NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Semaglutide for reducing the risk of major adverse cardiovascular events in people with cardiovascular disease and overweight or obesity

1 Recommendation

1.1 Semaglutide (up to a maintenance dose of 2.4 mg once weekly) can be used, within its marketing authorisation, alongside a reduced-calorie diet and increased physical activity, as an option for reducing the risk of a major adverse cardiovascular event (that is, cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with both:

- established cardiovascular disease (CVD), defined as at least 1 of the following:
  - previous myocardial infarction
  - previous ischaemic or haemorrhagic stroke
  - symptomatic peripheral arterial disease (they have intermittent claudication with an ankle-brachial index of less than 0.85 at rest, or have had a peripheral arterial revascularisation procedure or an amputation because of atherosclerotic disease), and
- a body mass index (BMI) of at least 27 kg/m^2.

Semaglutide can only be used if the company provides it according to the commercial arrangement (see section 2).

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What this means in practice

Semaglutide must be funded in the NHS in England for the condition and population in the recommendation, if it is considered the most suitable treatment option. Semaglutide must be funded in England within 90 days of final publication of this guidance. This guidance does not specify which setting semaglutide should be used in.

Further information on the secondary prevention of cardiovascular events is available in:

- NICE's guideline on acute coronary syndromes
- NICE's guideline on cardiovascular disease: risk assessment and reduction, including lipid modification
- NICE's clinical guideline on peripheral arterial disease: diagnosis and management.

There is enough evidence to show that semaglutide provides benefits and value for money, so it can be used routinely across the NHS in this population.

Why this recommendation was made

Standard care for established CVD in people with a BMI of at least 27 kg/m^2 includes lifestyle changes and medicines aimed at reducing the risk of a major adverse cardiovascular event.

Clinical trial evidence shows that semaglutide plus standard care reduces the risk of a major adverse cardiovascular event compared with placebo plus standard care in this population.

The cost-effectiveness estimates for semaglutide are within the range that NICE considers an acceptable use of NHS resources. So, it can be used.

2 Information about semaglutide

Marketing authorisation indication

2.1 Semaglutide (Wegovy, Novo Nordisk) is indicated 'as an adjunct to a reduced-calorie diet and increased physical activity to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight (body mass index [BMI] ≥27 kg/m^2)'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for semaglutide.

2.3 For this evaluation, semaglutide was considered at a maximum maintenance dose of 2.4 mg once weekly.

Price

2.4 The list price of semaglutide 2.4 mg is £175.80 per pack, of 1.7 mg is £124.53 per pack, and of 0.25 mg, 0.5 mg and 1.0 mg is £73.25 per pack (excluding VAT; BNF online accessed March 2026). Each pack contains 1 pen that delivers 4 doses.

2.5 The company has a commercial access agreement. This makes semaglutide available to the NHS with a discount. The details of this agreement are commercial in confidence.

Sustainability

2.6 Information on the Carbon Reduction Plan for UK carbon emissions for Novo Nordisk will be included here when guidance is published.

3 Discussion

This topic was done as a streamlined evaluation by the committee chair, vice chair and a subset of committee members (from here, the lead team). The lead team considered evidence submitted by Novo Nordisk, a review of this submission by the external assessment group (EAG) and responses from stakeholders. See the committee papers for full details of the evidence and NICE's manual on technology appraisal and highly specialised technologies guidance for more information on streamlined evaluations.

The condition

3.1 Cardiovascular disease (CVD) is usually associated with atherosclerosis, hypertension and an increased risk of thrombosis. The population in this evaluation includes people with established CVD. For the purposes of this evaluation, this is defined as people who have already had a myocardial infarction (MI) or an ischaemic or haemorrhagic stroke, or who have symptomatic peripheral arterial disease (PAD). This is in line with the population in the key clinical trial, SELECT (see section 3.3). People with established CVD are at high risk of having secondary cardiovascular events. Having a higher body mass index (BMI) also increases the risk of cardiovascular events.

Treatment pathway and positioning of semaglutide

3.2 Standard care for CVD includes lifestyle changes and medicines aimed at reducing the risk of secondary cardiovascular events. Lifestyle changes include improving diet, increasing physical activity, reducing alcohol intake, stopping smoking and managing weight. Medicines may include antihypertensive, lipid-lowering, antiplatelet and anticoagulant treatments. Semaglutide is positioned as another treatment option alongside standard care for the secondary prevention of cardiovascular events.

