NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Semaglutide for managing overweight and obesity

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using semaglutide in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using semaglutide in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 01 March 2022

Second appraisal committee meeting: 15 March 2022

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 Semaglutide is recommended as an option for weight management, including weight loss and weight maintenance, alongside a reduced-calorie diet and increased physical activity in adults, only if:

- they have at least 1 weight-related comorbidity and:
  - a body mass index (BMI) at least 35.0 kg/m^2, or
  - exceptionally, a BMI of 30.0 kg/m^2 to 34.9 kg/m^2 if they are referred to tier 3 services based on the criteria in NICE's clinical guideline on obesity: identification, assessment and management.

  Use lower BMI thresholds (usually reduced by 2.5 kg/m^2) for people from south Asian, Chinese, and Black African or Caribbean family backgrounds.

1.2 Prescribe semaglutide as part of a specialist weight management service with multidisciplinary input (such as a tier 3 or tier 4 service).

1.3 Only use semaglutide for a maximum of 2 years.

1.4 These recommendations are not intended to affect treatment with semaglutide that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Management of overweight and obesity in adults includes lifestyle measures alone or with orlistat, or referral to weight management services (such as tier 3 or 4), which might include liraglutide or bariatric surgery.

Clinical trial evidence shows that people lose more weight with semaglutide alongside supervised weight management support than with the support alone, and people lose more weight with semaglutide than with liraglutide. The evidence also

shows that semaglutide with lifestyle measures reverses prediabetes more frequently than lifestyle interventions alone, and may decrease the risk of cardiovascular disease.

People from some minority ethnic family backgrounds have an equivalent risk from obesity at a lower BMI than people from a White ethnic family background. Also, NICE's guideline on BMI recommends using lower BMI thresholds for people from south Asian, Chinese, and Black African or Caribbean family backgrounds when identifying the risk of developing type 2 diabetes and providing interventions to prevent it. So, a similar adjustment in the BMI threshold is appropriate when considering using semaglutide.

It is appropriate to use semaglutide alongside intensive lifestyle interventions that are provided in specialist weight management services because this is in keeping with the clinical trial.

For people who have at least 1 weight-related comorbidity and a BMI of at least 35 kg/m^2 or exceptionally a BMI of 30 kg/m^2 to 34.9 kg/m^2 and also meet the NICE criteria for referral to a tier 3 service, the cost-effectiveness estimates for semaglutide are likely to be within what is normally considered a cost-effective use of NHS resources. For these groups, semaglutide is recommended alongside intensive weight management in an appropriate multidisciplinary setting.

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 for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of ≥30 kg/m^2 (obesity), or ≥27 kg/m^2 to <30 mg/kg^2 (overweight) in the presence of at least one weight-related comorbidity'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics. An induction dose of 0.25 mg, titrated up every 4 weeks to 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg, is given, with a maintenance dose of 2.4 mg.

Price

2.3 The list price of semaglutide (Wegovy) 2.4 mg and 1.7 mg is commercial in confidence and cannot be reported here. The list price of semaglutide 0.25 mg, 0.5 mg and 1.0 mg is £73.25 per pack (4 pre-filled pens; excluding VAT; BNF online accessed January 2022).

3 Committee discussion

The appraisal committee considered evidence submitted by Novo Nordisk, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

Clinical need

Semaglutide would be a welcome new treatment option for people living with obesity

3.1 Overweight and obesity can be physically debilitating, and may lead to severe and potentially life-limiting conditions, fertility issues and symptoms such as skin infections. The social stigma associated with overweight and obesity can affect career prospects and self-confidence. The patient experts explained how obesity is a lifelong condition that needs medical intervention, can affect quality of life and has psychological and physical effects. They also explained that the ability to lose weight and maintain weight loss is challenging and a lifelong burden. This is despite people living with obesity having knowledge about lifestyle interventions including diet and increased physical activity. The patient experts explained that access to current treatment with liraglutide is limited to a specific population who have prediabetes and a risk factor for cardiovascular

disease. They thought that access to a new treatment option would provide hope for people living with obesity. Orlistat is the only other pharmacological treatment option available but is poorly tolerated by many people and rarely used. The patient experts also explained that, even after bariatric surgery, maintaining weight loss is challenging. The committee concluded that there is a large unmet need for many people living with obesity, and that semaglutide would be a welcome new treatment option.

