Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2497

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

Novo Nordisk

09 December 2022 *(Issued 08 September 2023)*

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

semaglutide (Wegovy®) is accepted for restricted use within NHSScotland.

Indication under review: 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

- ≥30kg/m^2 (obesity), or
- ≥27kg/m^2 to <30kg/m^2 (overweight) in the presence of at least one weight-related comorbidity.

SMC restriction: BMI of ≥30kg/m^2* in the presence of at least one weight-related comorbidity. Patients should be treated in a specialist weight management service.
**a lower BMI cut-off may be more appropriate for members of minority ethnic groups known to be at equivalent risk of the consequences of obesity at a lower BMI than the white population.*

In a phase III study, semaglutide, as an adjunct to diet and exercise, was associated with significant reduction in body weight compared with placebo in patients with a BMI ≥30kg/m² or ≥ 27kg/m² if they had at least one weight-related comorbidity.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chair,
Scottish Medicines Consortium

Indication

Semaglutide 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

- ≥30kg/m^2 (obesity), or
- ≥27kg/m^2 to <30kg/m^2 (overweight) in the presence of at least one weight-related comorbidity.[1-5]

Dosing Information

The maintenance dose of semaglutide is 2.4mg once-weekly, administered subcutaneously in the abdomen, in the thigh or in the upper arm at any time of the day.

This dose is reached by starting with a dose of 0.25mg, and to reduce the likelihood of gastrointestinal symptoms, the dose should be escalated over a 16-week period to the maintenance dose (based on the dose escalation schedule detailed in the Summary of product characteristics [SPC]). In case of significant gastrointestinal symptoms, delaying dose escalation or lowering to the previous dose until symptoms have improved should be considered.

If patients have been unable to lose at least 5% of their initial body weight after 6 months on treatment, a decision is required on whether to continue treatment, taking into account the benefit/risk profile in the individual patient.[1-5]

Product availability date

04 September 2023

Summary of evidence on comparative efficacy

Semaglutide is an agonist of the glucagon-like peptide-1 (GLP-1) receptor, which is present in several areas of the brain involved in appetite regulation. Semaglutide has direct and indirect effects on areas in the brain involved in the homeostatic and hedonic regulation of food intake. Additionally, 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; this 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.[1-5] The submitting company has requested that SMC considers semaglutide for use in patients with a BMI of ≥30kg/m^2 in the presence of at least one weight-related comorbidity. Patients should be treated in a specialist weight management service.

The key evidence supporting the efficacy and safety of semaglutide 2.4mg comes from an international, randomised, double-blind, parallel group, phase III study, STEP 1, which evaluated the efficacy and safety of semaglutide 2.4mg compared with placebo in adults with obesity (BMI

≥30kg/m^2), or overweight (BMI ≥27kg/m^2 to <30kg/m^2) with at least one weight-related comorbidity (hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease), and without diabetes or glycated haemoglobin (HbA_{1c}) ≥6.5% (48mmol/mol). Patients were eligible if they had a history of at least one self-reported unsuccessful dietary effort to lose body weight.[6, 7]

Patients were randomised in a 2:1 ratio to receive semaglutide at a dose of 2.4mg (dose reached following dose escalation initiated at a dose of 0.25mg) administered subcutaneously once a week for 68 weeks (n=1,306) or matching placebo (n=655); these were both in addition to lifestyle interventions including a reduced-calorie diet (500 kcal/day deficit) and increased physical activity (150 minutes per week).[6, 7]

The co-primary outcomes were change from baseline to week 68 in body weight (%) and the proportion of patients who achieve ≥5% body weight reduction from baseline to week 68.[6, 7] See Table 1 for more results.[6, 7]

Table 1. Co-primary outcomes and hierarchically tested secondary outcomes of STEP 1 (FAS population, outcomes presented in the hierarchical testing order used, primary treatment policy estimand)[6, 7]

