Healthcare Improvement Scotland | SMC Advice on new medicines

www.scottishmedicines.org.uk

SMC2092

# semaglutide 0.25mg, 0.5mg and 1mg solution for injection in pre-filled pen (Ozempic®)

Novo Nordisk Ltd.

9 November 2018 (*Issued 7 December 2018*)

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 (Ozempic®)** is accepted for restricted use within NHSScotland.

**Indication under review:** the treatment of adults with insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise:

- As monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- In addition to other medicinal products for the treatment of diabetes.

**SMC restriction:** In addition to other oral anti-diabetic medicines, or as an add-on to basal insulin, as an alternative glucagon-like peptide-1 receptor agonist option.

In five randomised comparative studies in patients with T2DMand receiving oral anti-diabetic agents and / or basal insulin, semaglutide once weekly was superior to the comparators for change in HbA1c.

SMC cannot recommend the use of semaglutide as monotherapy when metformin is considered inappropriate due to intolerance or contraindications as the company's submission related only to its use in addition to other medicinal products for the treatment of diabetes.

**Chairman**
**Scottish Medicines Consortium**

## Indication

For the treatment of adults with insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise:

- As monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- In addition to other medicinal products for the treatment of diabetes.

## Dosing Information

The starting dose is 0.25mg semaglutide once weekly. After 4 weeks the dose should be increased to 0.5mg once weekly. After at least 4 weeks with a dose of 0.5mg once weekly, the dose can be increased to 1.0mg once weekly to further improve glycaemic control. Semaglutide 0.25mg is not a maintenance dose. Weekly doses higher than 1.0mg are not recommended.

When semaglutide is added to existing therapy of sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia. When initiating treatment with semaglutide in combination with a sulfonylurea or an insulin, blood glucose self-monitoring may become necessary to adjust the dose of the sulfonylurea or the insulin to reduce the risk of hypoglycaemia.

Semaglutide is to be administered once weekly at any time of the day, with or without meals. Semaglutide is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed without dose adjustment.[1]

## Product availability date

2 January 2019

## Summary of evidence on comparative efficacy

Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist which has 94% amino acid sequence homology with human GLP-1,[2] an incretin hormone which stimulates insulin secretion and inhibits glucagon secretion to reduce blood glucose in a glucose dependent manner, delays gastric emptying, and reduces feelings of hunger which can reduce food intake and lead to weight loss.[3] In patients with type 2 diabetes (T2DM), the postprandial rise in endogenous GLP-1 is reduced or absent. GLP-1 receptor agonists can supplement or replace this deficiency.

The submitting company has requested that SMC considers semaglutide when positioned for use in line with the current use of other GLP-1 receptor agonists, in addition to other medicinal products for the treatment of diabetes (i.e. as an add-on therapy to oral anti-diabetic drugs [OADs] or basal insulin).

The Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) 2, 3, 4, and 7 studies compared semaglutide with active comparators as add-on therapy to a background of one or more OADs (ie as dual or triple therapy). The studies had a similar design and have been described together below. The SUSTAIN 5 study compared semaglutide with placebo when added to background basal insulin, and this study has been described separately.

SUSTAIN 2, 3, 4, and 7 were multi-centre, randomised, active-controlled, phase III studies of 30 to 56 weeks duration. SUSTAIN 3, 4 and 7 were open-label studies, while SUSTAIN 2 was a double-blind, double-dummy study. The studies included adults with T2DM (HbA1c 7.0 to 10.5% [53 to 91 mmol/mol]; 7.0% to 10.0% [53 to 86mmol/mol] for the SUSTAIN 4 study), receiving stable doses of OAD with; metformin alone or metformin in combination with a sulfonylurea in insulin-naïve patients in SUSTAIN 4; one or two OADs (metformin and / or thiazolidinediones, and / or sulfonylureas) in SUSTAIN 3; metformin alone in SUSTAIN 7; metformin, pioglitazone or rosiglitazone alone or a combination of either rosiglitazone or pioglitazone in addition to metformin in SUSTAIN 2.[4-7]