Current management

Some people living with obesity are referred to specialist weight management services, usually called tier 3 services

3.2 The current management of overweight and obesity in the NHS is broadly structured into tiered services. Tier 1 services provide universal interventions such as population level health promotion and advice. Tier 2 services include community-based diet, nutrition, lifestyle, and behaviour change advice for up to 12 weeks. Tier 3 services provide longer and more comprehensive multidisciplinary team assessment and interventions. These include dietary, lifestyle and behaviour modification advice, with or without drug therapy, and psychological support. The clinical experts explained that tier 3 services are traditionally offered in secondary care but there are equivalent services with similar multidisciplinary team support in community settings in some regions. Tier 3 services are normally accessed for up to 2 years. They are usually accessed by people with a body mass index (BMI) of 35 kg/m^2 or more plus 1 or more comorbidities, or with a BMI of 40 kg/m^2 or more with or without comorbidities. The specific nature of the comorbidities needed for referral may have regional variation. The clinical experts explained that the average BMI in tier 3 is well above 35 kg/m^2, at 46 kg/m^2. Tier 3 services are also accessed by a small number of people with a lower BMI of 30 kg/m^2 to 35 kg/m^2 who have a complex comorbidity that would benefit from weight loss. The clinical experts explained that this group

currently represents only about 1.5% of people in tier 3. They typically include people with particularly complex health needs or other significant co-existing conditions, such as muscular dystrophy. The committee was aware that NICE's quality standard on obesity: clinical assessment and management states that adults with a BMI of 30 kg/m^2 or more for whom tier 2 interventions have been unsuccessful should have a discussion about the choice of alternative interventions for weight management, including tier 3 referral. NICE's clinical guideline on obesity: identification, assessment and management recommends that referral to tier 3 services is considered for people in particular circumstances. This includes when the person has a complex disease state or needs that cannot be managed adequately in tier 2. The committee noted that, in clinical practice, very few people with a BMI of 30.0 kg/m^2 to 34.9 kg/m^2 are currently being referred to tier 3 services. This is despite the much larger population prevalence of having a BMI of 30.0 kg/m^2 to 34.9 kg/m^2 than a BMI of 35.0 kg/m^2 or more. Tier 4 services provide similar multidisciplinary team interventions to tier 3, but also manage bariatric surgery and bariatric medicine. A patient expert noted that semaglutide could be useful for treating weight regain after bariatric surgery. The patient and clinical experts highlighted that access to tier 3 services varies across England. The committee recognised that specialist weight management services in tiers 3 and 4 are only accessed by some people living with obesity. It also noted that they are rarely accessed by people with a BMI of less than 35.0 kg/m^2.

Treatment setting

Semaglutide should be used as part of a package of care provided in a specialist weight management service

3.3 The marketing authorisation for semaglutide specifies that it should be used as an adjunct to a reduced-calorie diet and increased physical activity (see section 2.1). The clinical experts explained that, in the NHS, a sustained programme of lifestyle interventions, including diet and physical

activity advice and management is only available in tier 3 (or equivalent specialist weight management services) and tier 4 services. They also stated the importance of only offering semaglutide with these interventions because this was a requirement in the trial that showed favourable results. The clinical experts did not consider that semaglutide is a 'stand-alone' treatment. Although tier 2 services include diet, nutrition, lifestyle and behaviour change advice, they are only accessed for 12 weeks (see section 3.2). This is not long enough to establish treatment with semaglutide, which has a 16-week dose escalation period. Also, there is a marketing authorisation requirement for reassessment at 6 months to see if treatment should be continued. Tier 2 services also do not include the support of a multidisciplinary team. The committee agreed that semaglutide should be used alongside specialist weight management interventions. These include dietary and physical activity interventions, as specified in the marketing authorisation, delivered by a multidisciplinary team, as suggested by the clinical experts. The committee agreed that, without accompanying support, the trial results used in the cost-effectiveness modelling might not be achieved in clinical practice. The committee noted that tier 2 services could not support delivery of semaglutide. It concluded that tier 3 (or equivalent) and tier 4 services could provide multidisciplinary specialist weight management interventions for a sustained period, so would be the most appropriate setting for semaglutide use.