	Semaglutide 2.4mg (n=1,306)	**Placebo (n=655)**	**Difference between semaglutide and placebo (95% CI)**
Baseline weight (kg)	105.4	105.2	-
Co-primary outcomes at week 68			
Change in body weight (%)	-15%	-2.4%	-12% (-13 to -12) p<0.001
Proportion of patients achieving weight loss ≥5%[a]	86%	32%	OR= 11.2 (8.9 to 14) p<0.001
Hierarchically tested secondary outcomes at week 68			
Proportion of patients achieving weight loss ≥10%[a]	69%	12%	OR= 14.7 (11 to 19), p<0.001
Proportion of patients achieving weight loss ≥15%[a]	51%	4.9%	OR= 19.3 (13 to 29), p<0.001
Change from baseline in waist circumference (cm)	-13.5	-4.1	-9.4 (-10 to -8.5), p<0.001
Change from baseline in systolic blood pressure (mmHg)	-6.2	-1.1	-5.1 (-6.3 to -3.9), p<0.001
Change from baseline in Physical functioning score (SF-36)	2.2	0.4	1.8 (1.2 to 2.4), p<0.001
Change from baseline Physical function domain (5-items) score (IWQoL-Lite for CT)	14.7	5.3	9.4 (7.5 to 11), p<0.001

CI = confidence interval; mg = milligram, kg = kilogram, N = number of patients, cm =centimetre, mmHg = millimetre of mercury, FAS = full analysis set; IWQOL-Lite-CT = Impact of Weight on Quality of Life–Lite Clinical Trials Version; OR = odds ratio; SF-36 = 36-item Short Form Health Survey.
[a]Denominators for the percentages of participants observed to have body-weight reduction of ≥5%, ≥10%, and ≥15%, at week 68 are the numbers of participants for whom data were available at the week 68 visit (1212 participants in the semaglutide group and 577 participants in the placebo group).

The submitting company conducted a post-hoc subgroup analysis of STEP 1 for patients with a BMI ≥30kg/m^2 in the presence of at least one weight-related comorbidity, which accounted for 75% (1,470/1,961) of the overall study population. Results were consistent with the primary analysis. [8]

Health Related Quality of Life (HRQoL) was assessed using the Short Form Health Survey version 2 (SF-36) Physical Functioning subscale and Impact of Weight on Quality of Life Clinical Trials (IWQOL-Lite-CT) Physical Function composite. Results for these two hierarchically tested secondary outcomes are detailed in Table 3 above. Although results show statistically significant benefits in physical functioning with both the SF-36 and IWQOL-Lite-CT; treatment differences appear small.[6]

In a subset of patients who had completed the 68-week treatment period of STEP 1, an off-treatment extension phase was conducted for a further year (until week 120). Exploratory extension analyses included 327 patients. In these, from week 0 to 68 of STEP 1 (randomised treatment phase), mean weight loss was 17% with semaglutide and 2.0% with placebo. Data from the final visit (week 120) were available from site visits for 290 patients (semaglutide group: n=197; placebo group: n=93). By week 120, a year after treatment withdrawal, patients who had previously been treated with semaglutide 2.4mg and placebo regained 12 (about two thirds) and 1.9 percentage points of lost weight, respectively, resulting in overall net losses from week 0 to week 120 of only 5.6% and 0.1%, respectively.[9]

Supportive evidence comes from:

- STEP 2 was an international, randomised, double-blind, placebo-controlled, phase III study, which included adults who reported at least one unsuccessful dietary effort to lose weight, with a BMI ≥27kg/m^2 and HbA_{1c} 7 to 10% (53 to 86mmol/mol) who had been diagnosed with type 2 diabetes (at least 180 days prior to screening). Patients were managed with diet and exercise alone, or treated with a stable dose of up to three oral glucose-lowering agents (metformin, sulfonylureas, sodium-glucose co-transporter-2 [SGLT2] inhibitors, or thiazolidinediones) for at least 90 days before screening; and were not treated with insulin. Patients were randomised equally and stratified by background diabetes treatment and $HbA_{1c,}$ to subcutaneous injection of semaglutide 2.4mg (n=404), or semaglutide 1.0mg (n=403), or matching placebo (n=403), once a week for 68 weeks, plus lifestyle interventions. The estimated change in mean bodyweight from baseline to week 68 was −9.6% versus -3.4% with semaglutide 2.4mg and placebo, respectively; this estimated treatment difference of -6.2% between semaglutide 2.4mg and placebo was statistically significant (95% CI −7.3 to −5.2; p<0.001). Mean weight change at week 68 for semaglutide 1.0mg was −7.0%. At week 68, more patients on semaglutide 2.4mg than on placebo achieved weight reductions of at least 5% (69% [267/388] versus 28% [107/376]; odds ratio = 4.9, 95% CI 3.6 to 6.6; p<0.001). A reduction of at least 5% of weight at week 68 with semaglutide 1.0mg was achieved by 57% of patients.[10]
- STEP 5 was an international, randomised, double-blind, placebo-controlled Phase III, study in obese, or overweight (BMI ≥27kg/m^2) adults with at least one weight-related comorbidity, and without diabetes or HbA_{1c} ≥6.5%, and a history of at least one self-reported unsuccessful dietary effort to lose body weight. Patients were randomised equally to once weekly

subcutaneous injection of semaglutide 2.4mg (n=152), or placebo (n=152), plus lifestyle interventions for 104 weeks. Semaglutide significantly reduced body weight from baseline to week 104 compared to placebo (-15% versus -2.6%, estimated treatment difference: -13% points [95% CI: -15 to -9.8]; p<0.001). Patients were more likely to lose at least 5% of their body weight with semaglutide versus placebo at week 104 (77% versus 34%; p<0.001).[11-13]

- STEP 8 was a randomised, open-label, active- and placebo-controlled, phase III study in adults with one or more self-reported unsuccessful dietary weight loss efforts and with a BMI of ≥30kg/m^2), or a BMI of ≥27kg/m^2 to <30kg/m^2 with at least one weight-related comorbidity, without diabetes or HbA_{1c} ≥6.5%. Patients were randomised in a 3:1:3:1 ratio to receive once-weekly subcutaneous semaglutide 2.4mg (n = 126), or matching placebo, or once-daily subcutaneous liraglutide, 3.0mg (with 4-week dose escalation; n = 127), or matching placebo, plus diet and physical activity. Placebo groups were pooled (n = 85). The mean weight change from baseline was –16% with semaglutide versus –6.4% with liraglutide (difference, –9.4 percentage points [95% CI, –12 to –6.8]; P < 0.001); weight change with pooled placebo was –1.9%.[14]

Summary of evidence on comparative safety

Overall, the nature, frequency and severity of adverse events was quite similar to existing data with semaglutide and others in the class.[6]

In the STEP 1 study, any treatment-emergent adverse event (AE) was reported by 90% (1,171/1,306) of patients in the semaglutide group and 86% (566/655) in the placebo group. In the semaglutide and placebo groups respectively, patients with a reported serious AE were 9.8% versus 6.4%, and patients discontinuing therapy due to AEs was 7.0% versus 3.1%.[7]

The most frequently reported treatment-emergent AEs of any grade with an incidence >10% were: nausea (44% in the semaglutide group versus 17% in the placebo group), diarrhoea (32% versus 16%), vomiting (25% versus 6.6%), constipation (23% versus 9.5%), nasopharyngitis (22% versus 20%), headache (15% versus 12%), dyspepsia (10% versus 3.5%), abdominal pain (10% versus 5.5%), upper respiratory tract infection (8.7% versus 12%).[7]