Details of the treatment groups in each study are included in table 1. Background treatments were continued throughout the studies.[4, 6] The dose of a sulfonylurea could be reduced if a patient experienced unacceptable hypoglycaemia in SUSTAIN 3.[4] In SUSTAIN 4, patients randomised to insulin glargine commenced treatment on a dose of 10 international units (IU) once daily. The insulin dose was to be titrated weekly to achieve a pre-breakfast self-measured plasma glucose level of 4. 0 to 5. 5mmol/L.[7] In SUSTAIN 7, patients randomised to dulaglutide received doses of 0·75mg or 1·5mg from the beginning of the study without dose escalation.[5] In SUSTAIN 2, 3, 4 and 7, for patients randomised to semaglutide, the dose was doubled every 4 weeks from a starting dose of 0·25mg until the maintenance dose of 0·5mg or 1·0mg was reached. Patients with unacceptable hyperglycaemia (plasma glucose greater than 15mmol/L) despite study medication were offered rescue medication at the discretion of the investigator.[4-7]

The primary outcome in the SUSTAIN studies was the change in HbA1c level from baseline, assessed at week 56 in SUSTAIN 2 and 3, week 30 in SUSTAIN 4 and week 40 in SUSTAIN 7 study. The primary analyses included all randomised patients who had received at least one dose of study treatment and contributed to the evaluation of that treatment. For the evaluation of efficacy outcomes the primary observation period was while patients were 'On-treatment without rescue medication'. [3-7] A mixed model of repeated measures (MMRM) analysis was conducted which assumed that data were missing at random. The results of the primary outcome and confirmatory secondary outcome, change in bodyweight from baseline, are presented in table 1.

SUSTAIN 5 was a multi-centre, double-blind phase IIIa study in adults (Japanese patients were required to be 20 years or older) with T2DM (HbA1c 7.0% to 10.0% [53.0 to 86mmol/mol]), receiving stable treatment with basal insulin (at least 0.25 IU/kg/day and / or 20 IU/day of insulin glargine, insulin detemir, insulin degludec, and / or neutral protamine Hagedorn insulin) alone or in combination with metformin for 90 days prior to screening. Patients were randomised to 30-weeks of treatment with semaglutide 0.5mg SC once weekly, semaglutide 1.0mg SC once weekly,

or matching placebo. Randomisation was stratified by HbA1c level at baseline (>8% or ≤8%) and the co-prescription of metformin (yes or no).[2] The primary outcome was the change in HbA1c level from baseline to week 30. The primary analysis was conducted using a MMRM in all randomised patients who had received one dose of study medicine and had data recorded prior to initiation of rescue therapy or discontinuation of study medicine.[2] The results of the primary and confirmatory secondary outcome are included in Table 1 below.

**Table 1: Adjusted mean changes from baseline in $HbA_{1c}$ and body weight with differences between semaglutide and comparators at study endpoint**

| | **$HbA_{1c}$ (%)** | | **Body weight (kg)** | |
|---|---|---|---|---|
| | **Mean change from baseline** | **Estimated treatment difference (95% CI)** | **Mean change from baseline** | **Estimated treatment difference (95% CI)** |
| **SUSTAIN 3 at 56 weeks (inadequate control with one or two OADs [dual or triple therapy])[4]** | | | | |
| Semaglutide 1.0mg weekly (n=404) | -1.5 | -0.62 (-0.80 to -0.44) p<0.001 | -5.6 | -3.78 (-4.58 to -2.98) p<0.001 |
| Exenatide ER 2mg weekly (n=405) | -0.9 | - | -1.9 | - |
| **SUSTAIN 2 at 56 weeks (inadequate control with one[a] or two OADs [dual or triple therapy])[6]** | | | | |
| Semaglutide 0.5mg weekly (n=409) | -1.3 | -0.77 (-0.92 to -0.62) p<0.001 | -4.3 | -2.35 (-3.06 to -1.63) p<0.001 |
| Semaglutide 1.0mg weekly (n=409) | -1.6 | -1.06 (-1.21 to -0.91) p<0.001 | -6.1 | -4.20 (-4.91 to -3.49) p<0.001 |
| Sitagliptin 100mg daily (n=407) | -0.5 | - | -1.9 | - |
| **SUSTAIN 4 at 30 weeks (inadequate control with metformin ± sulphonylurea [dual or triple therapy])[7]** | | | | |
| Semaglutide 0.5mg weekly (n=362) | -1.2 | -0.38 (-0.52 to -0.24) p<0.001 | -3.5 | -4.62 (-5.27 to -3.96) p<0.001 |
| Semaglutide 1.0mg weekly (n=360) | -1.6 | -0.81 (-0.96 to -0.67) p<0.001 | -5.2 | -6.33 (-6.99 to -5.67) p<0.001 |
| Insulin glargine daily(dose based on response)(n=360) | -0.8 | - | 1.2 | - |
| **SUSTAIN 7 at 40 weeks (inadequate control with metformin monotherapy [dual therapy])[5]** | | | | |
| Semaglutide 0.5mg weekly (n=301) | -1.5 | -0.40 (-0.55 to -0.25) p<0.001* | -4.6 | -2.26 (-3.02 to -1.51) p<0.001 |
| Dulaglutide 0.75mg weekly (n=299) | -1.1 | - | -2.3 | - |
| Semaglutide 1.0mg weekly (n=300) | -1.8 | -0.41 (-0.57 to -0.25) p<0.001* | -6.5 | -3.55 (-4.32 to -2.78) p<0.001 |

