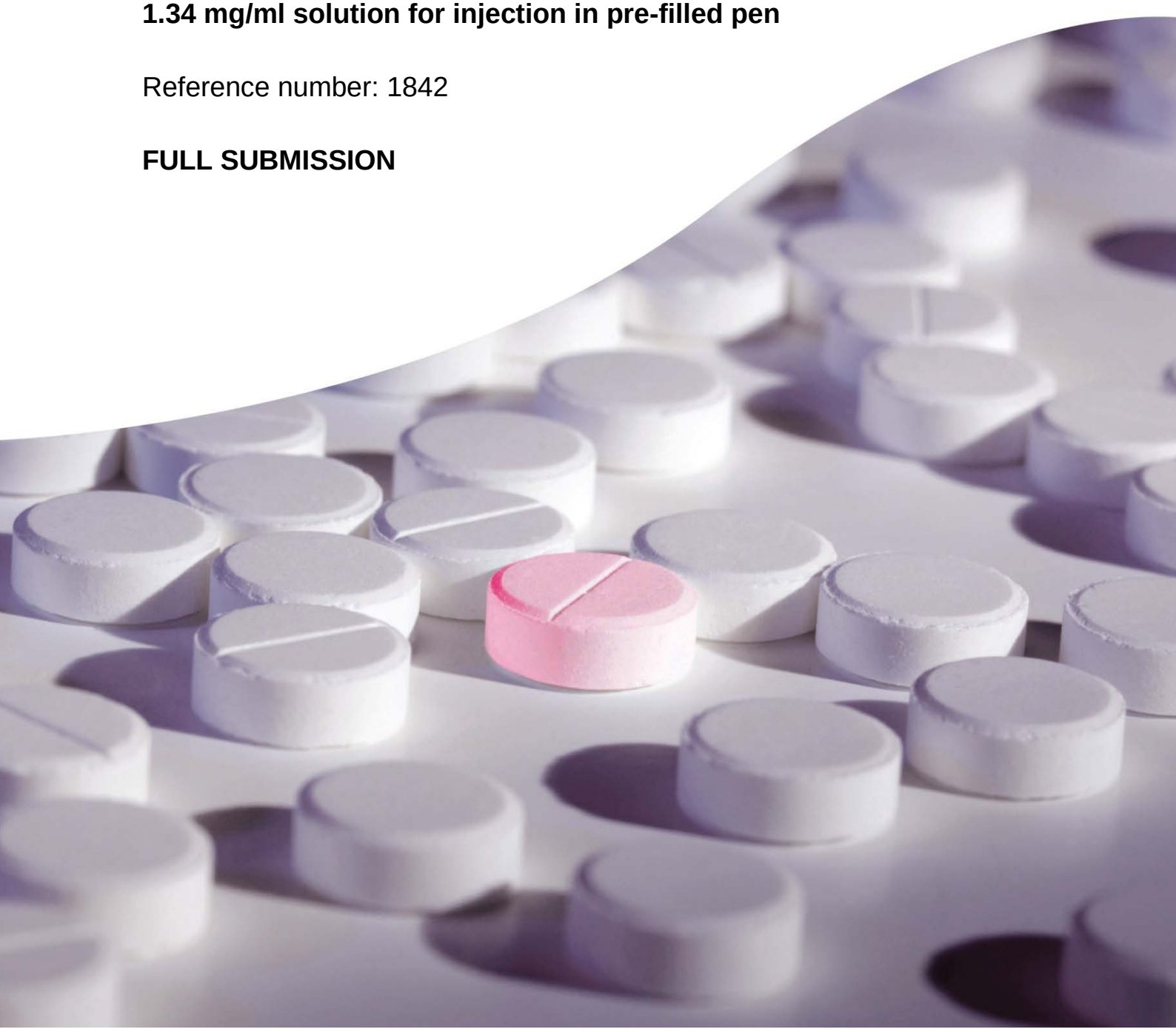
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Semaglutide (Ozempic®)
1.34 mg/ml solution for injection in pre-filled pen

Reference number: 1842

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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AWMSG Secretariat Assessment Report
Semaglutide (Ozempic®▼) 1.34 mg/ml solution for injection in pre-filled pen

1.0 KEY FACTS

Assessment details	Semaglutide (Ozempic®▼) for the treatment of adults with insufficiently controlled type 2 diabetes mellitus 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. The company has focused its submission on the treatment of insufficiently controlled type 2 diabetes mellitus in adults as an add-on therapy to oral antidiabetic medicines or basal insulin. Semaglutide is given by subcutaneous injection once a week, using a pre-filled pen device. ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. The company expects to launch semaglutide in the UK in [commercial in confidence text removed].
Current clinical practice	According to the National Institute for Health and Care Excellence guideline on the management of type 2 diabetes in adults, combination therapy with metformin, a sulphonylurea and a glucagon-like peptide (GLP-1) mimetic (such as semaglutide) can be considered if triple therapy is not effective, not tolerated or is contraindicated after second intensification of treatment[1]. The guideline also includes the option of a GLP-1 mimetic in people taking basal insulin with specialist care advice.
Clinical effectiveness	Two phase III open-label, head-to-head studies directly compared semaglutide with comparator GLP-1 mimetics: dulaglutide in patients taking metformin only (SUSTAIN 7 study) and exenatide extended-release in patients taking metformin and one or two other antidiabetic medicines (SUSTAIN 3 study). Results of both showed that semaglutide was associated with statistically significantly better glycaemic control (measured by reductions in HbA_{1c}) and weight loss. Indirect comparisons of semaglutide with liraglutide, dulaglutide and exenatide twice-daily added to two antidiabetic medicines were significantly in favour of semaglutide.