Clinical effectiveness

Clinical trials

3.3 The company presented evidence for semaglutide in this indication from SELECT, a multinational randomised double-blind placebo-controlled phase 3 trial. It enrolled 17,604 people with a BMI of at least 27 kg/m^2 and established CVD. Established CVD was defined as having had an MI, or ischaemic or haemorrhagic stroke, or having symptomatic PAD. Symptomatic PAD was defined as having 1 of the following:

- intermittent claudication with an ankle-brachial index (the ratio of systolic blood pressure in the ankle to the arm) of less than 0.85 at rest
- a peripheral arterial revascularisation procedure, or
- an amputation because of atherosclerotic disease.

The trial compared subcutaneous once-weekly semaglutide plus standard care (n=8,803) with placebo plus standard care (n=8,801). Standard care in SELECT included healthy lifestyle counselling and medicines to lower cardiovascular risk. Trial investigators were encouraged to optimise medicines according to treatment guidelines or local clinical practice. Treatments used by people in the trial included lipid-lowering medicines (90.1%), antiplatelet drugs (86.2%), beta-blockers (70.2%), angiotensin-converting-enzyme inhibitors (45.0%) and angiotensin-2 receptor antagonists (29.5%). The primary endpoint was the time from randomisation to first occurrence of a major adverse cardiovascular event (MACE) after randomisation. This was a composite endpoint consisting of cardiovascular death, non-fatal MI or non-fatal stroke. There was a statistically significant reduction in the risk of first MACE with semaglutide compared with placebo (hazard ratio [HR] 0.80; 95% confidence interval [CI] 0.72 to 0.90). The direction of effect was consistent across other secondary endpoints, including individual components of MACE:

- non-fatal MI (HR 0.72, 95% CI 0.61 to 0.85)
- non-fatal stroke (HR 0.93, 95% CI 0.74 to 1.15)
- coronary revascularisation (HR 0.77, 95% CI 0.68 to 0.87)
- hospitalisation for unstable angina (HR 0.87, 95% CI 0.67 to 1.13)
- heart failure hospitalisation or urgent heart failure visit (HR 0.79, 95% CI 0.60 to 1.03)
- cardiovascular death (HR 0.85, 95% CI 0.71 to 1.01)
- all-cause death (HR 0.81; 95% CI: 0.77 to 0.93).

The company also provided supportive evidence from the STEP-HFpEF and STEP-HFpEF DM trials. These trials compared semaglutide with placebo in people with heart failure and a preserved ejection fraction, and a BMI of at least 30 kg/m^2, with and without type 2 diabetes. But because these trials did not report outcomes directly relevant to this evaluation (that is, a reduction in MACE), the focus of the evaluation was the SELECT trial only. The lead team noted that the population in SELECT was aligned with the final scope and decision problem addressed by the company. It concluded that SELECT was appropriate for informing the lead team's recommendation.

Generalisability of SELECT to people with diabetes

3.4 SELECT excluded people with diabetes, but they are not excluded from the marketing authorisation for this indication. The company provided additional evidence to support using semaglutide in people with type 2 diabetes. This included evidence from 4 cardiovascular-outcomes trials, which showed that semaglutide reduced the risk of MACE in people with type 2 diabetes compared with placebo. The EAG noted that the cardiovascular-outcomes trials used different doses or routes of administration for semaglutide, and there were no specific inclusion criteria for previous cardiovascular events or BMI. But it was noted that a substantial proportion of people across the trials were relevant to this indication (that is, people who had had a previous cardiovascular event,

and people with overweight or obesity). The lead team noted that there were some limitations with the evidence presented by the company. But it also noted that the evidence showed a similar effect size for people with type 2 diabetes as that seen in SELECT. The lead team concluded that the clinical effectiveness of semaglutide seen in SELECT was likely to be generalisable to people with diabetes. So, it also concluded that this population should not be excluded from the recommendation.

Generalisability of SELECT to people with recent cardiovascular events

3.5 SELECT excluded people who had had any of the following cardiovascular events within 60 days before the day of screening:

- an MI
- a stroke
- a transient ischaemic attack
- hospitalisation for unstable angina.

But these groups are not excluded from the marketing authorisation for this indication. The company explained that excluding people with a recent cardiovascular event is common in cardiovascular-outcomes trials such as SELECT. The company added that including people with a recent cardiovascular event may confound and complicate the determination of primary and secondary endpoints in trials. This is because these groups may be at a higher risk of complications that are not preventable or modifiable by the study drug. The EAG noted that the clinical effectiveness of semaglutide in reducing the risk of MACE was seen shortly after starting treatment, before any substantial effect on weight loss was reported. This shows that there is a mechanism of action independent of weight loss. The lead team noted that the risk of a cardiovascular event is highest shortly after a previous event. So, it thought that it was plausible that semaglutide could be more clinically and cost effective if used earlier. It concluded that the recommendation

should not be restricted based on the time since a cardiovascular event.

