**Hertfordshire Medicines Management Committee (HMMC)**

**Semaglutide (Ozempic®) for Adults with Type 2 Diabetes**

**Recommended for Restricted Use in Primary, Community and Secondary Care**

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<td>Subcutaneous Glucagon-like peptide (GLP-1) receptor agonist</td>
<td>Type 2 diabetes in adults</td>
<td>December 2020 (Update from February 2019)</td>
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**HMMC Recommendation for Semaglutide as a GLP-1 Receptor Agonist (GLP-1 RA)**

**Option when a GLP-1 RA is indicated as Add-On Therapy in line with NICE Guideline NG28 for Type 2 Diabetes Mellitus (T2DM) in adults:**

1) **Green** - Restricted to be initiated in primary care for patients with no or mild diabetic retinopathy by healthcare professionals (GPs/practice pharmacists/nurses) with specialist interest and those who have undertaken the relevant training. Patients should have risks/benefits of treatment explained prior to initiation.

2) **Amber Initiation** - Recommended for restricted use following initiation by a specialist in secondary care or community setting in patients with moderate to severe retinopathy or maculopathy.

3) **Amber Protocol** - Patients initiated on a GLP-1 RA who are also on insulin should have a shared care protocol in place.

**Please note:** Each semaglutide pen is accompanied with needles to deliver the 4 doses available in each pen, therefore a single pen will last for one month**

NICE guidance recommends:

- Where triple therapy (metformin and 2 other oral antidiabetics) is not effective, not tolerated, or contraindicated, consider combination therapy with metformin, a sulfonylurea and a GLP-1 mimetic for adults with T2DM who:
  - have a BMI of 35 kg/m² or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or
  - have a BMI lower than 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA₁c and a weight loss of at least 3% of initial body weight in 6 months).

- In adults with type 2 diabetes, only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team.

**Background information**

Semaglutide is a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist. Semaglutide stimulates insulin secretion and inhibits glucagon secretion which reduces blood glucose, when the levels are high. The glucose and appetite effects are specifically mediated via GLP-1 receptors in the pancreas and the brain. Semaglutide reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite.

Semaglutide is administered weekly as it has an extended half-life. This may be injected via the subcutaneous route into the upper arm, abdomen or thigh. It may be administered at any time of day without regard for meals.

This HMMC recommendation is based upon the evidence available at the time of publication. The recommendation will be reviewed upon request in the light of new evidence becoming available.
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 of this treatment regime, the dose can be increased to 1mg once-weekly to further improve glycaemic control. Weekly doses higher than 1mg are not recommended. The day of weekly administration can be changed if required by the patient however there should be an interval of at least 3 days between 2 doses. (REF 1)

When semaglutide is added to existing therapy of sulfonylurea or insulin, the doses of sulfonylurea or insulin should be reduced accordingly to lower the risk of hypoglycaemia occurring (REF 1)

Semaglutide is available as pre-filled pens for subcutaneous injection. It is supplied as a clear, colourless solution. Each semaglutide pen is accompanied with needles to deliver the 4 doses available in each pen, therefore a single pen will last for one month. The cost of the needles are included in the cost of semaglutide and are not an additional cost. The pens are available in three doses supporting dose optimisation in individual patient needs

- Titration dose: 0.25mg
- Titration/maintenance dose: 0.5mg
- Maintenance dose: 1mg

New, unused pens must be stored in a refrigerator (2°C to 8°C) before use. Once in use, the pen must be stored for 56 days below 30ºC or in a refrigerator at 2°C to 8°C (REF 1)