	A network meta-analysis (NMA) in patients with diabetes uncontrolled on one or two antidiabetic medicines showed that semaglutide caused greater reductions in HbA_{1c} and body weight than liraglutide, exenatide twice-daily or dulaglutide. A second NMA in patients with diabetes receiving basal insulin showed similar results: semaglutide was associated with greater reductions in HbA_{1c} and body weight than dulaglutide, liraglutide, lixisenatide and exenatide twice-daily.
Cost-effectiveness	The company submission includes cost-utility analyses of semaglutide 0.5 mg and 1.0 mg for once weekly subcutaneous injection compared with other GLP-1 receptor agonists available in Wales for the treatment of adults with insufficiently controlled type 2 diabetes as part of dual or triple therapy with oral antidiabetic medicines or as add-on therapy to basal insulin. Semaglutide 0.5 mg and 1.0 mg as part of dual or triple therapy, or as an add-on to basal insulin is reported to produce small increases in quality-adjusted life-years (QALY) and slight cost savings and thus dominate all other GLP-1 receptor agonist treatment options available in Wales except lixisenatide where it is slightly more expensive and more effective but remains cost effective.
Budget impact	It is estimated that 320 people will receive semaglutide in Year 1 and 1,606 in Year 5. The company estimates a cumulative cost saving of [commercial in confidence figure removed] over a five-year period ([commercial in confidence figure removed] in Year 1 rising to [commercial in confidence figure removed] in Year 5) after introduction of semaglutide because the cost of most displaced GLP-1 receptor agonists is higher (liraglutide 1.8 mg as well as liraglutide 1.2 mg) or similar (dulaglutide, exenatide once-weekly) and no additional cost of needles is accrued.

This assessment report is based on evidence submitted by Novo Nordisk Ltd[2] and an evidence search conducted by AWTTC on 21 May 2018.

2.0 BACKGROUND

2.1 Condition and clinical practice

Type 2 diabetes is a chronic metabolic condition in which the body can't produce enough insulin or can't use it effectively, resulting in hyperglycaemia[1]. Type 2 diabetes is recognised to have an increased cardiovascular risk, because of its association with obesity, physical inactivity, raised blood pressure, disturbed blood lipid levels and a tendency to develop thrombosis. Diabetes is associated with long-term microvascular and macrovascular complications, and reduced quality of life and life expectancy[1].

During 2016–2017 the prevalence of diabetes in Wales was 5.9% and the disease register had 191,590 people aged 17 years and older with diabetes[3]. About 90% of people with diabetes have type 2 diabetes[4].

There is no known cure for type 2 diabetes[4]. It is a progressive condition that may be managed at first with diet and exercise but over time people may need medicines to help lower their blood sugar levels[4]. Most people will start on metformin treatment but if this doesn't sufficiently control blood glucose then other antidiabetic medicines are added, according to the National Institute for Health and Care Excellence (NICE) guideline treatment algorithm for blood glucose lowering therapy[1].

2.2 Medicine

Semaglutide is a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist[5]. When blood glucose is high, semaglutide stimulates the pancreatic islet cells to secrete insulin and inhibits glucagon secretion[5]. It also reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite[5].

Semaglutide was granted marketing authorisation by the European Medicines Agency in February 2018 to treat insufficiently controlled type 2 diabetes mellitus 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[6].

Semaglutide comes in a pre-filled pen for subcutaneous injection[5]. The starting dose is 0.25 mg semaglutide once weekly. After 4 weeks the dose should be increased to 0.5 mg once weekly. After at least 4 weeks with a dose of 0.5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycaemic control[5].

The NICE guideline on the management of type 2 diabetes in adults states that combination therapy with metformin, a sulphonylurea and a GLP-1 mimetic can be considered if triple therapy is not effective, not tolerated or is contraindicated[1]. However, this combination is only to be considered for adults with:

- a body mass index (BMI) ≥ 35 kg/m^2 or higher and specific psychological or other medical problems associated with obesity; or
- a BMI < 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities[1].

And, fourth-line GLP-1 mimetic treatment should only be continued if the person:

- has a reduction of HbA_{1c} (a surrogate measure of overall glucose control) by at least 11 mmol/mol (1.0%); and
- loses at least 3% of initial body weight in six months[1].

For people receiving insulin-based treatment, the NICE guideline states that combined therapy with insulin and a GLP-1 mimetic should only be offered with specialist care advice and ongoing support from a consultant-led multidisciplinary team[1].

The company has focused its submission on the use of semaglutide in accordance with the NICE guideline, that is: third- or fourth-line use or as an add-on to basal insulin to treat type 2 diabetes that is insufficiently controlled on triple therapy with oral antidiabetic medicines or basal insulin[2].

2.3 Comparators

The comparator(s) included in the company's submission are:

- dulaglutide (Trulicity®)
- liraglutide (Victoza®)
- exenatide extended-release (Bydureon®)
- exenatide twice-daily (Byetta®)
- lixisenatide (Lyxumia®)[2].

2.4 Guidance and related advice

- NICE pathway (2018) Type 2 diabetes in adults[7]
- Scottish Intercollegiate Guidelines Network (SIGN) (2017) Pharmacological management of glycaemic control in people with type 2 diabetes. SIGN guideline 154[8]
- NICE (2015; updated 2017) Type 2 diabetes in adults: management[1]
- SIGN (2010; updated 2017) Management of diabetes. SIGN clinical guideline 116[9]

The All Wales Medicines Strategy Group (AWMSG) has previously recommended the use of dulaglutide (Trulicity®) and lixisenatide (Lyxumia®)[10]. In the absence of submissions from the marketing authorisation holders, liraglutide (Victoza®) as monotherapy and exenatide twice-daily (Byetta®) as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone are not endorsed for use within NHS Wales[11,12].

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, semaglutide (Ozempic®) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation or by practitioners with a special interest in diabetes mellitus.

3.0 CLINICAL EFFECTIVENESS

The company's submission includes evidence from five randomised, controlled phase IIIb studies comparing semaglutide with sitagliptin (SUSTAIN 2), exenatide extended-release (SUSTAIN 3), insulin glargine (SUSTAIN 4), placebo (SUSTAIN 5) and dulaglutide (SUSTAIN 7)[2]. The submission also includes a long-term cardiovascular outcomes study (SUSTAIN 6), two network meta-analyses (NMAs), and indirect comparisons of semaglutide with dulaglutide, liraglutide and exenatide twice-daily[2]. Results from the SUSTAIN 7 and SUSTAIN 3 studies are covered in this report because they directly compared semaglutide with relevant comparators in Wales. Results from SUSTAIN 5 are included as evidence of semaglutide in combination with basal insulin and other antidiabetic medicines. The SUSTAIN studies comparing semaglutide with sitagliptin (SUSTAIN 2) and insulin glargine (SUSTAIN 4) are not discussed further because these are not relevant comparators in Wales.

