.4 mg resulted in a statistically significant reduction in BMI (%) from baseline to week 68 compared to placebo (Section 2.3). A higher proportion of subjects with semaglutide 2.4 mg achieved ≥5% body weight reduction compared to placebo. This was supported by a significant reduction in body weight (kg and %) and waist circumference from baseline to week 68. The treatment effect of semaglutide 2.4 mg was persistent throughout the 68 weeks on treatment. Beneficial effects of semaglutide 2.4 mg were also seen for waist circumference, glucose metabolism, lipids and weight-related quality of life (physical comfort and total score on IWQOL-Kids).

- **For patients with obesity and knee OA**, in STEP 9 (Knee OA), the weight loss observed with semaglutide 2.4 mg occurred early and continued throughout the study, consistent with the results of previous studies in STEP program. At the end of treatment (week 68), the weight loss achieved with semaglutide 2.4 mg was superior and clinically meaningful when compared to the placebo. While comparing the proportions, treatment with semaglutide 2.4 mg consistently demonstrated the clinically meaningful improvement in knee OA-related pain and physical function compared to the placebo. The knee-OA related pain improvements with Wegovy® were achieved without an increase in the use of pain medication. As such, it is acceptable to add the primary endpoints body weight and WOMAC Pain to the SmPC section 5.1.

- **For CVR reduction,** Trial 4388 (SELECT) demonstrated that semaglutide s.c. 2.4 mg once weekly added to standard of care, provided superior and clinically relevant CV risk reduction in people with established CV disease and overweight or obesity without history

of T1D or T2D. Furthermore, the results confirmed that semaglutide 2.4 mg led to clinically meaningful improvements in CV risk factors including lowering of blood pressure, improved lipid profile, reduction in inflammation, marked weight loss and improved glucose metabolism.

- The beneficial effect of semaglutide on MACE is considered clinically important, addressing an unmet medical need since no previous dedicated weight management CVOTs have been able to demonstrate a link between weight loss and CV risk reduction. However, the SELECT trial was not powered to evaluate the mono components for the composite endpoint.
- The patient population selected for this study is already a part of the target patient population for the weight loss indication in adults already approved for Wegovy. The exact mechanism of cardiovascular risk reduction has not been established. Mediation analyses are presented to support an independent effect of semaglutide on reduction of CV risk. However, mediation analyses may be considered hypothesis generating, but they are not considered an appropriate basis for a separate indication for the prevention of CV disease. Nonetheless, it is considered relevant to add the results of the SELECT trial in section 5.1 of the SmPC of Wegovy, since they demonstrate a link between weight loss and CV risk reduction.

- **For patients with HFpEF and obesity**, overall, treatment with semaglutide 2.4 mg showed superiority in improving physical function, reducing HF symptoms, inducing weight loss, and providing overall clinical benefit compared with placebo in patients with obesity-related HFpEF, with or without T2D. The treatment benefit of semaglutide over placebo was consistent across all subpopulations. The magnitude of benefit was directly related to the extent of weight loss. Collectively, these data support semaglutide-mediated weight loss as a key treatment strategy in patients with the HFpEF obesity phenotype. These benefits are not simply ascribable to mechanical effects of body weight reduction, as the semaglutide HFpEF trials also showed that semaglutide reduced NT-proBNP levels and dose of loop diuretics compared to placebo, consistent with a direct benefit on haemodynamic congestion.

➢ **Clinical Safety:**

- The four phase 3a trials (referred to as **STEP 1−4**) serve as the primary foundation for evaluating the safety of semaglutide 2.4 mg. The AE profile of semaglutide 2.4 mg was overall similar to that of semaglutide s.c. for T2D and oral semaglutide for T2D and other GLP-1 RAs:

- More AEs were reported with semaglutide compared to placebo, driven by non-serious and mild gastrointestinal AEs.

- Gastrointestinal AEs (in particular Nausea, Diarrhoea, Vomiting and Constipation) were the most common AEs with semaglutide 2.4 mg. The majority of gastrointestinal AEs were mild or moderate in severity and had onset during the dose escalation period. There was a dose-dependent increase in gastrointestinal AEs and in gastrointestinal AEs leading to permanent discontinuation of trial product (semaglutide 2.4 mg). A dose-response was also seen for AEs of fatigue and decreased appetite.
- Less common PTs reported for ≥2 to < 5% of subjects that occurred more frequently with semaglutide 2.4 mg than placebo were overall well-known side effects of the GLP-1 RA class with the only addition being Hair loss.
- In the phase 3a pool, the proportion of subjects with AEs with fatal outcome was low and similar with semaglutide 2.4 mg and placebo.
- More subjects with semaglutide 2.4 mg (9.3%) vs placebo (6.4%) reported serious AEs, mainly driven by gastrointestinal AEs and gallbladder-related disorders (primarily seen in STEP 3). The proportion of subjects with serious AEs that led to permanent treatment discontinuation was similar between semaglutide 2.4 mg and placebo.
- There was no increased risk of cardiovascular disorders, neoplasms (benign and malignant), hepatic disorders, acute renal failure or psychiatric disorders with semaglutide 2.4 mg. Also, the data do not support a causal relationship between semaglutide 2.4 mg treatment and the development of acute pancreatitis.
- The safety profile of semaglutide 2.4 mg was not affected to any clinically relevant extent by intrinsic factors (sex, age, race, ethnic origin, body weight, BMI, renal function and glycaemic status) or extrinsic factors (region and anti-diabetic background medication).