Population

Semaglutide is most appropriate for the population with the highest risk for the adverse effects of obesity

3.4 The NICE scope for this appraisal and semaglutide's marketing authorisation includes people with a BMI of 30 kg/m^2 or more (obese), or a BMI from 27 kg/m^2 to less than 30 kg/m^2 (overweight) and at least 1 weight-related comorbidity. The company presented evidence in its submission for its target population, which was a more restricted

population than the full marketing authorisation. It included people with a BMI of 30 kg/m^2 or more with at least 1 weight-related comorbidity. It suggested that these people may benefit most from pharmacological treatment and that they would be able to have treatment in specialist weight management services. The committee recalled that NICE's clinical guideline on obesity: identification, assessment and management recommends considering referral to tier 3 services in particular circumstances and that referral to tier 3 services isn't recommended for all people with a BMI of 30 kg/m^2 or more with any weight-related comorbidity. Only exceptionally, referrals are made for people within this population, for example, when the person has a complex disease state or needs that cannot be managed adequately in tier 2 (see section 3.2). The company also presented evidence for people with a BMI of 35 kg/m^2 or more with non-diabetic hyperglycaemia and high cardiovascular disease risk. This was in line with the population in NICE's technology appraisal guidance on liraglutide for managing overweight and obesity. At technical engagement, the company also presented a cost-effectiveness analysis for the full population in the NICE scope and marketing authorisation. The clinical experts explained that people with a BMI less than 30 kg/m^2 are not referred to tier 3 services. They added that these services are only rarely accessed by some people with a BMI between 30 kg/m^2 and 35 kg/m^2, and only if they have complex comorbidities (see section 3.2). The company agreed that it was acceptable to only consider semaglutide for people who are treated in tier 3 (or equivalent) or tier 4 services. It agreed that the population with a BMI between 27 kg/m^2 and 30 kg/m^2 or with a BMI between 30 kg/m^2 and 35 kg/m^2 without a weight-related comorbidity did not need further consideration. The committee agreed that this population was not generally at high enough risk for semaglutide use. NHS England proposed that a further population to consider is people with a BMI of 35 kg/m^2 or more and a high risk of cardiovascular disease based on risk factors. The patient experts explained that there was a potential disconnect between the needs of people living with obesity and current NHS provision within the tier system. The committee discussed

that current NHS specialist provision was clearly focused on providing intensive support for the highest risk population with a BMI of 35 kg/m^2 or more. It noted that stratifying by risk was a reasonable strategy in terms of absolute benefit. It also noted that very few people with a BMI of 30 kg/m^2 to 35 kg/m^2 are referred to tier 3 services. But, it agreed that people for whom tier 2 services have not been successful do have a potential route of referral based on criteria in NICE's clinical guideline on obesity (see section 3.2), although this rarely happens. If the recommendation for considering tier 3 referral in the NICE guideline were to be used more, it is not known how the population potentially eligible for semaglutide would or would not resemble the company's target population. The committee concluded that the appropriate population for semaglutide comprises people at the highest risk for the adverse effects of obesity, which is the population eligible for specialist weight management services.

Comparators

The comparators proposed by the company are appropriate

3.5 The company suggested that diet plus exercise was the appropriate comparator for semaglutide for its target population (people with a BMI of 30 kg/m^2 or more plus at least 1 weight-related comorbidity). For people with a BMI of 35 kg/m^2 or more, non-diabetic hyperglycaemia and a high risk of cardiovascular disease, liraglutide is recommended in NICE's technology appraisal guidance on liraglutide for managing overweight and obesity. So, liraglutide is the appropriate comparator for this population. The company proposed that orlistat should not be considered a comparator for semaglutide because it is not often used in practice. When it is, it is offered as a first-line option in primary care and would usually be tried before semaglutide would be considered. The clinical experts agreed that orlistat use is limited and that it is not a relevant comparator for semaglutide. The committee concluded that the appropriate comparators for semaglutide were:

- diet plus exercise for people with a BMI of 30 kg/m^2 or more and at least 1 weight-related comorbidity
- liraglutide for people with a BMI of 35 kg/m^2 or more, non-diabetic hyperglycaemia and a high risk of cardiovascular disease.

