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HEALTH TECHNOLOGY BRIEFING AUGUST 2020

Semaglutide for overweight individuals

NIHRIO ID	24078	**NICE ID**	10199
Developer/Company	Novo Nordisk Ltd	**UKPS ID**	655138

Licensing and market availability plans	Currently in Phase III clinical trials.

SUMMARY

Semaglutide is in clinical development for the treatment of overweight and obese individuals. Excess weight can place stress on both mental and physical health, leading a number of complications such as depression, low self-esteem, and increased risk of heart disease, stroke and type 2 diabetes. Weight can be affected by a number of factors such as diet, physical activity, genetics and general health conditions, however diet and exercise are the two main contributing factors. Being overweight is reversible through lifestyle changes such as increased exercise, healthy diet and a net calorie deficit, along with help through counselling and medication. If weight is not able to be controlled, surgery may be required. Therefore, there is an unmet need for pharmacological therapies that target both weight and glucose control.

Semaglutide, given as an injection under the skin, binds to, and activates the GLP-1 receptor. This reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite. It also reduces the preference of fat foods. This could be an alternative treatment compared to other medication and surgery, and appears to be well-tolerated by patients.

PROPOSED INDICATION

Adjunct to a reduced-calorie diet and increased physical activity for weight management in adults with an initial BMI of 30 kg/m^2 or greater, or adults with a BMI greater than 27 kg/m^2 in the presence of at least one weight-related comorbidity (e.g. dysglycaemia [pre-diabetes or Type 2 Diabetes], hypertension, dyslipidaemia or obstructive sleep apnoea).[a]

TECHNOLOGY

DESCRIPTION

Semaglutide binds to and activates the glucagon-like peptide-1 (GLP-1) receptor in order to increase insulin levels and suppress glucagon secretion. This action leads to the slowing of glucose absorption and lower post-meal blood glucose levels.[1-3] Semaglutide reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite. In addition, semaglutide reduces the preference for high fat foods.[3]

Semaglutide is in Phase III (STEP 1-7) development for weight management in adults with a BMI ≥30 kg/m^2, or BMI ≥27 kg/m^2 with the presence of at least one weight-related comorbidity (such as type 2 diabetes or hypertension).[4-10] It is proposed to be given at a final dosage of 2.4mg by a once-weekly subcutaneous injection. This is gradually built up through the following dosage escalation every four weeks: 0.25mg, 0.5mg, 1.0mg, 1.7mg and 2.4mg.[a]

INNOVATION AND/OR ADVANTAGES

There is an unmet need for pharmacological therapies that target both weight and hyperglycaemia in obese or overweight patients with type 2 diabetes. Bariatric surgery remains the most effective therapeutic option for obesity management in type 2 diabetes, however the associated risks and eligibility criteria negate this procedure in many patients.[11]

Semaglutide is the first investigational GLP-1 agonist that can have two different formulations: once-daily oral tablet and once-weekly injectable preparations, however for the proposed indication only the subcutaneous injection form will be available.[12] There does not appear to be a significant difference between the action of oral tablet and injection on fasting glucose reduction, and they are not recommended first-line therapy for patients inadequately controlled on diet and exercise.[13,14] Semaglutide injection is approved by the US FDA to decrease the risk of major heart problems in people with type 2 diabetes and heart disease, whereas the tablet form is not.[15] Semaglutide may be more cost effective and increase Quality-Adjusted Life-Years (QALYs) in comparison to similar treatment options, such as dulaglutide, particularly for type 2 diabetes treatment.[16]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Semaglutide is already licenced in the EU for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:[17]

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications

[a] Information provided by Novo Nordisk Ltd on UK PharmaScan.

- in addition to other medicinal products for the treatment of diabetes

The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea (very common), diarrhoea (very common) and vomiting (common). In general, these reactions were mild or moderate in severity and of short duration.[18]

Semaglutide is currently in Phase II development for:[19]
- HIV
- Non-alcoholic fatty liver disease
- Non-alcoholic steatohepatitis
- Type 1 diabetes
- Polycystic ovarian syndrome
- Major depression

Semaglutide is currently in Phase III development for:[19]
- Polycystic ovarian syndrome
- Non-alcoholic fatty liver disease
- Adolescent obesity