**Key points**

- Semaglutide is a once weekly GLP-1 receptor agonist
- The SUSTAIN trials 1-7 (phase III RCTs) demonstrated superiority of semaglutide in glycaemic control and weight loss compared with dulaglutide, exenatide once weekly, sitagliptin and insulin glargine 100units/ml.
- SMC and AWMSG have approved Semaglutide as an option where GLP-1 analogues are indicated.
- The SUSTAIN 6 trial results found a statistically significant reduction in the risk of Major Adverse Coronary Events (MACE) when semaglutide was added to standard care. Confirming as required by regulators for new diabetes drugs - non-inferiority compared to placebo. A post-hoc analysis indicated that semaglutide was superior to placebo.
- 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. The Summary of Product Characteristics for semaglutide recommends caution when administering it to people with diabetic retinopathy who are taking insulin.
- For other adverse effects Semaglutide showed a similar safety profile to other GLP-1 receptor agonists.
- Current local data indicates that liraglutide and dulaglutide are the most frequently used GLP-1 analogues.
- Semaglutide has a flat price across its different strengths. AWMSG evaluated the cost-effectiveness of semaglutide Once Weekly(OW) 0.5mg and 1.0mg compared with both daily and weekly GLP1 analogues. The results were that semaglutide 1.0mg and 0.5mg is reported to produce small increases in QALYs and slight cost savings and thus dominate all other GLP-1 mimetic options except lixisenatide where it is slightly more expensive but also more effective although remains cost-effective.
- Exenatide was the first GLP-1 introduced to the market. The patent of exenatide expires at the end of November 2021. This may have an influence on future cost-effectiveness of GLP-1 analogues. Liraglutide (Victoza, Novo Nordisk Limited) patent expiry August 2022.
- Key patient factors in relation to choice of GLP-1 mimetics to considered include:
  - Once-weekly GLP-1 treatments may be more convenient than daily GLP-1 mimetics.
  - The pre-filled device of semaglutide is more convenient than dulaglutide once weekly. The semaglutide device requires the needle to be attached, whereas the dulaglutide device contains a pre-attached hidden needle which the patient will not need to handle or see (relevant in people with needle phobia or problems with manual dexterity).

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Dulaglutide does not require dose titration whereas semaglutide will need to be titrated slowly every 4 weeks to improve gastrointestinal tolerability.

Evidence of Clinical Effectiveness

The SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) programme consisted of 7 phase 3 randomised controlled trials (RCT) evaluating the safety and efficacy of semaglutide in adults with T2DM.

The primary objective in trials 1–5 and 7 was the glycaemic efficacy by measuring patient’s HbA1c. The SUSTAIN 6 trial focused on cardiovascular outcomes as the primary objective.

SUSTAIN 1: Monotherapy (REF2): A 30 week double blind, randomised, parallel-group, international, placebo-controlled phase 3 trial. Eligible participants (n=388) were treatment-naive individuals aged 18 years or older with type 2 diabetes treated with only diet and exercise alone for at least 30 days before screening, with a baseline HbA1c of 7.0%–10.0% (53–86 mmol/mol). Participants were randomly assigned (2:2:1:1) to either once-weekly subcutaneously injected semaglutide (0.5 mg or 1.0 mg), or volume-matched placebo (0.5 mg or 1.0 mg). Mean baseline HbA1c was 8.05% (SD 0.85); at week 30, HbA1c significantly decreased by 1.45% (95% CI –1.65 to –1.26) with 0.5mg semaglutide (estimated treatment difference vs placebo –1.43%, 95% CI –1.71 to –1.15; p<0.0001), significantly decreased by 1.55% (–1.74 to –1.36) with 1.0 mg semaglutide (estimated treatment difference vs placebo –1.53%, –1.81 to –1.25; p<0.0001), and non-significantly decreased by 0.02% (–0.23 to 0.18) with placebo. Mean baseline bodyweight was 91.93 kg (SD 23.83); at week 30, bodyweight significantly decreased by 3.73 kg (95% CI –4.54 to –2.91) with 0.5 mg semaglutide (estimated treatment difference vs placebo –2.75 kg, 95% CI –3.92 to –1.58; p<0.0001), significantly decreased by 4.53 kg (–5.34 to –3.72) with 1.0 mg semaglutide (estimated treatment difference vs placebo –3.56 kg, –4.74 to –2.38; p<0.0001), and non-significantly decreased by 0.98 kg (–1.82 to –0.13) with placebo.