| | | | | |
|---|---|---|---|---|
| Dulaglutide 1.5mg weekly (n=299) | -1.4 | - | -3.0 | - |
| **SUSTAIN 5 at 30 weeks (inadequate control with basal insulin [add-on to basal insulin])** [2] | | | | |
| Semaglutide 0.5mg weekly (n=132) | -1.4 | -1.35 (-1.61 to -1.10) p<0.001 | -3.7 | -2.31 (-3.33 to -1.29) p<0.001 |
| Semaglutide 1.0mg weekly (n=131) | -1.8 | -1.75 (-2.01 to -1.50) p<0.001 | -6.4 | -5.06 (-6.08 to -4.04) p<0.001 |
| Placebo (n=133) | -0.1 | | -1.4 | |

ER=extended release, 95% CI=95% confidence intervals, *p-value for comparison of low dose semaglutide with low dose dulaglutide and comparison of high dose semaglutide with high dose dulaglutide [a]94% of patients were inadequately controlled on treatment with metformin monotherapy

Overall diabetes treatment satisfaction, reported as a component of the diabetes treatment satisfaction questionnaire (DTSQ), improved significantly more (p<0.05) in patients treated with semaglutide than in patients treated with exenatide ER (SUSTAIN 3), sitagliptin (SUSTAIN 2), insulin glargine (SUSTAIN 4) and placebo (SUSTAIN 5). Semaglutide was associated with a significant advantage over sitagliptin in SUSTAIN 2, and over exenatide ER in SUSTAIN 4 for the DTSQ question on self-perceived hyperglycaemia (p<0.05). [2-7]

SUSTAIN 6 was a 104-week, randomised, double-blind, placebo-controlled, phase III study designed to establish the cardiovascular safety of semaglutide. It enrolled patients with T2DM, aged ≥50 years with an HbA1c of ≥7% and established cardiovascular disease, chronic heart failure, or CKD stage 3 or higher and patients ≥60 years with one cardiovascular risk factor. Patients could have been treated with none to two OAD medicines with or without insulin. Semaglutide was non-inferior to placebo for the composite primary outcome of first occurrence of death from cardiac causes, non-fatal myocardial infarction (MI), or non-fatal stroke in the intention-to-treat population: 6.6% (108/1648) of semaglutide patients and 8.9% (146/1649) of placebo patients (hazard ratio 0.74 [95% CI: 0.58 to 0.95]). A *post-hoc* analysis indicated that semaglutide was superior to placebo for the primary outcome. Semaglutide treatment was associated with a higher risk of developing diabetic retinopathy complications compared to placebo (hazard ratio 1.76 [95% CI: 1.11 to 2.78])[1] and the number needed to harm for the development of serious retinopathy was 77.[2]The reduction of HbA1c and bodyweight in patients treated with semaglutide were greater (p<0.001) than the reductions in the placebo group; providing evidence of sustained benefit of semaglutide over 104 weeks of treatment.[8]