- Safety data from both **STEP 5 and STEP 8** did not include any unexpected safety findings in the two trials and the overall safety and tolerability profile showed overall the same safety profile as the phase 3a pool and the GLP-1 RA class, with gastrointestinal events as the most common events.

- Based on the safety data from **STEP Teens**, semaglutide 2.4 mg, administered once weekly as an adjunct to a reduced-calorie diet and increased physical activity, was well tolerated in adolescent subjects of ages 12 to < 18 years with overweight or obesity. There were no unexpected safety findings in the trial and the overall safety and tolerability profile reflected that of the original application, and the GLP-1 RA class generally. Gastrointestinal (GI) events were the most commonly reported adverse event (AE). Overall, the frequency, type and severity of adverse reactions in pediatric subjects aged 12 years and above were comparable to that observed in the adult population. No treatment differences on growth or pubertal development were noted.

- Based on the safety results from **STEP 9 (Knee OA)** study, there were no new or unexpected safety findings. The overall safety and tolerability profile was similar to previous findings with semaglutide 2.4 mg and that of other approved GLP-1 RAs. However, the number participants with malignant neoplasm SAEs, was higher in the semaglutide 2.4 mg group compared to the placebo group, but the totality of the data does not suggest an increased risk of malignant neoplasms associated with semaglutide 2.4 mg compared to placebo.

- The safety and tolerability profile of semaglutide 2.4 mg in people with **established CV disease and overweight or obesity and in patients with obesity-related HFpEF with and without T2D,** is in line with the safety profile previously reported for semaglutide and no new safety or tolerability concerns were identified for semaglutide 2.4 mg.

➢ **Clinical Immunogenicity:**

- Overall, the **low immunogenicity** observed with semaglutide s.c. 2.4 mg is consistent with that reported for semaglutide s.c. 1 mg for T2D (Ozempic®) and other GLP-1 analogues with high homology to the human GLP-1 amino acid backbone.
- The proportion of subjects that tested positive for anti-semaglutide antibodies at any time point post-baseline was low. Formation of anti-semaglutide antibodies **did not appear to influence** the semaglutide plasma concentrations (PK), efficacy or safety profile.
- Results suggests that the immunogenicity risk of semaglutide 2.4 mg is low and the benefit/risk ratio remains **favorable** for subjects with anti-semaglutide antibody formation. This is in line with previous experience with semaglutide.

➢ **Benefit/ Risk discussion:** Based on the magnitude and range of the benefits, the manageable and well-characterized risks, the level of evidence provided by the size and length of the clinical development programme, and in the light of the substantial and increasing global burden of the obesity and the current unmet medical need, the balance between the benefits and the risks identified for treatment with semaglutide 2.4 mg once weekly, it offers a convenient once-weekly efficacious treatment for patients with overweight or obesity, and a wide range of comorbidities, and has an acceptable safety profile.

*In conclusion the overall benefit/risk of* ***Wegovy (0.25 mg, 0.5 mg, 1 mg, 1.7 mg and 2.4 mg*** ***FlexTouch*** *is favorable in the treatment of:*

-Adults

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

- ≥30 kg/m2 (obesity), or
- ≥27 kg/m2 to < 30 kg/m2 (overweight) in the presence of at least one weight-related comorbidity e.g. dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidemia, obstructive sleep apnea or cardiovascular disease.

-Adolescents (≥12 years)

Wegovy 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 (obesity (BMI ≥95th percentile) as defined on sex- and age-specific BMI growth charts (CDC.gov) and
- body weight above 60 kg. Treatment with Wegovy 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.

**General Conclusion and Recommendations if any:**

- Based on the review of CTD modules and other supplementary documents, the product is approved.

**For more information, please visit EMA published assessment report link:**

**https://www.ema.europa.eu/en/documents/assessment-report/wegovy-epar-public-assessment-report_en.pdf**