SUSTAIN 2 - Head to head vs. Sitagliptin (REF3): A 56-week, randomised, double-blind, double-dummy, active-controlled, parallel-group, multicentre trial to compare the efficacy and safety of semaglutide vs. sitagliptin. A total of 1,231 patients with type 2 diabetes inadequately controlled on metformin and/or thiazolidinediones were randomised, and received once-weekly semaglutide 0.5 mg, once-weekly, semaglutide 1 mg or once-daily sitagliptin 100 mg. The primary endpoint was change in HbA1c at week 56. The trial was designed with 80% power to jointly establish non-inferiority and superiority with respect to the primary outcome. The secondary endpoint was change in body weight.

Change from baseline in HbA1c: Semaglutide 1 mg was SUPERIOR to sitagliptin 100 mg: -17.6 mmol/mol (-1.6%) vs. -6.0 mmol/mol (-0.5%), [estimated treatment difference: -11.62 mmol/mol (-1.06%) 95% CI: -13.25 to 9.99 mmol/mol (-1.21 to -0.91%), p<0.0001] Semaglutide 0.5 mg was SUPERIOR to sitagliptin 100 mg: -14.4 mmol/mol (-1.3%) vs. -6.0 mmol/mol (-0.5%), [estimated treatment difference: -8.42 mmol/mol (-0.77%) 95% CI: -10.05 to -6.78 mmol/mol (-0.92 to -0.62%), p<0.0001]. Change from baseline in weight: Semaglutide 1 mg SUPERIOR weight loss to sitagliptin 100 mg: -6.1 kg vs. -1.9 kg, [estimated treatment difference: -4.20 kg, 95% CI: -4.91 to -3.49, p<0.0001] Semaglutide 0.5 mg SUPERIOR weight loss to sitagliptin 100 mg: -4.3 kg vs. -1.9 kg, [estimated treatment difference: -2.35 kg 95% CI: -3.06 to -1.63, p<0.0001]

SUSTAIN 3 – Head to head vs Exenatide Once Weekly (OW) (REF4): A 56-week, randomised, open-label, active-controlled, parallel-group, multicentre trial to compare the efficacy and safety of semaglutide vs. exenatide OW. A total of 813 patients with type 2 diabetes inadequately controlled on metformin, metformin and sulfonylurea or thiazolidinediones were randomised to receive once-weekly semaglutide 1 mg (n=404) or exenatide OW 2 mg (n=405). The primary endpoint was change in HbA1c at week 56, and the key secondary endpoint was change in body weight at week 56. Baseline HbA1c: 67.7 mmol/mol (8.3%). Baseline weight: 95.8 kg

Change from baseline in HbA1c:
• Semaglutide 1 mg SUPERIOR to exenatide OW: -16.8 mmol/mol (-1.5%) vs. -10.0 mmol/mol (-0.9%), estimated treatment difference: -6.78 mmol/mol (-0.62%) 95% CI: -8.70 to -4.86 mmol/mol (-0.80 to -0.44%).

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The primary outcome was the first incident of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke i.e. major adverse coronary events (MACE) at baseline. 83% of patients had established cardiovascular disease, chronic kidney disease, or both.

- Semaglutide 0.5mg or 1mg significantly reduced the risk of the primary composite endpoint by 26% compared with placebo added to standard of care (6.6% vs. 8.9%, ARR 2.3%, HR 0.74, 95% CI: 0.58 to 0.95. p<0.001 for non-inferiority, p=0.02 superiority, post-hoc analysis).

- Semaglutide 0.5mg or 1mg significantly reduced the risk of non-fatal stroke by 39% compared with placebo added to standard of care (1.6% vs. 2.7%, ARR 1.1%, HR 0.61, 95% CI: 0.38 to 0.99, p=0.04).

- Nonfatal myocardial infarction occurred in 2.9% of the patients receiving semaglutide and in 3.9% of those receiving placebo (hazard ratio, 0.74; 95% CI, 0.51 to 1.08; P = 0.12); Rates of death from cardiovascular causes were similar in the two groups.