## Summary of evidence on comparative safety

In general, the adverse event (AE) profile of semaglutide is similar to other GLP-1 receptor agonists, with gastro-intestinal (GI) events commonly reported. In the SUSTAIN 3 study, the following were reported in the semaglutide 1.0mg weekly (n=404) and exenatide ER 2.0mg weekly (n=405) groups respectively; any AEs: 75% versus 76%, serious (grade 3 or higher) AEs: 9.4% versus 5.9%, AE leading to discontinuation: 9.4% and 7.2%. The most frequently reported AEs were

nausea (22% versus 12%), diarrhoea (11% versus 8.4%), severe or blood glucose confirmed symptomatic episode of hypoglycaemia (8.2% versus 8.1%), decreased appetite (7.9% versus 5.2%), injection-site reaction (1.2% versus 22%). There were six reports of cholelithiasis in the semaglutide group and two in the exenatide ER group.[4]

In the SUSTAIN 7 study, which compared semaglutide 0.5mg (n=301) with dulaglutide 0.75mg (n=299) (weekly low doses); and semaglutide 1.0mg (n=300) with dulaglutide 1.5mg (n=299) (weekly high doses), the following were reported for the respective groups; any AEs: 68% versus 62% and 69% versus 74%, serious AEs: 5.6% versus 8.0% and 7.7% versus 7.4%, nausea: 23% versus 13% and 21% versus 20%, diarrhoea: 14% versus 7.7% and 14% versus 18%, vomiting: 10% versus 4.0%, 10% versus 10%, decreased appetite: 8.3% versus 3.0% and 9.0% versus 10%, severe or blood glucose confirmed symptomatic episode of hypoglycaemia: 0.6% versus 1.0%, and 1.7% versus 1.7%, injection-site reaction: 1.3% versus 1.3% and 2.0% versus 2.7%. There was one report of cholelithiasis in the dulaglutide 0.75mg group, and two each in the semaglutide 1.0mg and dulaglutide 1.5mg groups.[5] A modest Increase in heart rate has been associated with semaglutide, this is a known but unexplained adverse effect of the GLP-1 receptor agonist class medicines and has not been associated with a negative effect on long term cardiovascular outcomes.[5]

## Summary of clinical effectiveness issues

Almost half of patients with T2DM on treatment experience uncontrolled hyperglycaemia, which is associated with microvascular and macrovascular complications which affect quality of life.[3] There are currently five GLP-1 receptor agonist preparations available in Scotland; dulaglutide (once weekly), exenatide (twice daily and once-weekly preparations), liraglutide, and lixisenatide (both once daily). The Scottish Intercollegiate Guideline Network (SIGN) guideline on the management of glycaemic control in T2DM patients, published in 2017,[9] lists GLP-1 receptor agonists as a third line and fourth line treatment option for patients uncontrolled on other anti-diabetic medicines. The submitting company has requested that SMC considers semaglutide when positioned for use in line with other GLP-1 receptor agonists; as an add-on therapy to OADs medicines (as dual or triple therapy) and as an add-on therapy to basal insulin.

For the primary outcome of change in HbA1c from baseline, semaglutide treatment was superior to; exenatide ER as dual or triple therapy (mainly metformin with or without a sulphonylurea) in SUSTAIN 3; dulaglutide as dual therapy (in addition to metformin) in SUSTAIN 7; sitagliptin when used as dual or triple therapy (mainly in addition to metformin monotherapy) in SUSTAIN 2, insulin glargine when used as dual or triple therapy (in addition to metformin with or without a sulphonylurea) in SUSTAIN 4, and placebo as add-on therapy to basal insulin in SUSTAIN 5. HbA1c is an established measure of blood glucose control over the preceding two to three months and reductions in HbA1c have been shown in large well-controlled studies to reduce the risk of diabetic complications.[10] Semaglutide was also associated with significantly greater reduction in body weight versus comparator treatment in each study. Reductions in bodyweight of overweight

and obese patients with T2DM have been associated with significant improvements in cardiovascular risk.[11]