PATIENT GROUP

DISEASE BACKGROUND

Body Mass Index (BMI) is used as a predictor of a healthy weight based on your height and weight, but other factors such as age and ethnic origin can influence whether you are more likely to develop health conditions as a result of a high BMI. A BMI cannot measure body fat percentage and only determines how much weight a person is carrying based on their current height and weight measurements.[20,21]

People who are overweight are those that measure at a BMI of between 25 and 29.9kg/m^2, whilst the range for obesity is between 30 and 39.9kg/m^2 (with morbid obesity exceeding 40kg/m^2). BMI is a starting point for estimating if a patient is more likely to be at an unhealthy weight, whether higher or lower than the BMI range 18.5 and 24.9, however further measures are used to provide a more accurate assessment such as waist size.[21]

There are a number of factors that can lead to a person becoming overweight, including excess calories, poor nutrition, sedentary lifestyle, genetic conditions such as Prader-Willi syndrome and medical conditions such as Cushing's and hypothyroidism.[22]

Being overweight or obese can lead to increased risk of developing comorbidities such as:[23,24]
- Cardiovascular disease such as stroke and heart disease
- Type 2 diabetes (T2D)
- Musculoskeletal disorders
- Cancers such as breast and bowel
- Depression

Common symptoms of being overweight include breathlessness, increased sweating, tiredness, joint and back pain, and difficulty completing physical activity.[24]

Most people across age, sex and ethnicity have the potential of becoming overweight depending on genetic and environmental factors, but this condition can be treated through

making lifestyle changes, through exercise and diet, to reduce overall weight and maintain health.[23,24]

CLINICAL NEED AND BURDEN OF DISEASE

Obesity affects approximately one in four adults in the UK, with the majority of adults in England being overweight or obese (67% of men and 60% women).[24,25] In 2018-19 over one million adults in England who were admitted to hospital had the diagnosis of obesity (ICD-10 E66) and 11,117 of admissions were directly attributed to obesity.[25,26] During 2018-19 nearly 119,000 bed days were for patients with obesity.[26]

Being overweight can lead to multiple comorbidities, for example in 2016-17 nine out of ten people with type 2 diabetes were overweight or obese.[2]

Depending on severity it is estimated that obesity reduces life expectancy by an average of 3 to 10 years.[24]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

NHS advises the best way to address being overweight is through a healthy, reduced-calorie diet and regular exercise. GPs can recommend weight-loss groups or exercise on prescription in addition. If physical, dietary and behavioural interventions are unsuccessful then pharmacological interventions may be considered. In some circumstances weight loss surgery may be recommended.[24,27,28]

CURRENT TREATMENT OPTIONS

Being overweight can be treated in a variety of ways, including the following examples:[27,28]

- **Lifestyle interventions**
  - Healthier, reduced-calorie diet
  - Moderate, regular physical activity
  - Weight-loss advice
- **Pharmacological interventions**
  - Orlistat
  - Naltrexone–bupropion
  - Liraglutide[29]
- **Surgery (in cases with severe to morbid obesity)**
  - Bariatric surgery
  - Single-anastomosis duodeno-ileal bypass with sleeve gastrectomy
  - Laparoscopic gastric plication

PLACE OF TECHNOLOGY

Semaglutide would be an adjunct to a reduced-calorie diet and increased physical activity for weight management in adults with an initial BMI of 30 kg/m^2 or greater or 27 kg/m^2 in the presence of at least one weight-related comorbidity. Semaglutide can be used alongside a calorie-reduced diet, exercise regime or weight-related counselling.[4-11]

CLINICAL TRIAL INFORMATION

Trial	**STEP 7; NCT04251156; Effect and Safety of Semaglutide 2.4 mg Once-weekly on Weight Management in Subjects With Overweight or Obesity** **Phase III – Not yet recruiting** **Location(s):** Brazil and China **Primary completion date:** Aug 2022
Trial design	Randomised, quadruple-blinded parallel assignment.
Population	N= 375 (planned); adults aged 18 years and over; body mass index (BMI) equal to or above 30 kg/m^2, or equal to or above 27 kg/m^2 with the presence of at least one weight-related comorbidity.
Intervention(s)	• Once-weekly subcutaneous injection of semaglutide through fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week[b]), until the target dose (2.4 mg) is reached and maintained, along with diet and physical activity counselling for 44 weeks
Comparator(s)	Matched placebo.
Outcome(s)	• Change in body weight [Time frame: from baseline at week 0 to week 44] • Subjects who achieve body weight reduction equal to or above 5% (yes/no) [Time frame: from baseline at week 0 to week 44] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**STEP 6; NCT03811574; Effect and Safety of Semaglutide Once-weekly in East Asian Subjects With Overweight or Obesity** **Phase III – Active, not recruiting** **Location(s):** Japan and South Korea **Primary completion date:** Oct 2020
Trial design	Randomised, quadruple-blinded parallel assignment.
Population	N= 401; adults aged 18 years and over; BMI more than or equal to 27.0 kg/m^2 with more than or equal to 2 weight-related comorbidities (treated or untreated) or BMI more