The SUSTAIN-6 trial achieved the primary endpoint confirming the non-inferiority of MACE with semaglutide compared to placebo and a post-hoc analysis indicated that semaglutide was superior to placebo for the primary outcome.

A comparison to other cardiovascular trial data is covered in the safety section of this ethical framework.

SUSTAIN 7 Head to head vs. dulaglutide 

A 40-week, randomised, open-label, active-controlled, parallel-group, multicentre, multinational, four-armed trial to compare (pairwise) the efficacy and safety of semaglutide vs. dulaglutide. A total of 1,201 patients with type 2 diabetes inadequately controlled on metformin were randomised, and received semaglutide 0.5 mg (n=301), semaglutide 1 mg (n=300), dulaglutide 0.75 mg (n=299) or dulaglutide 1.5 mg (n=299) once-weekly. Pre-trial dose of metformin continued throughout the trial. The primary endpoint was change in HbA1c at week 40, and the key secondary endpoint was change in body weight at week 40.

Baseline HbA1c: 66.4 mmol/mol (8.2%). Baseline weight: 95.2 kg

Change from baseline in HbA1c:
- Semaglutide 1 mg SUPERIOR to dulaglutide 1.5 mg: -19.4 mmol/mol (-1.8%) vs. -14.9 mmol/mol (-1.4%), estimated treatment difference: -4.47 mmol/mol (-0.41%) 95% CI: -6.2 to -2.7 mmol/mol (-0.57 to -0.25%), p<0.0001
- Semaglutide 0.5 mg SUPERIOR to dulaglutide 0.75 mg: -16.5 mmol/mol (-1.5%) vs. -12.1 mmol/mol (-1.1%), estimated treatment difference: -4.37 mmol/mol (0.40%) 95% CI: -6.1 to -2.7 mmol/mol (-0.55 to -0.25%), p<0.0001

Proportion achieving HbA1c <53 mmol/mol (7.0%):  
- Semaglutide 1 mg SIGNIFICANTLY more patients compared with dulaglutide 1.5 mg: 79% vs. 67%, p=0.0021
- Semaglutide 0.5 mg SIGNIFICANTLY more patients compared with dulaglutide 0.75 mg: 68% vs. 52%, p<0.0001

Change from baseline in weight:
- Semaglutide 1 mg SUPERIOR weight loss to dulaglutide 1.5 mg: -6.5 vs. -3.0 kg, estimated treatment difference: -3.55 kg 95% CI: -4.32 to -2.78 kg, p<0.0001
- Semaglutide 0.5 mg SUPERIOR weight loss to dulaglutide 0.75 mg: -4.6 kg vs. -2.3 kg, estimated treatment difference: -2.26 kg 95% CI: -3.02 to -1.51 kg, p<0.0001

Proportion achieving ≥5% weight loss:
- Semaglutide 1 mg SIGNIFICANTLY more compared with dulaglutide 1.5 mg: 63% vs. 30%, p<0.0001
- Semaglutide 0.5 mg SIGNIFICANTLY more compared with dulaglutide 0.75 mg: 44% vs. 23%, p<0.0001

Proportion achieving ≥10% weight loss:
- Semaglutide 1 mg SIGNIFICANTLY more compared with dulaglutide 1.5 mg: 27% vs. 8%, p<0.0001
- Semaglutide 0.5 mg SIGNIFICANTLY more compared with dulaglutide 0.75 mg: 14% vs. 3%, p<0.0001

**Dual NICE target**

Up to twice as many patients achieve the dual NICE target with semaglutide vs. dulaglutide at 40 weeks.

- NICE target: HbA1c reduction of ≥11.0 mmol/mol (1%), and weight loss of ≥3% of initial body weight in 6 months:
  - Semaglutide 1 mg was superior to dulaglutide 1.5 mg: 68% vs. 35%. Odds ratio: 3.11. 95% CI: 2.17 to 4.57

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4.46, p<0.0001

- Semaglutide 0.5 mg was superior to dulaglutide 0.75 mg: 53% vs. 25%. Odds ratio: 2.82. 95% CI: 1.95 to 4.08, p<0.0001

All 7 trials confirmed the superiority of semaglutide over the comparators in achieving glycaemic control in adults with T2DM.