3.1 SUSTAIN 7 and SUSTAIN 3 studies

These international, open-label studies compared semaglutide with dulaglutide (SUSTAIN 7) and with exenatide extended-release (SUSTAIN 3)[13,14]. Patients enrolled were ≥ 18 years, with type 2 diabetes and HbA_{1c} of 7.0–10.5% (53.0–91.0 mmol/mol) and on stable diabetes treatment for ≥ 90 days before screening[13,14]. Patients in SUSTAIN 7 were receiving metformin at a minimum dose of 1,500 mg/day or a maximal tolerated dose[13]. Patients in SUSTAIN 3 were receiving stable treatment with one or two oral antidiabetic medicines (metformin and/or a thiazolidinedione and/or a sulphonylurea)[14].

Patients were excluded if they had a glomerular filtration rate < 60 ml/min/1.73 m^2 (chronic kidney disease stage 3), a history of pancreatitis, an acute coronary or cerebrovascular event within 90 days before randomisation, or heart failure (New York Heart Association class IV), or were receiving chronic treatment with glucose-lowering medicines (other than those in the inclusion criteria) within 90 days of screening[14]. The SUSTAIN 7 study excluded patients with proliferative retinopathy or maculopathy requiring acute treatment[13].

Patients in the SUSTAIN 7 study were randomly assigned 1:1:1:1 to receive treatment once-weekly for 40 weeks with semaglutide 0.5 mg, dulaglutide 0.75 mg, semaglutide 1.0 mg or dulaglutide 1.5 mg[13]. All treatments were self-administered subcutaneously, using their respective patented pre-filled pen devices[13]. Patients in the SUSTAIN 3 study were randomised 1:1 to once-weekly semaglutide 1.0 mg (administered with a pre-filled pen injector) or once-weekly exenatide extended-release 2.0 mg (administered with a vial and syringe) for 56 weeks[14]. In both studies, the semaglutide dose was escalated: patients received a starting dose of 0.25 mg which doubled every four weeks until the study maintenance dose was reached (0.5 mg or 1.0 mg in SUSTAIN 7; 1.0 mg in SUSTAIN 3)[13,14].

The primary endpoint was change in percentage HbA_{1c} from baseline to week 40 (SUSTAIN 7) or week 56 (SUSTAIN 3)[13,14]. The European Medicines Agency considered a pre-defined non-inferiority margin of ≥ 0.3% (3 mmol/mol) as acceptable for a clinically meaningful reduction in HbA_{1c}[15]. A confirmatory secondary endpoint was change in body weight from baseline to week 40 (SUSTAIN 7) or week 56 (SUSTAIN 3)[13,14]. Key results from the SUSTAIN 7 and SUSTAIN 3 studies are shown in Table 1.

In the SUSTAIN 7 study, 1,199 patients were exposed to treatment and included in the efficacy and safety analyses[13]. After 40 weeks of treatment, reductions in HbA_{1c} were statistically significantly greater in patients treated with semaglutide 1.0 mg (−1.8%) than those treated with dulaglutide 1.5 mg (−1.4%; $p < 0.0001$ for both non-inferiority and superiority). Patients treated with semaglutide 1.0 mg also lost significantly more weight than those treated with dulaglutide 1.5 mg (−6.5 kg versus −3.0 kg; $p < 0.0001$ for both non-inferiority and superiority) (see Table 1).

After 40 weeks most domains of the patient-reported outcome short-form health survey 36 version 2 questionnaire (SF-36v2) improved for both doses of semaglutide and dulaglutide, although the changes were not significantly different[13]. Most items of the diabetes treatment satisfaction questionnaire had improved at Week 40 for both doses of semaglutide and dulaglutide. Patient perception of unacceptable hyperglycaemia significantly improved in semaglutide-treated patients compared with dulaglutide-treated patients[13].

In the SUSTAIN 3 study, 809 patients were exposed to treatment and were included in the efficacy and safety analysis[14]. Semaglutide showed superiority to exenatide extended-release in both the primary endpoint and confirmatory secondary endpoint. Patients treated with semaglutide for 56 weeks had a statistically significantly greater reduction in HbA_{1c} (−1.5%) compared with exenatide (−0.9%), and lost statistically significantly more weight (−5.6 kg compared with −1.9 kg). No significant differences between the treatment groups were seen for the domains assessed by the SF-36v2 health questionnaire. Patients treated with semaglutide had a significantly greater improvement in overall treatment satisfaction ($p = 0.0068$) and self-perceived hyperglycaemia ($p = 0.0200$) as measured by diabetes treatment satisfaction questionnaire scores (see Table 1)[14].

3.2 SUSTAIN 5 study

This double-blind study enrolled 397 adults with type 2 diabetes who were randomised to receive either semaglutide (0.5 mg or 1.0 mg) or placebo (0.5 mg or 1.0 mg) once weekly for 30 weeks as an add-on to basal insulin with or without metformin[16]. As add-on to basal insulin, semaglutide was superior to placebo in reducing HbA_{1c} and body weight. More hypoglycaemic events were reported in the semaglutide groups compared with the placebo group (see Table 1)[16].