[b] Information provided by Novo Nordisk

	than or equal to 35.0 kg/m^2 with more than or equal to 1 weight-related comorbidity (treated or untreated) according to the JASSO guideline.
Intervention(s)	• Participants will receive semaglutide injections once-weekly for 68 weeks. Participants will be initiated at a once-weekly dose of 0.25 mg and follow a fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), until the target dose (2.4 mg) is reached after 16 weeks. Participants will continue semaglutide 2.4 mg until week 68 • Participants will receive semaglutide injections once-weekly for 68 weeks. Participants will be initiated at a once-weekly dose of 0.25 mg and follow a fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5, 1.0 and 1.7 mg/week), until the target dose (1.7 mg) is reached after 12 weeks. Participants will continue semaglutide 1.7 mg until week 68
Comparator(s)	Matched placebo
Outcome(s)	• Change in body weight (percentage) [Time frame: week 0, week 68] • Participants with more than or equal to 5% body weight reduction from baseline [Time frame: week 68] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**STEP 5; NCT03693430; 2017-003726-32; Two-year Effect and Safety of Semaglutide 2.4 mg Once-weekly in Subjects With Overweight or Obesity** **Phase III – Active, not recruiting** **Location(s):** EU (not including UK), USA and Canada **Primary completion date:** Jan 2021
Trial design	Randomised, quadruple-blinded parallel assignment.
Population	N= 304; adults aged 18 years and over; body mass index (BMI) more than or equal to 30 kg/m^2 or more than or equal to 27 kg/m^2 with the presence of at least one weight-related comorbidity.
Intervention(s)	• Once weekly subcutaneous injection of semaglutide in escalating doses (0.25 mg/week, 0.5 mg/week, 1.0 mg/week, 1.7 mg/week, 2.4 mg/week). The dose will be escalated to next level every 4 weeks, until final dose of 2.4mg over 104-week treatment period in addition to reduced-calorie diet and increased physical activity
Comparator(s)	Matched placebo
Outcome(s)	• Change in body weight [Time frame: week 0, week 104] • Subjects who achieve (yes/no): body weight reduction more than or equal to 5% [Time frame: week 0, week 104]. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**STEP 4; NCT03548987; 2017-003473-34; Effect and Safety of Semaglutide 2.4 mg Once-weekly in Subjects With Overweight or Obesity Who Have Reached Target Dose During run-in Period** **Phase III – Completed** **Location(s):** EU (not including UK), USA and other countries **Study completion date:** Mar 2020
Trial design	Randomised, quadruple-blinded parallel assignment.
Population	N= 902; adults aged 18 years and over; body mass index greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 with the presence of at least one comorbidity (treated or untreated); history of at least one self-reported unsuccessful dietary effort to lose body weight.
Intervention(s)	• Run-in period: Participants will receive once-weekly subcutaneous injection of semaglutide at an escalating dose (0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2.4 mg) for 20 weeks (week 0 to week 20). The dose will be escalated to the next level every 4 weeks • Maintenance period: Participants will be randomised to receive once-weekly subcutaneous semaglutide injection for 48 weeks (from week 20 to week 68) This is in addition to reduced-calorie diet and increased physical activity during the trial period.
Comparator(s)	Matched placebo
Outcome(s)	Change from randomisation to week 68 in body weight (%) [Time frame: randomization (week 20), week 68]. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**STEP 3; NCT03611582; Effect and Safety of Semaglutide 2.4 mg Once-weekly as Adjunct to Intensive Behavioural Therapy in Subjects With Overweight or Obesity** **Phase III – Completed** **Location(s):** USA **Study completion date:** Apr 2020
Trial design	Randomised, quadruple-blinded parallel assignment.
Population	N= 611; adults aged 18 and over; body mass index more than or equal to 30 kg/m^2 or more than or equal to 27 kg/m^2 with the presence of at least one weight-related comorbidity; history of at least one self-reported unsuccessful dietary effort to lose body weight.
Intervention(s)	• Once weekly subcutaneous injection of semaglutide at escalating doses (0.25 mg/week, 0.5 mg/week, 1.0 mg/week, 1.7 mg/week, 2.4 mg/week). The dose will be escalated to next level every 4 weeks, until final dose of 2.4mg over 68-week treatment period along with intensive behavioural therapy.
Comparator(s)	Matched placebo