Summary of clinical effectiveness issues

Obesity is one of the most significant public health challenges globally, and Scotland has one of the highest levels of obesity worldwide. In 2019, 29% of adults in Scotland were obese and 66% were overweight or obese. Obesity has many serious health consequences, including hypertension, hyperglycaemia and various cancers. Obesity and overweight are also risk factors for cardiovascular disease and type 2 diabetes mellitus. They adversely affect physical and mental health and reduce quality of life. As the causes of obesity are multifactorial, treatment can be challenging. Options include dietary, behavioural and exercise counselling (often given as first-line), surgical interventions for some patients (although there are associative risks), and

pharmacotherapy used as an adjunct to lifestyle interventions. Two medicines currently available for weight management are orlistat, which has moderate efficacy but is associated with several side effects that limit tolerability and use, and the GLP-1 receptor agonist liraglutide.[6, 15] In May 2022, SMC issued advice (SMC2455) that liraglutide is accepted for restricted use in patients with a BMI ≥35kg/m²* (obesity class II and above) with non-diabetic hyperglycaemia (prediabetes) at high risk of type 2 diabetes, and high risk of cardiovascular disease. Patients should be treated in a specialist weight management service (*a lower BMI cut-off may be more appropriate for members of minority ethnic groups known to be at equivalent risk of the consequences of obesity at a lower BMI than the white population). The timing of SMC advice for liraglutide does not require it to be considered as a relevant comparator within this submission. Clinical experts consulted by SMC considered that semaglutide fills an unmet need in this therapeutic area due to the lack of effective, tolerable treatments.

In STEP 1, semaglutide 2.4mg, as add-on to lifestyle interventions, resulted in a body weight loss of -15% and the estimated treatment difference versus placebo was -12%, which was statistically significant and considered clinically relevant. This was supported by a statistically significant and clinically relevant increase in the proportion of patients who achieved at least 5% body weight loss and by confirmatory secondary outcomes (including the proportion of patients who achieved at least 10 or 15% body weight loss). Some glycaemic control effects were also seen with semaglutide 2.4mg, though they were considered relevant only in patients with prediabetes who improved to normoglycaemia. Although some quality of life improvements were seen with semaglutide 2.4mg, the clinical relevance of these was not considered demonstrated. Regulators also concluded that cardiovascular benefits had not yet been shown with semaglutide 2.4mg. [6]

The submitting company requested that SMC considers semaglutide for use in patients with a BMI of ≥30kg/m^2 in the presence of at least one weight-related comorbidity. STEP 1 was wider than this proposed positioning and subgroup data relevant to the proposed positioning (relevant subgroup accounted for 75% of the overall study population) were only analysed post-hoc; thus, results should be interpreted with caution. A lower BMI cut-off for treatment with semaglutide may be more appropriate for members of minority ethnic groups known to be at equivalent risk of the consequences of obesity at a lower BMI than the white population.

Subgroup analyses showed some inconsistencies based on sex and baseline body weight in the efficacy results. Female patients lost on average more weight compared with male subjects (estimated treatment difference versus placebo in female was -14%, while in male it was -8.0%) and it was considered that a difference in baseline weight between male and female patients (based on additional data) does not explain the treatment difference. Nonetheless, in both genders the observed weight loss was considered clinically relevant. Of note, the proportion of female patients (74%) was considerably larger than males, which regulators noted could have driven the mean overall results. In addition, a reduced treatment effect based on baseline body weight was present in patients with a higher body weight, mainly in those weighting more than 115kg, in whom the estimated treatment difference was only -7.9%. Regulators noted that it could therefore be anticipated that there will be an overall lower weight loss in patients with an initial

high body weight versus low body weight, who initiates treatment with semaglutide 2.4mg. However, the effect was still considered significant and clinically relevant. [6]