The cardiovascular outcome study, SUSTAIN 6, found that semaglutide was non-inferior to placebo for the composite primary outcome of the first occurrence of death from cardiac causes, non-fatal myocardial infarction (MI), or non-fatal stroke following 104 weeks of treatment.[8]

There are some limitations to the individual studies. The SUSTAIN 5 study required a mandatory insulin dose reduction for all patients with an HbA1c <8% at baseline to reduce the risk of hypoglycaemia in patients randomised to semaglutide. This reduction makes the study results difficult to interpret as the reduction of insulin dose in the placebo group is unlikely in clinical practice.[2] In SUSTAIN 4, the mean pre-breakfast fasting self-measured plasma glucose was 7.1mmol/L but the target range was 4.0 to 5.5mmol/L, suggesting that insulin glargine was not titrated as strictly as directed in the study protocol; although it has been suggested this may be similar to clinical practice.[3,7,12] Other limitations include differences in mean baseline HbA1c between groups in SUSTAIN 2, smaller than expected reductions in HbA1c for patients treated with exenatide ER weekly in SUSTAIN 3 (possibly due to a more complex administration using a vial and syringe rather than the prefilled pen)[4] and in SUSTAIN 4, a patient population with a more extensive baseline OAD history prior to commencing basal insulin may have been more relevant to Scottish clinical practice.[7]

No evidence was provided for the use of semaglutide as part of a four medicine therapy, in combination with sodium glucose co-transporter 2 inhibitors, and there is limited evidence in combination with pioglitazone.[3] The SPC notes that there is limited therapeutic experience of semaglutide in patients over 75 years and in patients with severe renal impairment as small numbers from these groups were included in the SUSTAIN studies.[3]

The SUSTAIN 3, 4, and 7 studies had an open-label design which may have biased the reporting of patient-reported outcomes such as AEs and health-related quality of life. Higher proportions of patients dropped out of the semaglutide treatment group than the comparator group due to adverse effects in SUSTAIN 2, 3, 4, 5, and 7. In the SUSTAIN 2 and 3 studies, mean HbA1c increased from week 23 and 30 to the end of the study. The magnitude of this increase over time is unclear but is considered to be consistent with other GLP-1 receptor agonists.[4]

The dose titration of semaglutide every four weeks to 1.0mg weekly was suggested to improve tolerability of AEs and it is uncertain to what extent the gastro-intestinal AEs of semaglutide contribute to the weight loss associated with semaglutide treatment.[3]

None of the studies reported details of adherence to / or changes to diet and exercise in the study groups during the study periods.

The duration of the cardiovascular outcome study may have been too short to see meaningful differences in cardiovascular death between semaglutide and placebo. Also, the study only

included patients aged 50 years or older with a high cardiovascular risk: results from this group may not be generalisable to whole Scottish population.

The submitting company suggested that the SUSTAIN 7 study versus dulaglutide is the key direct clinical evidence for semaglutide but this supports use as dual therapy in addition to metformin which is of uncertain clinical relevance in Scotland since this is generally not aligned with the existing guideline recommendations for the use of GLP-1 receptor agonists as a third or fourth line treatment option. Although dual therapy with a GLP-1 receptor agonists is possible for some patients when used as a third or fourth line treatment option, in the SUSTAIN studies many patients receiving semaglutide as part of dual therapy may have received it as a second line treatment.