Clinical evidence

The population in STEP 1 does not reflect the population distribution of overweight and obesity in clinical practice

3.6 STEP 1 was a randomised double-blind trial that compared a semaglutide once-weekly injection with placebo. Both groups also had lifestyle intervention including counselling, a reduced-calorie diet and increased physical activity with 68-week treatment and follow up. It included adults living with obesity (BMI of 30 kg/m^2 or more) with or without a comorbidity, or with overweight (BMI of 27 kg/m^2 to 29.9 kg/m^2) with at least 1 weight-related comorbidity. The comorbidities included hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease. People with type 2 diabetes were excluded from the trial. In the trial, 6.0% of people were categorised as having overweight (BMI of 27.0 kg/m^2 to 29.9 kg/m^2), 32.8% were categorised as having obesity category 1 (BMI of 30.0 kg/m^2 to 34.9 kg/m^2) and 61.2% were categorised as having obesity categories 2 or 3 (BMI of 35.0 kg/m^2 or more). The committee noted that this was the reverse of the weight distribution in clinical practice, where many more people would have a BMI of 30.0 kg/m^2 to 35.0 kg/m^2 than over 35.0 kg/m^2. The average BMI in the trial was 37.9 kg/m^2. The clinical experts explained that around 80% of people in tier 3 services have a BMI of 40.0 kg/m^2 or more and that 1.5% have a BMI of less than 35.0 kg/m^2 (see section 3.2). The company proposed that people with a BMI of 30.0 kg/m^2 or more with at least 1 comorbidity (its target population; see section 3.4) should be considered for semaglutide. This population made up 75.0% of STEP 1. The committee agreed that the company's target population was at higher risk than those outside the target population. However, it noted that only 32.8% of people in STEP 1 had a BMI of

30.0 kg/m^2 to 34.9 kg/m^2. However, if semaglutide was available for everyone with a comorbidity within this BMI range, as per the company's target population, it is highly likely that the average BMI of the treated population would be lower than the trial population. The committee recognised that the highest risk population should be treated. However, as more people with a lower BMI are included within a population, the less well this population would match the trial population. The committee also noted that any large increase in the number of people treated in specialist weight management services (with the associated multidisciplinary support) would have implications for service delivery and design. It acknowledged that this was outside its remit. However, it appreciated that it should be confident that the trial and modelled outcomes would be delivered in clinical practice if broader eligibility was to be accepted, and that it would be a cost-effective strategy for the NHS. The committee concluded that the population in STEP 1 had a larger proportion of a high-risk population and did not reflect the population distribution of overweight and obesity in clinical practice. It also concluded that the population in STEP 1 was unlikely to correspond with the distribution of people who could be eligible for semaglutide if everyone within the company's original target population (including anyone with a BMI of 30 kg/m^2 or more with any weight-related comorbidity) was recommended.

People with type 2 diabetes are not included in STEP 1, although they could be treated with semaglutide for weight management

3.7 The committee noted that STEP 1 did not include people with type 2 diabetes. It was aware that a lower dose of semaglutide is available for managing type 2 diabetes. The clinical experts explained that if someone with type 2 diabetes needs specialist weight management then it would be appropriate for them to have treatment for obesity within a tier 3 service (or equivalent). This would include semaglutide treatment at the higher dose indicated for managing overweight and obesity. They also explained that, based on their experience, they would expect people with type 2 diabetes to have less weight loss with semaglutide than seen in STEP 1.

This was also supported by data from the STEP 2 trial in people with type 2 diabetes. They noted that although people with type 2 diabetes would be likely to have less weight loss than people without type 2 diabetes, a small amount of weight loss is associated with greater health gain in a higher risk population such as this. The committee concluded that because STEP 1 did not include people with type 2 diabetes, it did not cover the whole population who would potentially be offered semaglutide in the NHS. The committee agreed that this introduced some uncertainty about the generalisability of the clinical-effectiveness results, and may have affected the reliability of the cost-effectiveness results.