Economic model

Model structure

3.6 The company developed a state-transition model. People entered the model in the 'established CVD' health state (see section 3.1). The risk of a further cardiovascular event (first modelled event) was estimated using parametric survival (time-to-event) extrapolations fitted to data from SELECT. First modelled events included MI, stroke, hospitalisation for heart failure, hospitalisation for unstable angina and coronary revascularisation. People who survived the first modelled event entered a 'post-event' health state, in which they were at risk of further events. People in the post-event state who had the same event (for example, a second MI) returned to the same post-event health state. People who had a different event (for example, a stroke after an MI) entered a post-event health state for people with more than 1 modelled event. People had an ongoing risk of further events. The model also tracked the development of chronic kidney disease and type 2 diabetes separately. Cardiovascular-related or non-cardiovascular-related death could occur from any health state. The types of events that were modelled were based on the endpoints in SELECT. The EAG noted that the company had included some events in which the difference between treatment arms did not show statistical significance (see section 3.3). The EAG preferred to exclude these events from its base case. The lead team noted that the benefit of semaglutide in reducing the risk of these events was less certain. It also noted that excluding these events resulted in a moderate increase in the incremental cost-effectiveness ratio (ICER). But it was reassured that results across all endpoints were consistent, and most were statistically significant. The lead team concluded that these events should be modelled in this evaluation.

Stopping treatment

3.7 The company used data from SELECT to determine how long people were on treatment with semaglutide. This was then used to calculate the cost for semaglutide in the model. The company used data for median time to stopping treatment, which was defined as the first time being off treatment for over 35 days. This was then used to determine a constant cycle (4-week) stopping rate. The exact stopping rate is considered confidential by the company, so cannot be reported here. The EAG noted that it was unclear how well the company's constant stopping rate reflected the stopping of semaglutide over the whole period of SELECT and for the remainder of model time horizon. The lead team noted that it would have been more appropriate to fit a range of parametric extrapolations to the data on stopping semaglutide from SELECT to provide a more accurate extrapolation of treatment stopping. It noted that, without this analysis, the company's estimates of treatment stopping, and so the costs associated with semaglutide, were uncertain. But, given the low ICERs (see section 3.10), this was not likely to affect decision making.

Adjustment of cardiovascular-event rates after trial period

3.8 The company modelled the increased risk of cardiovascular events for people who had developed diabetes using hazard ratios based on de Jong et al. (2020). The company explained that it only applied these hazard ratios after the SELECT follow-up period to avoid double counting cardiovascular events observed in the trial. The company also assumed that people who stopped semaglutide had no further benefit and had the same risk of cardiovascular events as people having standard care. The EAG noted that the company's extrapolations already reflected cardiovascular outcomes for a population in which a proportion had developed type 2 diabetes or stopped semaglutide by the end of follow up. So, it preferred not to apply any additional adjustments to cardiovascular-event rates from the end of the trial follow-up period.

The lead team noted that the EAG's approach of not adjusting cardiovascular-event rates after the end of the trial period for people who have stopped semaglutide resulted in a substantial decrease in the ICER. The lead team discussed that the stopping rate for semaglutide may not be constant over time, as assumed by the company (see section 3.7). It added that, without long-term data, it could not be assumed that the stopping rate would not increase. This may have resulted in a smaller reduction in the risk of events for people having semaglutide compared with placebo, after the trial period. The lead team added that there was further uncertainty because the risks of developing type 2 diabetes, having a cardiovascular event and stopping semaglutide are not independent. Trial evidence on the relationship between stopping treatment, cardiovascular events and developing type 2 diabetes would have been helpful to understand whether the adjustment was needed. The lead team concluded that, without further evidence, it was not clear whether a separate adjustment should have been applied for people who developed type 2 diabetes or stopped semaglutide after the observed trial period. The lead team considered both the company's and EAG's approaches in decision making, and noted that the ICERs remained low regardless of which approach was used (see section 3.10).