- Significantly more patients achieved an HbA1c target of <53 mmol/mol (7.0%) with semaglutide 1mg compared with dulaglutide, exenatide once weekly, sitagliptin 100mg and insulin glargine 100units/mL (mean dose 29.2 units) (p<0.0001 vs. exenatide once weekly, sitagliptin and insulin glargine and 0.0021 for semaglutide 1 mg vs. dulaglutide 1.5 mg).

- Significantly more patients achieved an HbA1c target of <53 mmol/mol (7.0%) with semaglutide 0.5mg compared with dulaglutide, sitagliptin 100 mg and insulin glargine 100 units/mL (p<0.0001 vs. sitagliptin and insulin glargine, p≤0.0001 for semaglutide 0.5mg vs. dulaglutide)

The secondary endpoint was the reduction in mean bodyweight, where semaglutide resulted in superior and sustained weight loss from baseline compared with dulaglutide, exenatide once weekly, sitagliptin and insulin glargine 100 units/mL (p<0.0001 for all comparisons).

Other relevant trials and meta-analysis
In the absence of head to head studies studies comparing semaglutide with liraglutide, lixisenatide and exanatide twice daily a network meta-analysis (NMA) in patients with diabetes uncontrolled on one or two antidiabetic medicines included 26 studies was included in the review conducted by The All Wales Medicines Strategy Group (AWMSG). The results showed that semaglutide 1mg caused statistically significantly greater reductions in HbA1c and body weight than liraglutide 1.8mg, exenatide 10mcg twice daily and dulaglutide 1.5mg. A second NMA in patients with diabetes receiving basal insulin was carried out using 8 studies. The results were similar, as the addition of semaglutide lead to significantly greater reductions in HbA1c and body weight than dulaglutide, liraglutide, lixisenatide and exenatide twice-daily.

SUSTAIN Study Limitations
The Scottish Medicines Consortium (SMC) in their review highlighted the follow limitations:

- 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.
- 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
- 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 agonist 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.

Safety
Regulatory guidance specifies the need to establish cardiovascular safety of new diabetes therapies in patients with type 2 diabetes in order to rule out excess cardiovascular risk

Comparator trials on cardiovascular outcomes with GLP-1 analogues
Liraglutide: The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial (n=59,340), demonstrated an ARR of 1.9% with a hazard ratio (HR) of 0.87 (95% CI 0.78, 0.97; P = 0.01 for superiority) for the primary composite outcome of cardiovascular death, nonfatal MI, and nonfatal stroke (major adverse cardiac events [MACE]) compared with placebo over 3.8 years. Each component of the composite contributed to the benefit, and the HR for cardiovascular death was 0.78 (95% CI 0.66, 0.93; P = 0.007; ARR 1.7%). The LEADER trial also demonstrated an HR of 0.85 (95% CI 0.74, 0.97; P 5 0.02; ARR 1.4%) for all-cause mortality (REF11)
The LEADER trial aimed to evaluate the effect on cardiovascular outcomes for liraglutide 1.8 mg versus placebo. There are no comparator data for the NICE-approved 1.2 mg dose. Prior to publication of the trial, it had been established by the preceding LEAD studies, published in 2009, that treatment with liraglutide was associated with slight decreases in weight and blood pressure; a mildly increased heart rate was also consistently reported across the LEAD program.

The LEADER study was heavily enriched with patients at high risk of having a CV event, with 81.3% of patients in the study having established CV disease at baseline. Whilst the study showed that liraglutide reduced the risk of a major adverse CV event in patients with established CV disease, there was no evidence of benefit in the 18.7% of patients with risk factors only for CV disease.

**Semaglutide**: In the Trial to Evaluate Cardiovascular and Other Longterm Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN 6) (n 5 3,297), semaglutide compared with placebo demonstrated an ARR of 2.3% with HR 0.74 for MACE (95% CI 0.58, 0.95; P 5 0.02 for superiority) over 2.1 years, but the reduction in events appeared to be driven by the rate of stroke rather than CVD death.