Table 1. Key endpoints of the SUSTAIN 7, 3 and 5 studies[2,13,14,16]

SUSTAIN 7* (in adults taking metformin)	Semaglutide 1.0 mg once weekly	Dulaglutide 1.5 mg once weekly	Treatment difference (95% CI)	p-value
Change in HbA1c from baseline at week 40 (%) - final analysis set	−1.8 (0.06)	−1.4 (0.06)	−0.41 (−0.57 to −0.25)	<0.0001
Change in body weight at week 40 (kg)	−6.5 (0.28)	−3.0 (0.27)	−3.55 (−4.32 to −2.78)	<0.0001
SUSTAIN 3 (in adults taking one or two antidiabetic medicines)	**Semaglutide 1.0 mg once weekly**	**Exenatide ER 2.0 mg once weekly**		
Change in HbA1c from baseline at week 56 (%)	−1.5	−0.9	−0.62 (−0.80 to −0.44)	<0.0001
Change in body weight at week 56 (kg)	−5.6	−1.9	−3.78 (−4.58 to −2.98)	<0.0001
SUSTAIN 5 (in adults taking basal insulin with or without metformin)	**Semaglutide 1.0 mg once weekly**	**Placebo 1.0 mg**		
Change in HbA1c from baseline at week 30 (%)	−1.8	−0.1	−1.75 (−2.01 to −1.50)	<0.0001
Change in body weight at week 30 (kg)	−6.4	−1.4	−5.06 (−6.08 to −4.04)	<0.0001
* Full analysis set CI: confidence interval; ER: extended-release; HbA1c: glycated haemoglobin; SE standard error				

3.3 Indirect comparisons and network meta-analyses

In the absence of head-to-head studies comparing semaglutide with liraglutide, lixisenatide and exenatide twice-daily in patients inadequately controlled on two oral antidiabetic medicines, the company conducted systematic literature searches in 2016 (updated 2017) and made indirect comparisons of semaglutide with liraglutide and exenatide twice-daily and dulaglutide[2].

For each indirect comparison the main outcomes of interest were change from baseline in HbA_{1c} and body weight[2]. The results are shown in Table 2. All comparisons were statistically significantly different in favour of semaglutide, which was associated with greater reductions in HbA_{1c} and body weight than liraglutide, exenatide twice-daily or dulaglutide[2].

Table 2. Results of indirect comparisons of GLP-1 receptor agonists as an add-on to patients with inadequately controlled diabetes taking two oral antidiabetic medicines[2]

Outcome	Treatment difference (95% CI)		
	Semaglutide 1.0 mg once weekly vs liraglutide 1.8 mg once daily	Semaglutide 1.0 mg once weekly vs exenatide 10 microgram twice daily	Semaglutide 1.0 mg once weekly vs dulaglutide 1.5 mg once weekly
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An NMA was only possible in patients whose diabetes is uncontrolled on one or two oral antidiabetic medicines[17], rather than two or more. The analysis included 26 studies. Results (shown in Table 3) showed that semaglutide 1.0 mg was associated with statistically significantly greater reductions in HbA_{1c} and body weight than liraglutide 1.8 mg, exenatide 10 micrograms twice daily and dulaglutide 1.5 mg[17].

A second NMA was conducted in the population of patients receiving basal insulin, for semaglutide as an add-on to basal insulin[18]. This included eight studies. The results were similar to the analysis in the population receiving one or two antidiabetic medicines. Semaglutide was associated with statistically significantly greater reductions in HbA_{1c} and body weight than dulaglutide, exenatide twice-daily, liraglutide and lixisenatide[18]. The company stated that it wasn't possible to compare semaglutide with exenatide extended-release.

Table 3. Results from NMAs reporting the treatment difference between semaglutide and other GLP-1 receptor agonists when added to treatment with one or two oral antidiabetic medicines or basal insulin[17,18]

	Relative treatment difference (95% CrI) at 24-week time point between semaglutide 1.0 mg once weekly and other GLP-1 receptor agonists when added to one or two antidiabetic medicines			
Outcome	**Exenatide ER** 2.0 mg once weekly	**Liraglutide** 1.2 mg once daily	**Liraglutide** 1.8 mg once daily	**Lixisenatide** 20 microgram once daily
HbA1c change from baseline (%)	−0.51 (−0.72 to −0.30)	−0.60 (−0.87 to− 0.32)	−0.36 (−0.58 to −0.13)	−0.93 (−1.19 to− 0.66)
Weight change from baseline (kg)	−2.35 (−2.74 to −1.97)	−2.03 (−2.55 to −1.51)	−1.75 (−2.16 to −1.34)	−2.96 (−3.48 to −2.45)
	Relative treatment difference (95% CrI) at 24-week time point between semaglutide 1.0 mg once weekly and other GLP-1 receptor agonists when added to basal insulin			
Outcome	**Exenatide** 10 microgram twice daily	**Dulaglutide** 1.5 mg once weekly	**Liraglutide** 1.8 mg once daily	**Lixisenatide** 20 microgram once daily
HbA1c change from baseline (%)	−0.99 (−1.35 to −0.64)	−0.92 (−1.27 to −0.57)	−0.49 (−0.81 to −0.17)	−1.39 (−1.77 to −1.01)
Weight change from baseline (kg)	−1.86 (−3.35 to −0.37)	−2.18 (−3.56 to −0.80)	−1.49 (−2.82 to− 0.17)	−3.29 (−4.60 to −1.98)
CrI: credible interval; ER: extended release; HbA1c: glycated haemoglobin				

3.4 Comparative safety

Semaglutide shows a similar safety profile to other GLP-1 receptor agonists[16]: similar proportions of patients experienced adverse events in the SUSTAIN 7 study (69% for semaglutide 1.0 mg and 74% for dulaglutide 1.5 mg)[13] and the SUSTAIN 3 study (75% for semaglutide 1.0 mg and 76% for exenatide extended-release)[14]. The proportions of serious adverse events were the same in the SUSTAIN 7 study (8% for semaglutide and dulaglutide) and similar in the SUSTAIN 3 study (9% for semaglutide and 6% for exenatide extended-release)[13,14].

More patients discontinued semaglutide treatment because of adverse events, compared with other treatments, including patients who discontinued treatment early because of gastrointestinal disorders[6]. The incidence of gastrointestinal adverse events was higher with semaglutide than with all comparators[6].

The most common adverse events reported in the SUSTAIN studies were consistent with those reported for GLP-1 receptor agonists and were mainly gastrointestinal adverse events: nausea, diarrhoea and vomiting[6]. These were generally mild or moderately severe and of short duration[5]. Equally low proportions of patients developed severe or blood-glucose confirmed hypoglycaemia: 2% for semaglutide 1 mg and dulaglutide 1.5 mg (SUSTAIN 7)[13]; and 8% for semaglutide 1 mg and exenatide extended-release (SUSTAIN 3)[14].