Outcome(s)	• Change in body weight [Time frame: week 0, week 68]. • Subjects who achieve (yes/no) body weight reduction more than or equal to 5% [Time frame: week 0, week 68]. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**STEP 2; NCT03552757; 2017-003414-10; Effect and Safety of Semaglutide 2.4 mg Once-weekly in Subjects With Overweight or Obesity and Type 2 Diabetes** **Phase III – Completed** **Location(s):** EU (including UK), USA, Canada and other countries **Study completion date:** May 2020
Trial design	Randomised, quadruple-blinded parallel assignment.
Population	N= 1210; adults aged 18 and over; Body Mass Index (BMI) greater than or equal to 27 kg/m^2; history of at least one self-reported unsuccessful dietary effort to lose body weight; diagnosed with type 2 diabetes (haemoglobin A1c 7-10% (53-86 mmol/mol) (both inclusive)) 180 days or longer prior to the day of screening.
Intervention(s)	• Once-weekly subcutaneous injection of semaglutide at escalating doses (0.25 mg/week, 0.5 mg/week, 1.0 mg mg/week). The dose will be escalated to next level every 4 weeks, until final dose of 1.0mg over 68-week treatment period • Once-weekly subcutaneous injection of semaglutide at escalating doses (0.25 mg/week, 0.5 mg/week, 1.0 mg mg/week, 1.7 mg/week and 2.4 mg/week). The dose will be escalated to next level every 4 weeks, until final dose of 2.4mg over 68-week treatment period This is in addition to reduced-calorie diet and increased physical activity.
Comparator(s)	Matched placebo
Outcome(s)	• Change in body weight [Time frame: week 0, week 68]. • Subjects who achieve (yes/no) body weight reduction greater than or equal to 5% [Time frame: week 0, week 68]. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**STEP 1; NCT03548935; 2017-003436-36; Effect and Safety of Semaglutide 2.4 mg Once-weekly in Subjects With Overweight or Obesity** **Phase III – Completed** **Location(s):** EU (including UK), USA, Canada and other countries **Study completion date:** Apr 2020
Trial design	Randomised, quadruple-blinded parallel assignment.

Population	N= 1964; adults aged 18 years and over; BMI greater than or equal to 30.0 kg/sqm or greater than or equal to 27.0 kg/m^2 with the presence of at least weight-related comorbidity (treated or untreated); history of at least one self-reported unsuccessful dietary effort to lose body weight.
Intervention(s)	• Once-weekly subcutaneous injection of semaglutide. Dose escalation of semaglutide will take place as follows: 0.25 mg from week 1 to 4, 0.5 mg from week 5 to 8, 1.0 mg from week 9 to 12, 1.7 mg from week 13 to 16 and 2.4 mg from week 17 to week 68 along with diet and physical activity counselling.
Comparator(s)	Matched placebo
Outcome(s)	• Change in body weight [Time frame: week 0, week 68]. • Subjects who achieve 5 or more percent body weight reduction (yes/no) [Time frame: week 68]. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The NHS indicative price for semaglutide injections are as follows:[30]

- Semaglutide 0.25mg/0.19ml; 1 pre-filled 1.5ml disposable injection (prescription only medicine) cost £73.25
- Semaglutide 0.5mg/0.37ml; 1 pre-filled 1.5ml disposable injection (prescription only medicine) cost £73.25
- Semaglutide 1mg/0.74ml; 1 pre-filled 3ml disposable injection (prescription only medicine) cost £73.25

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Liraglutide for managing overweight and obesity (TA10388). Expected publication date: November 2020
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- NICE interventional procedures guidance. Laparoscopic gastric plication for the treatment of severe obesity (IPG432). November 2012

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. NHS Standard Contract for Severe and Complex Obesity – All Ages (A05/S/a). October 2013[31]

OTHER GUIDANCE

- UK Department of Health and Social Care. Tackling obesity: empowering adults and children to live healthier lives. July 2020[32]
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ADDITIONAL INFORMATION

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