The SUSTAIN 6 study was heavily enriched with patients at high risk of having a CV event, with 83% of patients in the study having established CV disease at baseline. Whilst the study showed that semaglutide reduced the risk of a major adverse CV event in patients with established CV disease, there was no evidence of benefit in the 17% of patients with risk factors only for CV disease. The proportion of a typical type 2 diabetes population that has established CV disease is in the order of 21.6%.

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) compared exenatide extended-release with placebo over 3.2 years in 14,752 participants with type 2 diabetes. While the medication was safe (noninferior), the HR for MACE in the entire trial was 0.91 (95% CI 0.83, 1.0; P 5 0.06) not reaching the threshold for demonstrated superiority versus placebo; ARR was 0.8% (49). All-cause death was lower in the exenatide arm (ARR 1%, HR 0.86 [95% CI 0.77, 0.97]), but it was not considered to be statistically significant in the hierarchical testing procedure applied.

**Lixisenatide**, a short-acting GLP-1 receptor agonist, did not demonstrate CVD benefit or harm in a trial of patients recruited within 180 days of an acute coronary syndrome admission.

**Dulaglutide**: REWIND Cardiovascular outcomes trial – Dulaglutide

The Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial of the glucagon-like peptide 1 (GLP-1) receptor agonist dulaglutide (n=9901) was a multicentre, randomised, double-blind, placebo-controlled trial. It included a greater proportion of individuals with type 2 diabetes with high cardiovascular risk but without prior established cardiovascular disease (CVD) (68.5%), a higher female population (46.3%), and with longer follow-up (median 5.4 years) than prior CVOTs.

The primary outcome was the first occurrence of the composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes (including unknown causes), which was assessed in the intention-to-treat population. The primary major adverse cardiovascular event (MACE) outcome occurred in 2.7 per 100 patient-years with an HR of 0.88 (95% CI 0.79, 0.99) in favour of dulaglutide. There was no difference in the MACE effect in the subpopulations with and without a history of CVD, although the treatment effect of dulaglutide did not reach statistical significance when the groups were considered separately. All-cause mortality did not differ between groups 10.8% in the dulaglutide group vs 12.0% in the placebo group; HR 0.90, 95% CI 0.80-1.01; p=0.067).

The REWIND trial differs from previous cardiovascular outcomes trials with GLP-1 receptor agonists in several ways. First, the other trials were designed to show noninferiority to placebo with respect to cardiovascular events, whereas REWIND prospectively tested the hypothesis that dulaglutide was superior. Second, most of the participants in REWIND did not have previous cardiovascular disease or a previous cardiovascular event. Thus, the average cardiovascular incidence of participants assigned to placebo was 2.7%, which was lower than the annual placebo incidence rates for the same composite outcome of 3.9% or higher in the other trials. 2347 (47.4%) participants assigned to dulaglutide reported a gastrointestinal adverse event during follow-up compared with 1687 (34.1%) participants assigned to placebo (p<0.0001).
Taken together, it appears that among patients some GLP-1 receptor agonists may provide cardiovascular benefit, with evidence of benefit for liraglutide 1.8mg, dulaglutide and semaglutide, and less certain for exenatide. There is no evidence of cardiovascular benefit with lixisenatide.

Comments on limitations of the SUSTAIN 6 trial

**AWMSG comments**

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

**SMC comments**

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

**Other safety factors**

The SUSTAIN 6 trial found there to be a lower risk of new or worsening nephropathy with semaglutide, however the rates of retinopathy complications (the requirement for photocoagulation or the use of an intravitreal agent; vitreous haemorrhage; or blindness) were increased and occurred in 3% of patients on semaglutide vs 1.8% with placebo (HR, 1.76; 95% CI 1.11 to 2.78; p=0.02) (REF 7). The number needed to harm for the development of serious retinopathy was 77. A post-hoc analysis (REF 21) of the SUSTAIN 6 trial assessed semaglutide vs. placebo, both in addition to standard of care), and found 70.6% of patients with no history of diabetic retinopathy had no increase in the risk of retinopathy symptoms with semaglutide, however in the remaining 29.4% with previous history, a small number of patients did experience an early worsening of retinopathy symptoms.