Semaglutide is more effective than placebo for treating overweight and obesity

3.8 The company presented the full trial analysis and a post-hoc subgroup analysis of STEP 1. The full trial population (n=1,961) included adults living with obesity (BMI of 30 kg/m^2 or more) or overweight (BMI of 27 kg/m^2 to 29.9 kg/m^2) with at least 1 weight-related comorbidity. The post-hoc subgroup analysis (n=1,470) included adults with a BMI of 30 kg/m^2 or more with at least 1 weight-related comorbidity. Weight-related outcomes favoured semaglutide compared with placebo in the full trial population. The difference in mean percentage change in body weight at 68 weeks was -12.4%. It also favoured semaglutide in the post-hoc subgroup analysis. The difference in mean percentage change in body weight at 68 weeks was -12.2%. There was also an increase in the proportion of people shifting from non-diabetic hyperglycaemia to normoglycaemia from baseline to week 68 with semaglutide treatment. However, this was greater in the post-hoc subgroup analysis population than the full trial population. The proportion who shifted from non-diabetic hyperglycaemia to normoglycaemia in the full trial population was 79.8% with semaglutide compared with 39.1% with placebo (40.7% treatment difference). The proportion who shifted from non-diabetic hyperglycaemia to normoglycaemia in the post-hoc population was 79.2% with semaglutide compared with 20.0% with placebo (59.2% treatment

difference). The committee concluded that this analysis showed that semaglutide was clinically effective with benefits for weight and prediabetes in the full trial population and the post-hoc analysis subgroup.

Semaglutide is more effective than liraglutide for weight loss

3.9 Liraglutide is the appropriate comparator for people with a BMI of 35 kg/m^2 or more, non-diabetic hyperglycaemia and a high risk of cardiovascular disease (liraglutide-eligible subgroup; see section 3.5). At the time of submission, there was no head-to-head trial data available comparing semaglutide with liraglutide. So, the company presented an indirect treatment comparison using individual patient data from STEP 1 and SCALE 1839 (a randomised controlled trial of liraglutide compared with placebo) to estimate the effectiveness of semaglutide compared with liraglutide in the liraglutide-eligible subgroup. The results of the indirect treatment comparison showed that weight-related outcomes favoured semaglutide compared with liraglutide. The difference in mean percentage change in body weight at 68 weeks was -5.81%. At technical engagement, the company submitted direct head-to-head data for semaglutide compared with liraglutide (both alongside a lifestyle intervention) from the STEP 8 trial. STEP 8 was a randomised controlled trial including 388 adults living with obesity (BMI of 30 kg/m^2 or more) or overweight (BMI of 27 kg/m^2 to 29.9 kg/m^2) with at least 1 weight-related comorbidity (hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease) and without type 2 diabetes. Results for the full trial population supported the results from the indirect treatment comparison. The difference in mean percentage change in body weight at 68 weeks was -9.38%. The ERG explained that the results were for the full trial population and not the liraglutide-eligible subgroup. The company explained that the liraglutide-eligible subgroup made up a small proportion of the trial population so a subgroup analysis was not appropriate. The committee concluded that direct trial evidence for the subgroup would have been preferred. However, it agreed that the results from both the

indirect treatment comparison and the full population of STEP 8 showed that semaglutide is more effective than liraglutide for weight loss.

The company's economic model

The company's model is only suitable for decision making for treatment in specialist weight management services

3.10 The company submitted a cohort-transition model with 11 health states to estimate the cost effectiveness of semaglutide in 2 subgroups:

- compared with diet and exercise for people with a BMI of 30 kg/m^2 or more with at least 1 weight-related comorbidity
- compared with liraglutide for people with a BMI of 35 kg/m^2 or more with non-diabetic hyperglycaemia and a high risk of cardiovascular disease.

The treatment effects for each subgroup were sourced from the full trial population of STEP 1 and applied to the populations of interest with different baseline risks. The model was based on a previous model used for NICE's technology appraisal of liraglutide for managing overweight and obesity, and on assumptions and service use in a tier 3, or equivalent specialist multidisciplinary weight management, setting. People entered the model in a normal glucose tolerance state (46.6%) or non-diabetic hyperglycaemic state (53.4%), based on the prevalence in STEP 1. A once-only transition was used to incorporate the proportion of people reversing from non-diabetic hyperglycaemia to normal glucose tolerance based on STEP 1 data. Transitions between health states were based on type 2 diabetes status and cardiovascular events, estimated from risk equations. The committee expressed concern about the validity of risk equations (see section 3.15). However, it concluded that the perspective of use in tier 3 (or an equivalent specialist weight management service) was appropriate.