SUSTAIN 6 was a long-term, cardiovascular study of semaglutide as an add-on to standard of care (including insulin) in 3,297 patients with diabetes and established, or at

high risk of, cardiovascular disease[19]. Results showed a statistically significant 26% reduction in risk of a composite of non-fatal stroke, non-fatal myocardial infarction, cardiovascular death and time to first occurrence of major adverse cardiovascular event in patients treated with semaglutide for 104 weeks (hazard ratio 0.74; $p < 0.001$)[19].

A significantly increased risk of diabetic retinopathy complications was seen in patients treated with semaglutide compared with placebo, particularly in patients taking insulin who had a history of diabetic retinopathy (3.0% versus 1.8% in the SUSTAIN 6 study)[6].

The Summary of Product Characteristics for semaglutide recommends caution when administering it to people with diabetic retinopathy who are taking insulin[5].

3.5 Ongoing studies

There is an ongoing phase III study comparing the safety and efficacy of semaglutide versus liraglutide 1.2 mg as add-on to one to three antidiabetic medicines; expected to complete third quarter 2018[2].

3.6 AWTTC critique

- The SUSTAIN studies show that once-weekly semaglutide treatment was related to clinically meaningful reductions in HbA_{1c} that were significantly greater than those seen with comparator medicines, but did not increase the risk of hypoglycaemia (except for in combination with a sulphonylurea or insulin)[6]. The company has focused its submission on the treatment of insufficiently controlled type 2 diabetes mellitus in adults as an add-on therapy to oral antidiabetic medicines or basal insulin[2].
- SUSTAIN 7 patients were taking metformin only and this does not reflect where semaglutide will be used in clinical practice in Wales as NICE guidelines recommend the use of GLP-1 after triple therapy in patients with specified BMI or for whom starting insulin therapy would have implications[13]. The company undertook an indirect comparison which showed that semaglutide was associated with significantly greater reductions in HbA_{1c} and weight than dulaglutide 1.5 mg, liraglutide 1.8 mg and exenatide 10 micrograms when added to two oral antidiabetic medicines.
- The NMA reported adding semaglutide to one to two oral antidiabetic medicines was associated with greater reductions in HbA_{1c} and weight than exenatide, liraglutide and lixisenatide. There is uncertainty regarding this NMA as it does not reflect where semaglutide will be used in addition to two oral antidiabetic medicines. There were differences in study design relating to the percentage of patients who had prior treatment with metformin, the baseline HbA_{1c} and differences in when results were reported. The literature search for the indirect comparisons and NMAs was last updated in August 2017 and more recent publications are not included in the analysis.
- The cardiovascular outcomes study (SUSTAIN 6) only enrolled people with a high cardiovascular risk, so it may not be possible to generalise the results to the general diabetes population[6].
- Results from the diabetes treatment satisfaction questionnaires in the SUSTAIN 3 study showed increased patient satisfaction with semaglutide[14], and patient-perceived unacceptable hyperglycaemia was improved with semaglutide treatment in the SUSTAIN 7 study[13].
- Semaglutide is a once-weekly treatment that can be self-administered using a pre-filled pen device. The weekly administration may make it a more convenient treatment option than a daily GLP-1 receptor agonist, such as liraglutide, lixisenatide or exenatide twice-daily.

4.0 COST-EFFECTIVENESS

4.1 Context

The company's submission includes cost-utility analyses of semaglutide 0.5 mg and 1.0 mg for once-weekly subcutaneous injection compared with other GLP-1 receptor agonist alternatives available in Wales, including: dulaglutide 1.5 mg once weekly, liraglutide 1.2 mg and 1.8 mg once daily, exenatide once weekly and twice daily and lixisenatide once daily for the treatment of adults with insufficiently controlled type 2 diabetes as part of dual or triple therapy with oral antidiabetic medicines or as add-on therapy to basal insulin[2].

The CORE diabetes model is used to estimate the changes in total cost, total quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs) over a 50-year time horizon (base case) from an NHS perspective[20]. The CORE diabetes model is a web-based diabetes policy analysis tool which can be adapted to different treatment options and uses real-time simulations, standardised risk equations and patient level data to estimate disease progression based on 15 inter-dependent semi-Markov sub-models. It simulates progression of a variety of disease-specific complications (such as cardiac, arterial, ophthalmic and renal disease as well as ulcer and amputation), relevant physiological parameters (for example, HbA_{1c}, systolic blood pressure, lipids and body mass index) and the modification of the risk factors by treatment and predicts patient outcomes accordingly. The model assumes that patients are treated with semaglutide and the comparators for three years at which point these treatments are discontinued and treatment intensification takes place using alternative therapy options. No further treatment effects are modelled apart from the effects of hypoglycaemia.

Patient baseline characteristics (including demographics, ethnicity, biomarker risk factors and pre-existing co-morbidities), treatment effects on HbA_{1c}, blood pressure, cholesterol level and body mass index and severe and non-severe hypoglycaemic adverse events were obtained from the SUSTAIN 7 study for dual therapy[13], the SUSTAIN 3 two oral antidiabetic medicines subgroup[21] and entire SUSTAIN 3 population for triple therapy and the SUSTAIN 5 study for use as add-on to basal insulin therapy[16], as well as from published literature and indirect comparison and NMA conducted by the company. Diabetes-related mortality was taken from UK-specific life tables for 2017 published by the World Health Organization[22]. Complications due to concomitant medications and diabetes-related screening frequency were based on published values[23-26].

Cost data include treatment costs (including medication costs, insulin intensification, concomitant treatment, administration costs, costs associated with self-blood glucose monitoring and needles), cost of co-morbidities (such as myocardial infarction, stroke, eye complications, kidney disease, ulcer etc.) and management costs (cost of statins, aspirin, ACE inhibitors, screening costs and nurse time). Medicine costs were obtained from MIMS (March 2018)[27], published unit costs[28] and other costs were taken from various publications identified through a systematic literature review[29].

Health state utility values were taken from a systematic review of utility values and disutilities for type 2 diabetes economic modelling[30]. Disutilities are applied for adverse events and disease-related complications and body mass index above 25 kg/m^2 based on published values[30-32].

Extensive deterministic one-way sensitivity analysis as well as probabilistic sensitivity analysis and scenario analyses are undertaken to account for uncertainties and limitations of the data and test the robustness of the results to reasonable changes in values of key parameters.