During the SUSTAIN trials, semaglutide appeared to have a safe and well-tolerated profile. The side effects were of mild or moderate severity and of short duration. The most common adverse events reported were gastrointestinal (GI) disorders, primarily nausea as well as diarrhoea and vomiting. More patients discontinued semaglutide treatment because of adverse events, including gastrointestinal disorders, compared with other treatments. Patients with impaired renal function must carefully consider these GI adverse reactions as they may result in dehydration.

Semaglutide shows a similar safety profile to other GLP-1 mimetics as similar proportions of patients experienced adverse events in the SUSTAIN 3 study (75% for semaglutide 1mg and 76% for exenatide extended-release) and the SUSTAIN 7 study (69% for semaglutide 1.0 mg and 74% for dulaglutide 1.5 mg). The proportions of serious adverse events occurring 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).

There was low numbers of patients who developed severe or blood-glucose confirmed hypoglycaemia: 2% for semaglutide 1 mg and dulaglutide 1.5 mg (SUSTAIN 7); and 8% for semaglutide 1 mg and exenatide extended-release (SUSTAIN 3).

In SUSTAIN 7 there was a modest Increase in heart rate 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.

The product license in the SPC for semaglutide appears to be the same as liraglutide with no specific license for cardiovascular risk reduction but the SPCs reference the trials.

In relation to diabetic retinopathy concerns (Dec 2020):

- SUSTAIN 1-5 & 7 – showed that the proportion of subjects with adverse events of diabetic retinopathy were similar for semaglutide and comparators across the trials. However these trials did exclude patients with known proliferative retinopathy or maculopathy requiring acute treatment and subjects with baseline HbA1c >10.0/10.5% were not included
In SUSTAIN 6 - A significantly larger proportion of subjects had diabetic retinopathy complications with semaglutide compared with placebo. Compared with the overall SUSTAIN 6 study population, subjects who had event adjudication committee-confirmed diabetic retinopathy complications were characterised by:

- Having a longer duration of diabetes
- Higher baseline HbA1c
- Receiving insulin treatment at baseline
- Having a history of diabetic retinopathy
- Having a history of proliferative diabetic retinopathy at baseline
- Having a history of treatment with laser therapy or intravitreal

The Summary of Product Characteristics for Ozempic (https://www.medicines.org.uk/emc/product/9748/smpc) lists the following:

### 4.4 Special warnings and precautions for use Diabetic retinopathy

In patients with diabetic retinopathy treated with insulin and semaglutide, an increased risk of developing diabetic retinopathy complications has been observed (see section 4.8). Caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin. These patients should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded.

### 4.8 Undesirable effects Diabetic retinopathy complications

A 2-year clinical trial investigated 3,297 patients with type 2 diabetes, with high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose. In this trial, adjudicated events of diabetic retinopathy complications occurred in more patients treated with semaglutide (3.0%) compared to placebo (1.8%). This was observed in insulin-treated patients with known diabetic retinopathy. The treatment difference appeared early and persisted throughout the trial. Systematic evaluation of diabetic retinopathy complication was only performed in the cardiovascular outcomes trial. In clinical trials up to 1 year involving 4,807 patients with type 2 diabetes, adverse events related to diabetic retinopathy were reported in similar proportions of subjects treated with semaglutide (1.7%) and comparators (2.0%).

### Cost of treatment and Cost Effectiveness

Costs are based on MIMS list prices (2018)

- One semaglutide pen (Flat pricing across all doses, including needles): £73.25
- Annual cost per year*: £955.52

Each semaglutide pen is accompanied with 4 needles, as each pen delivers 4 doses. Therefore the cost of semaglutide includes the needles.

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

Costs are based on MIMS list prices (2018)

Costs of administration and cost of needles are not included. This table does not imply therapeutic equivalence of drugs or the stated doses.
According to ePACT prescribing data for Hertfordshire- Liraglutide and Dulaglutide are locally the most frequently used GLP-1 mimetics.