Assumptions in the economic model

It is reasonable to assume that people stop treatment after 6 months if they do not have an adequate response

3.11 The company included a stopping rule in the model for people who had less than 5% weight loss after 6 months. This was based on the marketing authorisation, which states that a decision on continuing treatment for these people should be made at 6 months. The clinical experts agreed that most people would not want to continue semaglutide treatment after 6 months without a greater benefit, especially considering the side effects associated with it. They explained that treatment assessment at 6 months was in line with what is expected in practice and that the stopping rule was appropriate. The committee concluded that it was appropriate to include the stopping rule for people with less than 5% reduction in body weight at 6 months in the model, in line with the marketing authorisation.

Obesity is a long-term condition, so limiting treatment to 2 years is not ideal

3.12 The company included an assumption in the model that people would take semaglutide for a maximum of 2 years, and that there would be no retreatment. The patient experts explained that obesity is a lifelong condition, and that continued treatment was important for maintaining weight loss. This is still a challenge after people have reached their target weight loss. They noted that having only 2 years of semaglutide treatment would not be ideal. However, they still thought it would be highly beneficial for helping weight loss over a 2-year period which would give people the opportunity to incorporate more physical activity into their lifestyles, with improved mobility and reduced pain. The model also included the assumption that there would be no retreatment with semaglutide. The clinical experts explained that some people who have regained weight after weight loss with semaglutide may wish to take it again. They also noted that rereferral into tier 3 services was not usual but does happen occasionally. The committee agreed that it may not be appropriate for

semaglutide treatment to be stopped after 2 years. It noted that treatment for other chronic conditions is not stopped after a certain period when it is tolerated and effective. It also agreed that retreatment with semaglutide may be appropriate for some people. The committee understood that the 2-year treatment course and lack of retreatment aligns with the time spent in tier 3 services. It also agreed that it was necessary to provide semaglutide alongside lifestyle interventions provided in such services (see section 3.3). The committee concluded that treating a chronic condition such as obesity for only 2 years is not ideal. However, it accepted that the model was based on a single course of treatment of no longer than 2 years. It concluded that the assumption that treatment would be stopped at 2 years without retreatment was reasonable in the context of NHS tier 3 services.

The assumptions for weight gain are uncertain

3.13 The company included an assumption that, at 3 years after stopping semaglutide (with a 2-year treatment period), weight would be in line with what it would be in the average population after 5 years of only diet and exercise. The company also assumed that people whose glucose tolerance became normal on treatment would revert to being prediabetic 3 years after treatment stopped. The clinical experts noted that the assumptions around the rate of weight gain after treatment are very uncertain. However, they thought that, on average, most people would regain an unspecified amount of weight after stopping semaglutide. The committee discussed that a 3-year period for weight regain was arbitrary, and the assumptions made would affect the cost-effectiveness estimates. It concluded that this was an area of significant uncertainty, with no evidence base to support whether 3 years was a reliable estimate.

The assumption that all people develop type 2 diabetes after a cardiovascular event is not correct

3.14 The company included a simplifying assumption in the model that all people who have a cardiovascular event develop type 2 diabetes within

the following year. The clinical experts explained that people are more likely to be diagnosed with type 2 diabetes after a cardiovascular event, but that this relationship is not causal. However, they did agree that some people would be diagnosed with type 2 diabetes after a cardiovascular event. So, because the model could only include this assumption for none or all of the people in the model, they thought it was reasonable to include it. The committee noted that the ERG's scenario analysis, which removed this assumption, had minimal effect on the incremental cost-effectiveness ratio (ICER). The committee concluded that the true proportion of people who would be diagnosed with type 2 diabetes would fall somewhere between none and all people who had a cardiovascular event.

The cardiovascular and diabetes risk equations are the only available method for modelling long-term health outcomes but are highly uncertain

3.15 The company's model used risk equations to estimate the risk of long-term cardiovascular events such as an acute coronary event or stroke, and the risk of developing type 2 diabetes. These equations were based on surrogate outcomes from STEP 1 including BMI, systolic blood pressure, total cholesterol, high density lipoprotein and HbA1c levels. The NHS England representative explained that the risk equations used had not been validated by any data showing beneficial cardiovascular outcomes with weight loss in people without diabetes. They quoted a real-world, large UK study (with a follow up of up to 6 years) that did not show a reduction in cardiovascular events related to sustained weight loss alone. The clinical experts highlighted that a reduction in cardiovascular events has been shown with GLP-1 inhibitors (the same class of drug as semaglutide) in people with diabetes. However, they accepted this had not yet been shown in people without diabetes. The committee was also aware that risk equations were based on an assumption of a steady state. They were not designed for estimating long-term risk when using an intervention with a time limited benefit (such as a 2-year treatment course; see section 3.12). Also, risk equations are not prognostic on an individual