In the absence of direct comparative evidence, the submitting company presented three Bayesian network meta-analyses (NMAs) to compare semaglutide with other GLP-1 receptor agonists as add-on therapy to basal insulin (eight studies in the base case network), as dual therapy (13 studies in the base case network); and as combined dual and triple therapy (26 studies in the base case network). The submitting company also presented three Bucher method indirect treatment comparisons (ITC) which compared semaglutide with dulaglutide (1.5mg and 0.75mg once weekly), with liraglutide 1.8mg once daily and with exenatide 10 microgram twice daily as triple therapy. In all settings, semaglutide 1.0mg weekly was likely to be superior (Bayesian NMAs, supported by SUCRA ranking score of 100% in each NMA) or was statistically significantly superior (Bucher method) to all comparators with respect to change from baseline in HbA1c and in bodyweight at time of assessment; with the exception of exenatide ER 2mg once weekly for the outcome HbA1c change from baseline in the dual therapy setting, for which the effect was similar (the company used direct evidence for this comparison in the economic analysis). Overall, the NMAs were well-conducted. However, there were some limitations including a lack of formal heterogeneity testing of the studies used in the three NMAs and lixisenatide, a GLP-1 receptor agonist licensed for this indication, was not included in the analyses. There may also be a weaning effect (increases in HbA1c were seen in GLP-1 receptor agonists treatment groups following 23 weeks of treatment in SUSTAIN 2 and 3), which may add some uncertainty to comparing results from different time-points, but the company used a time-window approach to mitigate this risk.[4, 6] The clinical relevance of examining the relative effects of GLP-1 receptor agonists for dual therapy in Scotland is limited. For the three Bucher ITCs different assessment time-point results were used from each of the studies. Indirect comparative evidence was used in the economic case where direct evidence was absent.

The once weekly administration of semaglutide may be preferable to once or twice daily alternatives within the GLP-1 receptor agonist class. Clinical experts consulted by SMC considered that the place in therapy of semaglutide is as an alternative GLP-1 receptor agonist option for patients with inadequate glycaemic control on earlier lines of therapy.

## Summary of comparative health economic evidence

The company submitted a cost utility analysis comparing semaglutide (1.0mg and 0.5mg) weekly to dulaglutide (1.5mg) weekly, liraglutide (1.8mg and 1.2mg) once daily, exenatide (10microgram) twice daily, and exenatide ER (2mg) once weekly in patients with T2DM. The company positioned semaglutide for use where GLP-1 receptor agonists are likely to be prescribed in addition to other medicinal products for the treatment of diabetes i.e. as an add-on therapy to OADs or basal insulin. SMC clinical experts indicated that semaglutide will provide an alternative to other GLP-1 receptor agonists. For the economic analysis the company divided the population into three subgroups. The results for the following T2DM patient subpopulations were provided;

- Patients with inadequate glycaemic control on OADs as part of dual therapy
- Patients with inadequate glycaemic control on OADs as part of triple therapy
- Patients with inadequate glycaemic control on basal insulin (with or without up to two OADs)

The economic analysis focuses on the semaglutide 1.0mg dose as this is priced at parity with the semaglutide 0.5mg dose and is assumed to be more effective. The CORE diabetes model was used to estimate the cost effectiveness of semaglutide versus comparator treatments over a duration of 50 years. For the key clinical parameters HbA1c and body mass index (BMI), the model assumes a treatment effect in year 1, followed by the treatment effect being maintained up to year three. After year three, patients are assumed to discontinue active treatment and receive an intensification of basal insulin. Modifiable risk factors and risk equations were used within the model to capture disease progression. Complications associated with T2DM were modelled via the inclusion of 17 interdependent Markov sub-models/health states.

The clinical data used in the economic analysis came from a mixture of direct studies,[2,4,5] NMAs and Bucher indirect comparisons. Baseline patient characteristics were taken from the pivotal studies described above. The key drivers of clinical efficacy within the model were change in HbA1c and BMI. Based on the NMAs and Bucher indirect comparisons semaglutide 1.0mg weekly resulted in a significant improvement for the outcomes change in HbA1c and change in bodyweight from baseline to time of assessment, compared to all comparators where direct data was lacking. Results from direct studies further supported this efficacy conclusion.

Utility values were taken from a range of published literature including a number of UK studies, where quality of life data were elicited using the EQ-5D. The base case utility for diabetes with no complications was estimated to be 0.785. An additive approach was used such that in a given year, patients with multiple complications were assumed to occupy the health state with the lowest utility within the model (associated with existing complications) and disutilites were applied for any events occurring throughout the year. A disutility was also applied to a unit increase in BMI.

Treatment acquisition costs were included in the model as well as the cost of basal insulin and concomitant medication (metformin, sulphonylurea and thiazolidinedione). Administration and self-monitoring costs were also included (needles, test strips and lancets). The model also captured costs associated with treating complications / adverse events and distinguished between differential costs incurred in year 1 and subsequent years. Adverse event costs including non-severe and severe hypoglycemia were applied for the first 3 years and were based on data from one of the pivotal studies.[5]

The base case results are outlined in the tables below.