4.2 Results

The results of the base-case analysis are detailed in Table 4. Semaglutide 1.0 mg and 0.5 mg as part of dual and triple therapy and as an add-on to basal insulin is reported to produce small increases in QALYs and slight cost savings and thus dominate all other GLP-1 receptor agonist treatment options available in Wales except lixisenatide where it is slightly more expensive but also more effective although remains cost effective.

Table 4. Results of the base case analysis[2]

As add-on to one antidiabetic medicine (dual therapy)			
	Semaglutide 0.5 mg	**Dulaglutide 1.5 mg**	**Difference**
Total cost per patient	¶¶	£21,693	¶¶
Total life-years	13.64	13.60	+0.04
Total QALYs per patient	9.00	8.96	+0.04
ICER (£/QALY gained)	¶¶		
	Semaglutide 1.0 mg	**Dulaglutide 1.5 mg**	**Difference**
Total cost per patient	¶¶	£21,693	¶¶
Total life-years	13.70	13.60	+0.10
Total QALYs per patient	9.06	8.96	+0.10
ICER (£/QALY gained)	¶¶		
As add-on to two antidiabetic medicines (triple therapy)			
	Semaglutide 0.5 mg	**Dulaglutide 1.5 mg**	**Difference**
Total cost per patient	¶¶	£22,422	¶¶
Total life-years	14.16	14.16	+0.01
Total QALYs per patient	9.32	9.31	+0.01
ICER (£/QALY gained)	¶¶		
	Semaglutide 1.0 mg	**Dulaglutide 1.5 mg**	**Difference**
Total cost per patient	¶¶	£22,422	¶¶
Total life-years	14.20	14.16	+0.05
Total QALYs per patient	9.37	9.31	+0.06
ICER (£/QALY gained)	¶¶		
	Semaglutide 0.5 mg	**Liraglutide 1.8 mg**	**Difference**
Total cost per patient	¶¶	£23,799	¶¶
Total life-years	14.16	14.13	+0.04
Total QALYs per patient	9.32	9.29	+0.03
ICER (£/QALY gained)	¶¶		
	Semaglutide 1.0 mg	**Liraglutide 1.8 mg**	**Difference**
Total cost per patient	¶¶	£23,799	¶¶
Total life-years	14.20	14.13	+0.08
Total QALYs per patient	9.37	9.29	+0.08
ICER (£/QALY gained)	¶¶		

	Semaglutide 0.5 mg	Liraglutide1.2 mg	Difference
Total cost per patient	¶¶	£22,744	¶¶
Total life-years	14.10	14.05	+0.05
Total QALYs per patient	9.27	9.22	+0.06
ICER (£/QALY gained)	¶¶		
	Semaglutide 1.0 mg	**Liraglutide1.2 mg**	**Difference**
Total cost per patient	¶¶	£22,127	¶¶
Total life-years	13.62	13.50	+0.12
Total QALYs per patient	8.97	8.86	+0.12
ICER (£/QALY gained)	¶¶		
As add-on to basal insulin			
	Semaglutide 0.5 mg	**Dulaglutide 1.5 mg**	**Difference**
Total cost per patient	¶¶	£37,160	¶¶
Total life-years	13.04	12.99	+0.05
Total QALYs per patient	7.76	7.71	+0.05
ICER (£/QALY gained)	¶¶		
	Semaglutide 1.0 mg	**Dulaglutide 1.5 mg**	**Difference**
Total cost per patient	¶¶	£37,160	¶¶
Total life-years	13.10	12.99	+0.11
Total QALYs per patient	7.82	7.71	+0.11
ICER (£/QALY gained)	¶¶		
	Semaglutide 0.5 mg	**Liraglutide 1.8 mg**	**Difference**
Total cost per patient	¶¶	£38,274	¶¶
Total life-years	13.04	13.03	+0.01
Total QALYs per patient	7.76	7.76	0.00
ICER (£/QALY gained)	¶¶¶		
	Semaglutide 1.0 mg	**Liraglutide 1.8 mg**	**Difference**
Total cost per patient	¶¶	£38,274	¶¶
Total life-years	13.10	13.03	+0.07
Total QALYs per patient	7.82	7.76	+0.06
ICER (£/QALY gained)	¶¶		
	Semaglutide 1.0 mg	**Lixisenatide 20 micrograms**	**Difference**
Total cost per patient	¶¶	£36,800	¶¶
Total life-years	13.10	12.90	+0.20
Total QALYs per patient	7.82	7.64	+0.19
ICER (£/QALY gained)	¶¶¶		

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year
¶¶: commercial in confidence figure removed
*Based on head-to-head study data; † Based on indirect treatment comparison using two oral diabetes medicines data only; § Based on network meta-analysis of dual and triple therapy data combined; ¶ Based on network meta-analysis

One-way sensitivity analysis showed that, for dual therapy, semaglutide at both doses remained dominant or cost-effective across all analyses when compared to dulaglutide. Probabilistic sensitivity analyses showed that, at a willingness-to-pay threshold of £20,000 per QALY gained, the probability of semaglutide 1.0 mg being cost effective compared with dulaglutide 1.5 mg is [commercial in confidence figure removed], respectively.

As part of triple therapy, semaglutide 1.0 mg remains dominant or cost-effective in all one-way sensitivity analyses. At the £20,000 per QALY gained threshold, the probability of semaglutide 1.0 mg being cost-effective is [commercial in confidence figure removed] compared with dulaglutide 1.5 mg, [commercial in confidence figure removed] compared with liraglutide 1.8 mg, and [commercial in confidence figure removed] compared with liraglutide 1.2 mg.

Considering add-on therapy to basal insulin, the probability of semaglutide 1.0 mg being cost-effective at £20,000 per QALY gained is [commercial in confidence figure removed] compared with dulaglutide 1.5 mg, [commercial in confidence figure removed] compared with liraglutide 1.8 mg, and [commercial in confidence figure removed] compared with lixisenatide.

Table 5 summarises the results of the scenario analyses.