basis. The ERG explained that there was no practical alternative to using risk equations in the modelling. The committee accepted that there was no data available on the effect of semaglutide treatment on long-term cardiovascular outcomes. However, it agreed that even a temporary improvement in weight, diabetic status and risk parameters seen with semaglutide in STEP 1 may reduce the long-term risk of cardiovascular events and development of type 2 diabetes, but that there was no evidence that this was the case. It noted that if the long-term cardiovascular outcomes included in the model were not realised, there could be a large increase in the cost-effectiveness results. The committee concluded that it had not been presented with any alternative method of estimating long-term health outcomes. So, it accepted that risk equations were the only method available, despite being highly uncertain.

Cost-effectiveness estimate

Because of the uncertainty the committee would have to have a high level of confidence that the ICER was no higher than £20,000 per quality-adjusted life year gained

3.16 NICE's guide to the methods of technology appraisal notes that, above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, decisions about the acceptability of a technology as an effective use of NHS resources will consider the degree of certainty around the ICER. The committee noted the uncertainties in the modelling assumptions, particularly:

- the rebound in weight gain after semaglutide is stopped (see section 3.13)
- the calculation of long-term benefits using risk equations based on data about a temporary benefit (see section 3.15)
- the possible implications for NHS delivery of services.

Based on these uncertainties, the committee agreed that it would need

to have a high level of confidence that the ICER would not be above £20,000 per QALY gained.

The ERG and company's assumptions are reasonable

3.17 The company's base-case analysis included:

- a stopping rule for people who have not lost at least 5% initial body weight at 6 months (see section 3.11)
- a maximum treatment duration of 2 years (see section 3.12)
- no retreatment throughout the full time horizon of the model (see section 3.12)
- weight regain in line with weight gain expected without semaglutide treatment, and a return to the original glycaemic state 3 years after stopping treatment (see section 3.13)
- that 100% of people with non-diabetic hyperglycaemia develop type 2 diabetes after a cardiovascular event (see section 3.14).

The ERG's base case included some of the same assumptions as the company's, with the following differences:

- people with hyperglycaemia do not automatically develop type 2 diabetes after a cardiovascular event (see section 3.14)
- there is a natural weight increase per year of 0.30 kg (compared with the company's assumption of 0.46 kg)
- weight no longer increases after age 66 (compared with the company's assumption of age 68)
- natural weight decreases by 0.30 kg after age 66 (compared with the company's assumption of weight remaining constant)
- the annual cost of sleep apnoea is £1,081 (compared with the company's assumption of £274).

The committee concluded that the company's and the ERG's assumptions were reasonable and that, individually, none of the

assumptions that differed between the analyses had a major effect on the ICER.

Semaglutide is cost effective compared with liraglutide in both the company's and ERG's base case

3.18 For the population who were eligible for liraglutide (people with a BMI of 35 kg/m^2 or more with non-diabetic hyperglycaemia and high cardiovascular risk), the company's base-case ICER was dominant (that is, semaglutide is more effective and costs less than liraglutide). The ERG's base-case ICER was £600 per QALY gained. The committee concluded that semaglutide was cost effective compared with liraglutide.

The ICERs for semaglutide compared with diet and exercise are uncertain, so a restricted version of the company's original target population is appropriate

3.19 The company presented cost-effectiveness estimates for semaglutide in comparison with diet plus exercise for people with a BMI of 30 kg/m^2 or more with at least 1 weight-related comorbidity (company's original target population; see section 3.4). For this population, the company's base-case ICER was £14,827 per QALY gained and the ERG's base-case ICER was £16,337 per QALY gained. In STEP 1, 60% of people had a BMI of 35.0 kg/m^2 or more and 33% had a BMI of 30.0 kg/m^2 to 34.9 kg/m^2, and the average BMI was 38.0 kg/m^2 (see section 3.6). The company's original target population made up 75% of the STEP 1 trial population (see section 3.6). The committee questioned whether this population in the trial represented the population who, in practice, would be eligible for treatment if the company's original target population were to be recommended. This was because, in the general population, the prevalence of BMI between 30.0 kg/m^2 and 34.9 kg/m^2 far exceeds that of BMI over 35.0 kg/m^2. In the trial and the modelled population, it was a smaller percentage (see section 3.2). Scenario analyses done by the ERG showed that, if the mean starting BMI was 32.5 kg/m^2, the ICER increased from the base case of £16,337 per QALY gained (including a mean