**Table 2: Base case results in dual therapy population**

| Treatment | Incremental costs | Incremental quality adjusted life years (QALYs) | Incremental cost effectiveness ratio (ICER) |
|---|---|---|---|
| Semaglutide 1.0mg vs. Dulaglutide 1.5mg | -£111 | 0.10 | Dominant |
| Semaglutide 0.5mg vs. Dulaglutide 1.5mg | -£45 | 0.003 | Dominant |
| Semaglutide 1.0mg vs. Liraglutide 1.8mg | -£1,542 | 0.07 | Dominant |
| Semaglutide 1.0mg vs. Liraglutide 1.2mg | -£346 | 0.12 | Dominant |
| Semaglutide 1.0mg vs. Exenatide 2.0mg (ER) | -£301 | 0.10 | Dominant |
| Semaglutide 1.0mg vs. Exenatide 10µg | -£628 | 0.12 | Dominant |

A dominant result indicates that semaglutide is less costly and more effective

**Table 3: Base case results in triple therapy population**

| Treatment | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|
| Semaglutide 1.0mg vs. Dulaglutide 1.5mg | -£167 | 0.06 | Dominant |
| Semaglutide 1.0mg vs. Liraglutide 1.8mg | -£1,578 | 0.08 | Dominant |
| Semaglutide 1.0mg vs. Liraglutide 1.2mg | -£376 | 0.10 | Dominant |
| Semaglutide 1.0mg vs. Exenatide 2.0mg | -£419 | 0.17 | Dominant |
| Semaglutide 1.0mg vs. Exenatide 10µg | -£741 | 0.13 | Dominant |

A dominant result indicates that semaglutide is less costly and more effective

**Table 4: Base case results in add on to insulin population**

| Treatment | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|
| Semaglutide 1.0mg vs. Dulaglutide 1.5mg | -£344 | 0.11 | Dominant |
| Semaglutide 1.0mg vs. Liraglutide 1.8mg | -£1,433 | 0.06 | Dominant |
| Semaglutide 1.0mg vs. Exenatide 10µg | -£667 | 0.12 | Dominant |

A dominant result indicates that semaglutide is less costly and more effective

The following limitations were noted:

- The company did not consider lixisenatide to be a relevant comparator on the basis that it is the GLP-1 receptor agonist with the lowest market share. Based on SMC expert responses to date, dulaglutide and exenatide are the comparators most likely to be displaced in Scotland. Therefore the omission of lixisenatide may not be a concern. It is worth noting, however, that lixisenatide is the lowest costing GLP-1 receptor agonist.
- There is a lack of direct comparative data versus some comparators and as such the economic analysis incorporates outcomes from NMAs and Bucher method comparisons, which had some limitations. This may introduce some uncertainty into the results.
- The base case results included non-significant differences for some outcomes. However, the company provided sensitivity analyses removing all non-significant differences and semaglutide 1.0mg remained dominant versus all comparators in all subgroups.

Despite the uncertainties outlined above, the economic case has been demonstrated.

## Summary of patient and carer involvement

No patient group submission was received.

## Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) guideline 154 includes a treatment algorithm which outlines the first, second, third, and fourth line treatment options for patients with T2DM. In addition to lifestyle interventions it is recommended that either a sulphonylurea, SGLT2 inhibitor, dipeptidyl peptidase-4 (DPP-4) inhibitor, or pioglitazone is added to first line treatment (usually metformin) if a patient has failed to reach their HbA1c target within three to six months. The algorithm recommends the addition of a further agent, from a different class, if after a further three to six months a patient receiving dual therapy has failed to achieve their glycaemic target. The guidance recommends that the addition of an injectable agent (either a GLP-1 RA or basal insulin) be considered as a third line treatment option. If after receiving triple therapy for

three to six months a patient has failed to meet their HbA1c target, guided by the patient profile an additional agent can be added following specialist assessment.[9]