STEP 1 excluded patients with type 2 diabetes. Some patients with type 2 diabetes and overweight/obesity may be treated in practice with semaglutide 2.4mg and relevant data for this population come from STEP 2 study. The weight loss effects seen in these patients were lower than those seen in patients without type 2 diabetes (estimated treatment difference for semaglutide 2.4mg versus placebo was only -6.2%) but still considered clinically relevant. Of note, patients receiving insulin were excluded from STEP 2, thus there are no data for semaglutide 2.4mg in patients with type 2 diabetes receiving insulin, though regulators considered it plausible that these patients might also benefit from semaglutide 2.4mg. In addition, in STEP 1, the vast majority of patients were <65 years old and there are limited data in older patients.[6]

Overall, there is some uncertainty about the generalisability of STEP 1 study results to the population that would be eligible for treatment in practice (which may include a higher proportion of patients >115kg, a smaller proportion of female patients than in STEP 1, may include patients with type 2 diabetes, and have a different BMI distribution from that of the population included in STEP 1).

Maintenance of treatment for up to 2 years was shown in STEP 5; however, after a longer treatment period, it remains uncertain if weight gain may occur. In addition, continuous treatment with semaglutide 2.4mg is needed to maintain weight loss benefits; evidence (including from the extension phase of STEP 1) demonstrated that after treatment discontinuation, although no risk of gaining weight compared to treatment initiation was identified, weight is regained (only about 5% weight loss was still present a year after treatment discontinuation).

Clinical experts consulted by SMC considered that semaglutide is a therapeutic advancement in the treatment of obesity. Weekly subcutaneous injections may impact patients who at present may receive no pharmacotherapy for their weight management. Semaglutide would be delivered as part of specialist weight management services and access to such services may vary throughout Scotland.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing semaglutide with diet and exercise to diet and exercise alone in adult patients with a BMI of ≥30 kg/m^2 in the presence of at least one weight-related comorbidity. SMC clinical experts agree this is a suitable population in the Scottish context.

The model was a cohort state transition model with a lifetime (40 years) horizon, adapted from a previous model employed in assessment of liraglutide (e.g. SMC2378), with 11 health states reflecting combinations of non-diabetic hyperglycaemia, type 2 diabetes, obstructive sleep apnoea, acute coronary syndrome (ACS) and stroke, and osteoarthritis. The cohort enters the

model in either normal glucose tolerance or non-diabetic hyperglycaemia health states. Following initiation of semaglutide, at six months a stopping rule determines whether patients have adequate progress in terms of weight loss to continue beyond this point on treatment.

Efficacy data from the STEP 1 full analysis data set are used for the pre-response assessment period, followed by early responder efficacy for patients who continue treatment with semaglutide. STEP 1 efficacy from week 68 is assumed to continue through year two based on STEP 5 study data that showed responders experience small additional weight loss between year one and year two. Patients who discontinue pharmacotherapy treatment continue to receive diet and exercise support. Tunnel states are employed to model a 'catch-up' post pharmacotherapy discontinuation (or completion of semaglutide treatment course) to control arm status. In the base case this a linear three-year process. Risk equations (from secondary sources) are employed to model the probability of events conditional on body mass index and other risk factors (SBP, total and HDL cholesterol), which are modified as a result of treatment. Changes at one year were (for semaglutide and diet and exercise alone, respectively): weight -18.47% versus -2.44%; SBP -7.63mmHg versus -1.14mmHg; TC -9.20mg/dl versus +0.18mg/dl, HDL-C 2.97mg/dl versus 1.07mg/dl. A number of reasonable assumptions were made in order to constrain the number of health states and minimise complexity. Bariatric surgery at 1.15% per annum was modelled up to age 57 for minimum BMI of 35kg/m^2.

A general mortality rate was calculated excluding cause-specific mortality relating to comorbidities. Hazard ratio adjustments for comorbidities (ACS and stroke) were applied to these, along with case fatality estimates for acute events. Mortality was further adjusted according to BMI using a function estimated by the submitting company based on data reported in Bhaskaran et al (2018).[16] Relative to BMI of 25kg/m^2 the HR was approximately 1.2 for BMI 30 rising to 1.5 and higher at BMI ≥35kg/m^2.