starting BMI of 38.7 kg/m^2) to £22,192 per QALY gained. Therefore, expanding the population to include large numbers with a lower BMI would increase the ICER. There was additional underlying uncertainty related to model inputs. This included the average time to weight regain (see section 3.13), and the percentage of people with type 2 diabetes who would be treated in practice (see section 3.7). The company's scenario analysis assuming weight regain over 1 year rather than 3 years increased the ICER to £23,686 per QALY gained. Its scenario analysis including people with type 2 diabetes in the model increased the ICER to £21,277 per QALY gained. The committee also discussed the major underlying concern about the reliability of using risk equations to predict cardiovascular events, noting that these were predictions alone and not based on clinical evidence (see section 3.15). It discussed that the long-term cardiovascular benefits included in the model were highly uncertain and that the ICER could be much higher if these benefits were not reached (see section 3.15). It also discussed that only providing semaglutide for a maximum of 2 years was not ideal for treating a chronic condition (see section 3.12). It noted that the ICER increased when treatment duration was increased in the model because of a plateauing of the benefits seen with semaglutide. The committee was aware that referral to tier 3 services for people with a BMI of less than 35.0 kg/m^2 is exceptional and, according to 1 clinical expert, the population of people with a BMI of less than 35.0 kg/m^2 in tier 3 services is 1.5% (see section 3.2). There would therefore be big implications for NHS service delivery if the population were to be significantly expanded as in the company's original target population. The committee considered that it therefore needed to have a high level of confidence that this was a cost-effective strategy for the NHS. Given the high level of uncertainty, particularly around the long-term outcomes, the committee agreed that it was appropriate to consider a population who were at the highest risk for the adverse effects of obesity and were likely to gain the most benefit from semaglutide, therefore increasing the likelihood of semaglutide being a cost-effective treatment. Therefore, the committee concluded that it was

appropriate to consider the company's original target population for treatment with semaglutide, but only if they also meet the criteria for treatment in specialist weight management services.

Other factors

There are equality issues related to people from some minority ethnic family backgrounds

3.20 The committee noted that people from some minority ethnic family backgrounds are at an equivalent risk of the consequences of obesity at a lower BMI than people from a White ethnic family background. Also, NICE's public health guideline on BMI recommends using lower BMI thresholds for south Asian, Chinese, and Black African or Caribbean family backgrounds when identifying the risk of developing type 2 diabetes and providing interventions to prevent it. The committee agreed that a similar adjustment would be suitable when considering treatment with semaglutide.

Conclusion

Semaglutide is recommended for some people living with obesity

3.21 The committee noted that the estimated ICERs for the company's original target population were below what would normally be considered a cost-effective use of NHS resources. However, it discussed the high levels of uncertainty associated with these estimates, and that the population in the model may not have been representative of the company's original target population (see section 3.19). It also discussed that semaglutide should be used alongside lifestyle interventions available in specialist weight management services, in line with its marketing authorisation (see section 3.3). Therefore, the committee agreed that semaglutide, when used as part of a specialist weight management service for a maximum of 2 years, could be recommended for people:

- with at least 1 weight-related comorbidity and:

- a BMI of at least 35.0 kg/m^2, or
- exceptionally, a BMI of 30.0 kg/m^2 to 34.9 kg/m^2 if they are referred to tier 3 services based on the criteria in NICE's clinical guideline on obesity: identification, assessment and management.

They noted that lower BMI thresholds (usually reduced by 2.5 kg/m^2) should be used for people from south Asian, Chinese, and Black African or Caribbean family backgrounds.

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 clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months 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 recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

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 is living with overweight or obesity and the doctor responsible for their care thinks that semaglutide is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by NICE 3 years after publication of the guidance. NICE welcomes

comment on this proposed date. NICE will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, appraisal committee
January 2022

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

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

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

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

Albany Meikle
Technical lead

Joanna Richardson
Technical adviser

Thomas Feist

Project manager

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