Semaglutide is cost-neutral compared with other once-weekly GLP-1 mimetics, and slightly cost saving compared to exenatide once weekly. Several of the SUSTAIN trials found semaglutide to have lower costs with better clinical outcomes vs. dulaglutide and exenatide once weekly over patients’ lifetimes due to lower incidence of diabetes-related complications.

Exenatide was the first GLP-1 introduced to the market. The patent of exenatide expires in November 2021. This may have an influence on future cost-effectiveness of GLP-1 analogues.

AWMSG evaluated the cost-effectiveness of semaglutide OW 0.5mg and 1.0mg compared with dulaglutide 1.5mg OW, liraglutide 1.2mg and 1.8mg once daily, exenatide OW 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 an add on therapy to basal insulin. The results were that semaglutide 1.0mg and 0.5mg is reported to produce small increases in QALYs and slight cost savings and thus dominate all other GLP-1 mimetic options except lixisenatide where it is slightly more expensive but also more effective although remains cost-effective. AWMSG advised that in general, while semaglutide 1.0mg 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 dominating its comparators in the base case.

From local prescribing data the introduction of semaglutide in drug costs would be cost neutral as the most displaced GLP-1 receptor mimetics would be liraglutide 1.2mg, dulaglutide which have similar costs.

### The needs of the population

The needs of the population appear to be moderate to low as there are other GLP-1 mimetics on the market approved by NICE. In patients with established cardiovascular disease GLP-1 analogues, like semaglutide, with proven cardiovascular benefit may be preferred. There are many alternative antidiabetic drugs including insulin which in combination with other treatment options can help achieve glycaemic control such as weight management programmes (dietary advice and physical activity programmes).

### The needs of the community

The needs of the community are high as the incidence of diabetes is increasing nationally. The impact on the health economy appears to be low as semaglutide when used in its recommended place in therapy (NICE) appears to be cost effective.

### Policy Drivers

**NICE:** Not considered. The manufacturers Novo Nordisk have requested NICE to scope semaglutide on the grounds that the evidence for it is different to that of other GLP-1 analogues. The HMMC recommendation will be reviewed in line with any future guidance from NICE (See [https://www.nice.org.uk/guidance/proposed/gid-ta10438](https://www.nice.org.uk/guidance/proposed/gid-ta10438))

**All Wales Medicines Strategy Group (AWMSG):** Semaglutide (Ozempic®) is recommended as an option for restricted use within NHS Wales for the treatment of insufficiently controlled type 2 diabetes mellitus in adults as an add-on therapy to oral antidiabetic medicines or basal insulin. Semaglutide (Ozempic®) is not recommended for use within NHS Wales as monotherapy when metformin is considered inappropriate due to intolerance or contraindications.

**Scottish Medicine Consortium (SMC):** Semaglutide is accepted for restricted use. In addition to other oral anti-diabetic medicines, or as an add on to basal insulin, as an alternative GLP-1 agonist

### Equity:

People with diabetes would be considered as disabled under the Equality Act. The change is that Semaglutide (Ozempic®) can be initiated by community or secondary care specialists or by primary care clinicians (like GPs, diabetes specialist nurses, diabetes specialist pharmacists) with expertise in the use of GLP-1 / Semaglutide (Ozempic®) for the treatment of patients with Type 2 Diabetes Mellitus (T2DM). The patients will be assessed for appropriateness before initiation of the treatment by a clinician.

This HMMC recommendation is based upon the evidence available at the time of publication. The recommendation will be reviewed upon request in the light of new evidence becoming available.
References
1) Ozempic® SmPC. Summary of Product Characteristics https://www.medicines.org.uk/emc/product/9748/smpc#PRODUCTINFO
5) Aroda, VR. 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):355-366

Implementability: No impact anticipated
This HMMC recommendation is based upon the evidence available at the time of publication. The recommendation will be reviewed upon request in the light of new evidence becoming available.