Baseline utility is also estimated as a function of BMI using a polynomial model with utility declining beyond approximately 25kg/m^2 based on UK observational data reported by Søltoft et al (2009).[17] Age adjustments were also modelled based on this data. A scenario analysis employed utilities derived from SF-36 data reported at baseline by patients enrolled in STEP 1 and mapped to EQ-5D using a published algorithm. Acute decrements were applied to events based principally on Sullivan et al's (2011)[18] catalogue of utility values in the (three month) cycle in which events occur: ACS -0.063, stroke-0.117, knee replacement -0.194 and bariatric surgery -0.184. Longer term decrements are also applied of approximately 0.037 (varying slightly according to comorbidity). Minor decrements were applied for adverse events of non-severe hypoglycaemia and severe gastrointestinal events.

Health event and state costs were sourced mainly from NHS schedule of costs (2019/20). Separate estimates were applied for cardiovascular states in the first year following an event and in the post-first year period. Treatment costs included the acquisition cost of semaglutide and the cost of diet and exercise. The model accounts for lower semaglutide usage during titration before accruing at the (commercial in confidence) list price for semaglutide 2.4mg per week until the end of year two (the maximum treatment period). Scenario analysis considered treatment through

year three. Diet and exercise costs were represented as health care visits with GP (quarterly) and practice nurse (other months), plus an estimated annual blood pressure medication cost. As noted above semaglutide would need to be delivered as part of specialist weight management services.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

Deterministic sensitivity analyses were undertaken for individual parameters with the most influential presented by the company; with the exception of discounting, none of these analyses indicated any sensitivity in the ICER. Scenario analyses were also undertaken. Table 2 below presents the base case result and selected scenario analyses.

Table 2: Base case and selected scenario analyses results, with PAS

		ICER (£)
0	**Base case**	**13,512**
1	Catch up: Linear rate with 2 years	16,805
2	Time horizon 20 years	14,754
3	Incidence of first CV event in normal glucose tolerance: Framingham Heart study	12,506
4	Incidence of type 2 diabetes: Framingham Offspring	16,235
5	Incidence of first CV event in type two diabetes: QRisk3	12,685
6	Incidence of recurrent CV event in type 2 diabetes: Framingham Recurring Coronary Heart Disease	13,768
7	Data from STEP 2 (diabetes trial)	19,045
8	Data from STEP 2 analysed in Core Diabetes Model	15,874
9	Semaglutide non-responder effectiveness as placebo non-responders	14,355
10	Maximum treatment duration 3 years + STEP 5 data for years 2+	12,264
11	Baseline BMI 30kg/m^2	30,732

There was some impact on the ICER of predicting type 2 diabetes incidence based on the Framingham Offspring study and substituting the STEP 2 data (diabetes) for STEP 1. Of note, however, was the impact when a speedier reversion to a natural history BMI or lower baseline BMI were applied.

The following potential weaknesses in the economic case are noted:

- The base case analysis is for a population with mean baseline BMI of 38kg/m^2. However, this is based on the mean of patients in the relevant sub-population of STEP 1 the mean in the target population in Scotland may differ. The submitting company has highlighted that the ICER for a baseline BMI of 30kg/m^2 is substantially higher than that generated in the base case, and the ICER in practice may therefore be sensitive to alternative distributions of BMI in treated patients in Scotland.
- Non-responders to semaglutide are assigned a prognosis based on effectiveness of diet and exercise. This may fail to account for a lesser degree of effectiveness of diet and exercise in this group compared to the overall diet and exercise population in STEP 1. While this remains a

limitation of the modelling, additional sensitivity analysis was provided where non-responders experience no change in efficacy and this had minimal impact on the ICER.