Costs for healthy lifestyle counselling

3.9 As described in section 3.2, semaglutide is positioned alongside existing lifestyle interventions and medicines for established CVD. The company explained that, in SELECT, people in both arms were offered lifestyle advice (including leaflets) on healthy diet, smoking cessation and physical activity. It added that this represented standard care in clinical practice. The company's model did not include any healthy lifestyle counselling costs in either the semaglutide or placebo arms. The company assumed (based on clinical expert advice) that the lifestyle interventions that would be offered alongside semaglutide would be similar to those already offered to people with established CVD in practice. So, it thought that it

was reasonable to assume no additional lifestyle intervention costs would be associated with introducing semaglutide. Instead, it assumed that these costs would be covered by the health-state costs already applied in the model.

The EAG's clinical experts agreed with the company's approach. The lead team understood that the lifestyle intervention used in SELECT included healthy lifestyle counselling delivered 9 times in the first year of treatment, and 4 times a year in the following years on treatment. It considered whether the company's approach of not including a separate cost for healthy lifestyle counselling was appropriate and reflected clinical practice. It recalled that the effect of semaglutide was seen soon after starting treatment (see section 3.5), which suggested that the benefit of semaglutide was independent of weight loss. So, it was likely that the additional benefit of semaglutide was mostly independent of the lifestyle interventions offered. It also noted that the healthy lifestyle counselling used in SELECT was the same for people in both arms. So, the relative treatment effect should not have been affected. The lead team concluded that the additional cost of introducing healthy lifestyle counselling for people having semaglutide compared with standard care was uncertain. But it added that it would need to be substantial for semaglutide not to be cost effective, given the low ICERs (see section 3.10).

Cost-effectiveness estimates

3.10 The lead team preferred to include events in the model in which the difference between treatment arms did not show statistical significance (see section 3.6). When including this assumption, the ICERs ranged from £6,878 (using the EAG's approach to adjusting cardiovascular-event rates) to £14,594 (using the company's approach to adjusting cardiovascular-event rates). As well as the approach for adjusting cardiovascular-event rates, uncertainties were noted with:

- the modelled time on semaglutide (see section 3.7)
- the additional costs for healthy lifestyle counselling with semaglutide compared with standard care (see section 3.9).

The lead team discussed that its preferred ICERs were substantially lower than £20,000 per quality-adjusted life year (QALY) gained. Substantial increases in the costs associated with semaglutide would be needed for it to no longer be considered cost effective. So, the uncertainties around time on semaglutide and costs of healthy lifestyle counselling were acceptable. The lead team concluded that, even if plausible higher costs with semaglutide were included, its preferred ICERs would be below £20,000 per QALY gained.

Equality

3.11 The lead team noted that people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean ethnic backgrounds are at a higher risk for CVD at lower BMI thresholds. This means that BMI-based criteria for treatment eligibility may not account for ethnic variations in risk. The lead team acknowledged this. But it noted that recommending semaglutide for people with a baseline BMI lower than 27 kg/m^2 would fall outside of the marketing authorisation for semaglutide. It also noted there was no evidence of semaglutide's safety or efficacy in a population with a baseline BMI of lower than 27 kg/m^2 to justify this. The lead team concluded that recommending semaglutide in line with the marketing authorisation across all groups would protect patient safety and was a legitimate aim. The lead team also noted that people with language difficulties or cognitive impairments may have difficulty adhering to treatment plans and may struggle to self-administer semaglutide. But it discussed that this should not be a barrier to treatment and that implementation plans for such groups could help alleviate any inequalities issues. The lead team noted that any lifestyle interventions offered should

be accessible to all people, including those with language difficulties and cognitive impairment.

Conclusion

3.12 Clinical trial evidence shows that semaglutide plus standard care reduces the risk of a MACE compared with placebo plus standard care for people with established CVD (previous MI, stroke or PAD) and a BMI of at least 27 kg/m^2. The cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, semaglutide can be used.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendation in this evaluation within 90 days of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has established cardiovascular disease (previous myocardial infarction, previous ischaemic or haemorrhagic stroke, or symptomatic peripheral arterial disease [evidenced by intermittent claudication with an ankle-brachial index of less than 0.85 at rest, or a peripheral arterial revascularisation procedure, or an amputation because

of atherosclerotic disease]) and a body mass index of at least 27 kg/m^2 and the healthcare professional responsible for their care thinks that semaglutide is the right treatment, it should be available for use, in line with NICE's recommendation.

5 Evaluation committee members and NICE project team

Evaluation committee members

This topic was considered as a streamlined evaluation by the chair, vice chair and a subset of committee A.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

Chair

James Fotheringham

Vice Chair, technology appraisal committee A

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager, and an associate director or principal technical adviser.

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