GLP-1 RA therapy should be considered in patients with a body mass index of ≥30kg/$m^2$ (or ethnicity-adjusted equivalent) in combination with OADs or basal insulin (or both) as third- or fourth-line treatment, when there is inadequate glycaemic control on earlier lines of therapy. The guideline also recommends patients with T2DM and established cardiovascular disease, should be considered for treatment with GLP-1 RAs with proven cardiovascular benefit.[9]

National Institute of Clinical and Healthcare Excellence (NICE) guideline 28 makes similar recommendations to SIGN.[13]

## Additional information: comparators

Other GLP-1 receptor agonists: dulaglutide, exenatide extended release, exenatide, liraglutide, lixisenatide.

## Cost of relevant comparators

| Medicine | Dose Regimen | Cost per year (£)* |
|---|---|---|
| **Semaglutide** | **0.5mg or 1.0mg subcutaneous (SC) once weekly** | **952** |
| Liraglutide | 1.2 or 1.8mg SC once daily | 952 to 1428 |
| Exenatide | 5 microgram or 10 microgram SC twice daily | 994 |
| Exenatide extended release | 2mg SC once weekly | 954 |
| Dulaglutide | 1.5mg SC once weekly | 952 |
| Lixisenatide | 20 microgram SC once daily | 703 |

*Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 3 September 2018, except the cost for semaglutide which was taken from the company submission. Costs do not take any patient access schemes into consideration. *Cost per year are based on maintenance doses and do not account for dose titration or initiation packs.*

## Additional information: budget impact

The submitting company estimated there would be 8,468 patients eligible for treatment with semaglutide in year 1, rising to 9,632 in year 5. The estimated uptake rate was 5% in year 1 (423 patients), rising to 25% in year 5 (2,408 patients). A 6.67% discontinuation rate was applied to all years.

The gross impact on the medicines budget was estimated to be £378k in year 1 rising to £2.1m in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be savings of £34k in year 1 rising to £196k in year 5.

**References**


1. European Medicines Agency. Ozempic® (semaglutide) Summary of Product Characteristics. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004174/WC500244163.pdf.
2. Rodbard HW, Lingvay I, Reed J, de la Rosa R, Rose L, Sugimoto D*, et al.* Semaglutide Added to Basal Insulin in Type 2 Diabetes (SUSTAIN 5): A Randomized, Controlled Trial. J Clin Endocrinol Metab. 2018;103(6):2291-301. Epub 2018/04/25.
3. European Medicines Agency. Semaglutide (Oezempic) EPAR. 2018 [cited 07 May 2018]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004174/WC500244165.pdf.
4. Ahmann AJ, Capehorn M, Charpentier G, Dotta F, Henkel E, Lingvay I*, et al.* Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial. Diabetes care. 2018;41(2):258-66.
5. Pratley RE, Aroda VR, Lingvay I, Ludemann J, Andreassen C, Navarria A*, et al.* Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. The Lancet Diabetes and Endocrinology. 2018;6(4):275-86.
6. Ahren B, Masmiquel L, Kumar H, Sargin M, Karsbol JD, Jacobsen SH*, et al.* Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. The lancet Diabetes & endocrinology. 2017;5(5):341-54.
7. Aroda VR, Bain SC, Cariou B, Piletic M, Rose L, Axelsen M*, et al.* Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. The lancet Diabetes & endocrinology. 2017;5(5):355-66.
8. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA*, et al.* Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. New England Journal of Medicine. 2016;375(19):1834-44.
9. Scottish Intercollegiate Guidelines Network. SIGN 154: Pharmacological management of glycaemic control in people with type 2 diabetes. Available at: http://www.sign.ac.uk/assets/sign154.pdf. 2017 [cited.
10. European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. 2012 [cited 07 May 2018]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf.
11. Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG*, et al.* Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care. 2011;34(7):1481-6. Epub 2011/05/20.
12. FDA. Medical Review. 2017 [cited 07 May 2018]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209637Orig1s000MedR.pdf.
13. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management (NG28). Available at: https://www.nice.org.uk/guidance/ng28. 2015 [cited.


This assessment is based on data submitted by the applicant company up to and including 09 October 2018.

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.

**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.*