- SMC clinical experts noted that tier 3 or 4 services to support weight maintenance may not be available to support the non-pharmacological weight maintenance interventions that underpin both arms in the model. There may therefore be substantial barriers in Scotland to monitoring patients in the manner reflected in the model, with substantial implications for service provision, particularly with a BMI threshold of 30kg/m^2, rather than at higher levels.
- Long term mortality estimates adjust for comorbidities and BMI. The submitting company stated this was to ensure mortality would not be underestimated, but conceded that some double counting of mortality implications was possible. However, additional scenario analyses provided by the submitting company indicated the cost-effectiveness analyses were not sensitive to removal of individual components of the elevated mortality owing to BMI and comorbidities.
- The cost-effectiveness analysis is based on efficacy according to the secondary estimand in the clinical study which reflects the efficacy of patients who stay on the randomised treatment for the entire planned duration of the trial and without initiating other anti-obesity therapies (i.e. a per protocol analysis). The primary assessment was regardless of premature discontinuation of trial product or initiation of other anti-obesity therapies (weight management drugs or bariatric surgery) – an intention to treat analysis, which is less prone to bias. Additional scenario analysis suggested this would increase the ICER by 32%.

Despite these issues, the economic case has been demonstrated.

Summary of patient and carer involvement

No patient group submission was received.

Additional information: guidelines and protocols

The National Institute of Health and Clinical Excellence (NICE) Clinical guideline number 189 (CG189): Obesity: identification, assessment and management, was published in November 2014. This guideline recommends that, pharmacological treatment be considered only after dietary, exercise and behavioural approaches have been started and evaluated. In addition, drug treatment should only be considered in people who have not reached their target weight loss or have reached a plateau on dietary, activity and behavioural changes. Bariatric surgery is a treatment option for people with obesity if specified criteria are fulfilled and all appropriate non-surgical measures have been tried but the person has not achieved or maintained adequate, clinically beneficial weight loss.[19]

The Scottish Intercollegiate Guidelines Network (SIGN) Management of Obesity (SIGN 115) guideline was published in February 2010 but it has been withdrawn in February 2020. The guideline detailed recommendations on improving diet and physical activity, and also had advice

for bariatric surgery. Regarding orlistat, the guideline made the following recommendation: "Orlistat should be considered as an adjunct to lifestyle interventions in the management of weight loss. Patients with BMI ≥28 kg/m^2 (with comorbidities) or BMI ≥30 kg/m^2 should be considered on an individual case basis following assessment of risk and benefit." Bariatric surgery was described as a treatment option for people with obesity if specified criteria were fulfilled and all appropriate non-surgical measures had been tried but had not resulted in significant and sustained improvement in comorbidities.[20]

Additional information: comparators

Diet and exercise alone.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Semaglutide	**16-week dose expansion:** **Week 1–4: 0.25mg once weekly** **Week 5–8: 0.5mg once weekly** **Week 9–12: 1mg once weekly** **Week 13–16: 1.7mg once weekly** **Maintenance dose: 2.4mg SC once weekly**	**Year 1: 1,926** **Subsequent year: 2,285**

Costs from the company submission.

Additional information: budget impact

The company estimated there would be 4,843 patients eligible for treatment with semaglutide each year. The uptake rate was estimated to be 25% in year 1 (1,211 patients) rising to 90% in year 5 (4,359 patients). While market share is projected to increase with a constant eligible population, treated numbers of patients decline in year 4 and year 5 (1,484 and 642 respectively). This is due to the submitting company assuming that by year four most patients will already have been treated with semaglutide 2.4mg or diet and exercise so that the numbers of patients treated begins to decline.

SMC is unable to publish the budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget.