Table 5. Results of scenario analyses[2]

Scenarios	ICER	Plausibility
Scenario 1: Comparing semaglutide 1.0 mg once weekly to exenatide 2.0 mg once weekly in triple therapy	Cost difference: ¶¶ QALY difference: 0.17 ¶¶	This scenario is plausible as exenatide once-weekly is an alternative GLP-1 receptor agonist treatment currently available and in use in Wales.
Scenario 2: Comparing semaglutide 0.5 mg once weekly to exenatide 2.0 mg once weekly in triple therapy	Cost difference: ¶¶ QALY difference: 0.05 ¶¶	This scenario is plausible as exenatide once-weekly is an alternative GLP-1 receptor agonist treatment currently available and in use in Wales.
Scenario 3: Comparing semaglutide 1.0 mg once weekly to exenatide 10 microgram twice daily in triple therapy	Cost difference: ¶¶ QALY difference: 0.12 ¶¶	This scenario is plausible as exenatide twice-daily is an alternative GLP-1 receptor agonist treatment currently available and in use in Wales.
Scenario 4: Comparing semaglutide 0.5 mg to lixisenatide 20 mg once daily in triple therapy	Cost difference: ¶¶ QALY difference: 0.11 ¶¶	This scenario is plausible as lixisenatide is an alternative GLP-1 receptor agonist treatment currently available and in use in Wales.
Scenario 5: Comparing semaglutide 1.0 mg to lixisenatide 20 mg once daily in triple therapy	Cost difference: ¶¶ QALY difference: 0.16 ¶¶	This scenario is plausible as lixisenatide is an alternative GLP-1 receptor agonist treatment currently available and in use in Wales.
Scenario 6: Comparing semaglutide 0.5 mg to exenatide 10 microgram twice daily in triple therapy	Cost difference: ¶¶ QALY difference: 0.08 ¶¶	This scenario is plausible as exenatide twice-daily is an alternative GLP-1 receptor agonist treatment currently available and in use in Wales.
Scenario 7: Comparing semaglutide 0.5 mg to lixisenatide 20 mg once daily as add-on therapy to basal insulin	Cost difference: ¶¶ QALY difference: 0.12 ¶¶	This scenario is plausible as lixisenatide is an alternative GLP-1 receptor agonist treatment currently available and in use in Wales.
Scenario 8: Comparing semaglutide 0.5 mg to exenatide 10 microgram twice daily as add-on therapy to basal insulin	Cost difference: ¶¶ QALY difference: 0.06 ¶¶	This scenario is plausible as exenatide twice-daily is an alternative GLP-1 receptor agonist treatment currently available and in use in Wales.

Scenario 9: Comparing semaglutide 1.0 mg to exenatide 10 microgram twice daily as add-on therapy to basal insulin	Cost difference: ¶¶ QALY difference: 0.12 ¶¶	This scenario is plausible as exenatide twice-daily is an alternative GLP-1 receptor agonist treatment currently available and in use in Wales.
¶¶: commercial in confidence figure removed GLP-1: glucagon-like peptide-1; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year		

Semaglutide 1.0 mg is cost-saving in most scenarios and dominates exenatide 2.0 mg once weekly and 10 microgram twice daily. Semaglutide 1.0 mg is [commercial in confidence figure removed] more expensive compared with lixisenatide but remains cost-effective at an ICER of [commercial in confidence figure removed].

4.3 AWTTC critique

The results of the base case cost-utility analysis show that using semaglutide as an add-on to one or two antidiabetic medicines and as an add-on to basal insulin produced small increases in QALYs with small cost savings in most analyses in people with type 2 diabetes mellitus.

The submission is characterised by strengths and limitations. Reasonable justifications are provided for the assumptions applied to the model.
Strengths of the economic analysis are as follows:

- The submission gives a very detailed and transparent account of the methods, data sources and analyses undertaken and the company acknowledges and addresses the main limitations by conducting extensive deterministic and probabilistic sensitivity analyses.
- The comparators included in the analysis appear appropriate as they include all licensed add-on therapies for the patient group with type 2 diabetes in need of triple therapy considering a GLP-1 receptor agonist.
- The CORE diabetes model is an externally validated and a regularly updated and reviewed web-based tool commonly used to assess health technologies for diabetes.
- The methodology of the systematic literature review, indirect comparisons of semaglutide versus dulaglutide, liraglutide, exenatide twice-daily and NMA informing the comparisons of semaglutide versus liraglutide 1.2 mg and 1.8 mg, lixisenatide and exenatide once-weekly in dual, triple and add-on therapy to basal insulin appears robust and valid and the company acknowledges, and where possible addresses, any sources of bias and uncertainty.

Limitations of the economic analysis include:

- The analyses are limited by a lack of head-to-head study data which are only available for the comparison of semaglutide to dulaglutide (from the SUSTAIN 7 study[13]) and exenatide once-weekly (from SUSTAIN 3 study[14]). The remainder of analyses rely on data from indirect treatment comparisons and NMAs which will introduce bias and uncertainty.
- Efficacy data for a number of the triple therapy comparisons of semaglutide with liraglutide, exenatide and lixisenatide (relating to various dosage comparisons) were based on an NMA combining data of one and two oral antidiabetic treatments. The inclusion of studies investigating dual therapy in the triple therapy comparison will introduce bias, the extent of which is impossible to predict.
- While the CORE diabetes model is a validated and frequently used online tool, it lacks transparency in its methods and coding. Furthermore, due to the large volume of detail to support the extensive number of analyses provided by the company, it is difficult to follow and cross-check the model to the results reported by the company.

- The model assumes that patients remain on GLP-1 receptor agonists for three years after which treatment is intensified with insulin. It is unclear how appropriate this assumption is in relation to Welsh current practice.
- Furthermore, efficacy data over the three-year treatment period are based on study follow-up data over 30 to 56 weeks. It is therefore unclear whether efficacy would be sustained over the three years. Any change or reduction in efficacy would affect the model results.
- Utility values are based on a systematic review which includes references between 1995 and 2013[30]. Because some of these sources are dated, changes in diabetes care in recent years may affect patient quality of life and reduce applicability of utility and disutility values to the current population of type 2 diabetes patients.
- In general, while semaglutide 1.0 mg dominates other comparators in the base case analysis, differences in costs and QALYs are very small and the uncertainties around the key parameters will make the ICER inherently unstable which could cause the results to shift. This is reflected in the relatively low probabilities of semaglutide being cost-effective at the £20,000 threshold despite it dominating its comparators in the base case. However, the company has addressed this in extensive sensitivity analyses which showed that semaglutide remained dominant and cost-effective, respectively, in all analyses.