*Other data were also assessed but remain confidential.**

References

1. Novo Nordisk Limited. Semaglutide (Wegovy) 2.4 mg, FlexTouch solution for injection in pre-filled pen. Summary of Product Characteristics. Electronic Medicines Compendium. www.medicines.org.uk Last updated 24 Jun 2022.
2. Novo Nordisk Limited. Semaglutide (Wegovy) 0.25 mg, FlexTouch solution for injection in pre-filled pen. Summary of Product Characteristics. Electronic Medicines Compendium. www.medicines.org.uk Last updated 24 Jun 2022.
3. Novo Nordisk Limited. Semaglutide (Wegovy) 0.5 mg, FlexTouch solution for injection in pre-filled pen. Summary of Product Characteristics. Electronic Medicines Compendium. www.medicines.org.uk Last updated 24 Jun 2022.
4. Novo Nordisk Limited. Semaglutide (Wegovy) 1 mg, FlexTouch solution for injection in pre-filled pen. Summary of Product Characteristics. Electronic Medicines Compendium. www.medicines.org.uk Last updated 24 Jun 2022.
5. Novo Nordisk Limited. Semaglutide (Wegovy) 1.7 mg, FlexTouch solution for injection in pre-filled pen. Summary of Product Characteristics. Electronic Medicines Compendium. www.medicines.org.uk Last updated 24 Jun 2022.
6. European Medicines Agency (EMA). European Public Assessment Report. Semaglutide (Wegovy. 11/11/2021, EMEA/H/C/005422/0000. www.ema.europa.eu
7. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I*, et al.* Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021;384(11):989.
8. Novo Nordisk. STEP 1 subgroup data – change from baseline. 19 April 2021
9. Wilding, JPH, Batterham, RL, Davies, M, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. Diabetes Obes Metab. 2022; 24(8): 1553- 1564. doi:10.1111/dom.14725.
10. Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L*, et al.* Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet (London, England). 2021;397(10278):971-84. Epub 2021/03/06.
11. Novo Nordisk. Press Release. Wegovy™ demonstrated significant and sustained weight loss in two-year study in adults with obesity. Available at: https://www.novonordisk-us.com/content/nncorp/us/en_us/media/news-archive/news-details.html?id=85378. Date: Nov 05 2021.
12. Kushner RF, Calanna S, Davies M, et al. Semaglutide 2.4 mg for the Treatment of Obesity: Key Elements of the STEP Trials 1 to 5. Obesity (Silver Spring). 2020;28(6):1050-1061. doi:10.1002/oby.22794.
13. ClinicalTrials.gov. Study Results. Two-year Research Study Investigating How Well Semaglutide Works in People Suffering From Overweight or Obesity (STEP 5). NCT03693430. Last Update Posted: March 23, 2022.
14. Rubino DM, Greenway FL, Khalid U, et al. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial. JAMA. 2022;327(2):138–150. doi:10.1001/jama.2021.23619.
15. Scottish Government. Diet and healthy weight: monitoring report 2020. Published 27 October 2020. Available from: https://www.gov.scot/publications/diet-healthy-weight-monitoring-report-2020/pages/3/.
16. Bhaskaran K, dos-Santos-Silva I, Leon DA, et al. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK. Lancet Diabetes Endocrinol. 2018; 6(12):944-53.
17. Søltoft F, Hammer M and Kragh N. The association of body mass index and health-related quality of life in the general population: data from the 2003 Health Survey of England. Qual Life Res. 2009; 18(10):1293-9.

18. Sullivan P, Slejko J, Sculpher M and Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Medical Decision Making. 2011; 31(6):800-4.
19. National Institute for Health and Care Excellence. Obesity: identification, assessment and management (CG189) available at: https://www.nice.org.uk/guidance/cg189/resources/obesity-identification-assessment-and-management-pdf-35109821097925. 2014.
20. Scottish Intercollegiate Guidelines Network (SIGN). Guideline 115: Management of Obesity - A National Clinical Guideline. available at: https://www.sign.ac.uk/assets/sign115.pdf. 2010.

This assessment is based on data submitted by the applicant company up to and including 24 August 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:
No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.