4.4 Review of published evidence on cost-effectiveness

A literature search by AWTTC did not identify any studies relevant to the cost-effectiveness of semaglutide compared with other GLP-1 receptor agonists as part of dual and triple therapy and as an add-on to basal insulin in adults with insufficiently controlled type 2 diabetes.

5.0 BUDGET IMPACT

5.1 Context and methods

The company estimates a current prevalence of type 2 diabetes in Wales of 156,570 adults. This is based on an adult population of 2,485,244[33] of which 7% have diabetes[34] with 90% having type 2 diabetes[35]. An annual incidence of 2,651 people is applied based on an increase of 2,946 people diagnosed with diabetes in Wales between 2016 and 2017[4] of whom 90% are assumed to be diagnosed with type 2 diabetes. Annual mortality rate is assumed to be 1.6% taking into account general population mortality[36] adjusted for the standardised mortality rate for people with type 2 diabetes[37]. Of all people with type 2 diabetes, 4.09% are thought to be treated with GLP-1 receptor agonists[38] with an estimated uptake of semaglutide of 5% in Year 1, increasing to 25% in Year 5. This results in 320 people receiving semaglutide in Year 1 and 1,606 in Year 5. GLP-1 receptor agonist treatment costs were calculated based on list prices[27] taking into account an average GLP-1 receptor agonist discontinuation rate of 6.67%[13] and including the cost of needles[11] where not included in the pack. Treatment costs were then weighted according to market share[39].

5.2 Results

The estimated net budget impact is presented in Table 6. The company estimates that cost-savings of [commercial in confidence figure removed] could be made after introduction of semaglutide over a five-year period because the cost of many displaced GLP-1 receptor agonists is higher (liraglutide 1.8 mg as well as liraglutide 1.2 mg) or similar (dulaglutide, exenatide once-weekly) and no additional cost of needles is accrued.

Table 6. Company reported costs associated with the use of semaglutide[2]

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients (all licensed indications)	156,673	156,775	156,875	156,974	157,071
Sub-population of eligible patients (on GLP-1 receptor agonist treatment)	6,408	6,412	6,416	6,420	6,424
Uptake of new medicine (%)	5.00%	10.00%	15.00%	20.00%	25.00%
Number of patients receiving new medicine	320	641	962	1,284	1,606
Medicine acquisition costs in a market without new medicine	£6,064,695	£6,069,952	£6,071,863	£6,076,918	£6,080,783
Medicine acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶
Net supportive medicines costs	£0	£0	£0	£0	£0
Net medicine acquisition costs (savings/costs) - including supportive medicines where applicable	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶: commercial in confidence figure removed					

Semaglutide and dulaglutide include needles in the medicine acquisition costs but these are additional costs at the point of dispensing for liraglutide, exenatide twice-daily and lixisenatide. Depending on needle costs, which range from £2.19 to £30.08 per 100 needles; this could result in additional cost savings between [commercial in confidence figure removed] over five years.

The company presents extensive sensitivity analysis including changes to the impact of needle price (highest and lowest available brands), semaglutide-specific discontinuation rate, proportion of patients with type 2 diabetes treated with GLP-1 receptor agonists (+/- 10%), uptake of semaglutide (2.5%, 5%, 7.5%, 10%, 12.5% or 10%, 20%, 30%, 40%, 50%), prevalence of type 2 diabetes (+/-10%), annual mortality associated with type 2 diabetes (+/-10%), dulaglutide market share (24.9% all years or 24.9%, 27.39%, 29.88%, 32.37%, 34.86%), and lixisenatide market share (5.4% or 0%). The results show that semaglutide offers a cost saving of between [commercial in confidence figures removed] over five years in all but one scenario; this scenario is where semaglutide displaces all lixisenatide market share and is associated with additional cost of [commercial in confidence figure removed] over the five-year period. Using the actual discontinuation rate for semaglutide of 9.67% results in cost savings of [commercial in confidence figure removed] over 5 years.

5.3 AWTTC critique

Strengths and weaknesses of the budget impact analysis are as follows:

- The submission gives a detailed and transparent account of the methods and data sources used in the budget impact analysis.
- Prevalence, incidence and mortality rates are assumed to remain constant over the five-year time horizon. It is unclear how realistic the forecasted patient numbers are.

- Uptake rates are estimates and any changes to the uptake rate will affect the budget impact of semaglutide.

5.4 Comparative unit costs

Annual acquisition costs for different treatment regimens used as add-on (dual or triple therapy) treatments of type 2 diabetes are shown in Table 7.

Table 7. Examples of medicine acquisition costs

Regimens	Frequency and route of administration	Approximate annual cost per patient
Glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists)		
Semaglutide Ozempic®	1.0 mg once weekly: subcutaneous injection (28 days)	¶¶
Dulaglutide - Trulicity®	1.5 mg once weekly: subcutaneous injection (28 days)	£955.52
Liraglutide - Victoza®	0.6 mg, 1.2 mg or 1.8 mg once daily: subcutaneous injection (30-45 days)	£955.49–£1,435.80
Lixisenatide - Lyxumia®	20 micrograms once daily: subcutaneous injection (28 days)	£755.68
Exenatide - Byetta®	5 micrograms or 10 micrograms twice daily: subcutaneous injection (30 days)	£997.01
Exenatide - Bydureon®	2 mg once weekly: subcutaneous injection (28 days)	£956.96

¶¶: commercial in confidence figure removed

Not all regimens may be licensed for use in this patient population. See relevant Summaries of Product Characteristics for full licensed indications and dosing details[5,40-44].

Costs are based on Monthly Index of Medical Specialities (MIMS) list prices as of 1 June 2018[27], assuming vial wastage. Cost of semaglutide supplied by company[2]. Costs of administration and cost of needles are not included. This table does not imply therapeutic equivalence of drugs or the stated doses.

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