

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final Appraisal Document

**Semaglutide for managing overweight and
obesity**

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:

- it is used for a maximum of 2 years, and within a specialist weight management service providing multidisciplinary management of overweight or obesity (including but not limited to tiers 3 and 4), and
- they have at least 1 weight-related comorbidity and:
 - a body mass index (BMI) of at least 35.0 kg/m², or
 - a BMI of 30.0 kg/m² to 34.9 kg/m² and meet the criteria for referral to specialist weight management services in [NICE's clinical guideline on obesity: identification, assessment and management](#).

Use lower BMI thresholds (usually reduced by 2.5 kg/m²) for people from south Asian, Chinese, and Black African or Caribbean family backgrounds.

1.2 Consider stopping semaglutide if less than 5% of the initial weight has been lost after 6 months of the maintenance dose.

1.3 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 specialist 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
- more weight is lost with semaglutide than with liraglutide
- in people with non-diabetic hyperglycaemia, semaglutide plus lifestyle measures helps normalise blood glucose more frequently than lifestyle measures alone
- semaglutide 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 lifestyle interventions that are provided in specialist weight management services (offered in the NHS for a limited time). This is because it is in keeping with the clinical trial, and there is no evidence of effectiveness if semaglutide is used as a single stand-alone treatment. Also, the marketing authorisation specifies use as an adjunct to a reduced-calorie diet and increased physical activity.

For people who have at least 1 weight-related comorbidity and a BMI of at least 35 kg/m² or a BMI of 30 kg/m² to 34.9 kg/m² and also meet the NICE criteria for referral to a specialist weight management 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 lifestyle interventions 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/m² (obesity), or ≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight-related comorbidity e.g. dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the [summary of product characteristics](#).

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 (Ozempic) 0.25 mg, 0.5 mg and 1.0 mg is £73.25 per pack (excluding VAT; BNF online accessed June 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, as well as 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 treatment with liraglutide is limited to a specific population who have non-diabetic hyperglycaemia and a risk factor for cardiovascular disease. They thought that access to a new treatment option would provide hope for more 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 tier 3 services) but NHS provision varies

3.2 The 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 places. The clinical and patient experts explained that specialist weight management services such as tier 3 services are not available everywhere across England and Wales. They are normally accessed for up to 2 years by people with a body mass index (BMI) of 35 kg/m² or more plus 1 or more comorbidities, or with a BMI of 40 kg/m² or more with or without comorbidities. The specific nature of the comorbidities needed for referral may vary across different services. Also, the length of time they can be accessed may be shorter than 2 years in different areas of the country. The clinical experts explained that the average BMI in tier 3 is well above 35 kg/m², at 46 kg/m². Tier 3 services are also accessed by a small number of people with a lower BMI of 30 kg/m² to 35 kg/m² who have a complex comorbidity that would benefit from weight loss. The clinical experts explained that this group represents only about 1.5% of people in tier 3. However, the population prevalence of a BMI of 30 kg/m² to 35 kg/m² is much greater than that of a BMI of over 35 kg/m². People with a BMI of 30 kg/m² to 35 kg/m² accessing tier 3 services typically have 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/m² 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 specific circumstances. This includes, for example, 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/m² to 34.9 kg/m² are referred to tier 3 services. 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 committee noted the consultation comments highlighting that specialist weight management services such as tier 3 are not available in all parts of the country. Other consultation comments suggested that people with severe mental illness are excluded from accessing specialist weight management services. The committee acknowledged these comments but agreed that it was outside its remit to address the whole of the NHS weight management service provision and referral criteria. The committee noted that NHS services for overweight and obesity are under review and welcomed this, but was not aware of any planned or confirmed changes to these services. The committee concluded that, ideally, all people living with obesity eligible for specialist weight management services according to NICE's clinical guideline on obesity should have access to these services.

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 specialist weight management services such as tier 3 and 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 an initial 16-week dose escalation period. In addition, the marketing authorisation specifies reassessment at 6 months to see if treatment with semaglutide 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 noted that the clinical trial included adjunct physical activity, dietary advice and behaviour change interventions similar to the treatment provided in specialist weight management services (see section 3.6). Without the accompanying support provided by these services, 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 recognised that specialist weight management services such as tier 3 or 4 are not available to everyone across England and Wales (see section 3.2). However, the clinical experts explained that service provision is under review. The committee concluded that, as in the marketing authorisation and clinical trial evidence, these services are the only appropriate setting that can provide the necessary multidisciplinary specialist weight management interventions for a sustained period alongside semaglutide treatment. Therefore, the committee agreed that semaglutide should only be available within a specialist weight management service.

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/m² or more (obesity), or a BMI from 27 kg/m² to less than 30 kg/m² (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/m² 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 specific circumstances and that referral to tier 3 services is not recommended for all people with a BMI of 30 kg/m² or more with any weight-related comorbidity. Only rarely are referrals made for people within this population, for example, when they have 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/m² 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 of less than 30 kg/m² 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/m² and 35 kg/m², 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 have treatment in specialist weight management services.

It agreed that the population with a BMI between 27 kg/m² and 30 kg/m² or with a BMI between 30 kg/m² and 35 kg/m² 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/m² 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 NHS provision within the tier system. The committee discussed that NHS specialist provision is clearly focused on providing intensive support for the highest-risk population with a BMI of 35 kg/m² 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/m² to 35 kg/m² 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. This 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/m² or more plus at least 1 weight-related comorbidity). For people with a BMI of 35 kg/m² or more, non-diabetic hyperglycaemia and a high risk of cardiovascular disease, liraglutide alongside a reduced-calorie diet and increased physical activity 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:

- weight management support, diet and exercise for people with a BMI of 30 kg/m² or more and at least 1 weight-related comorbidity
- liraglutide plus weight management support, diet and exercise for people with a BMI of 35 kg/m² 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 the general population

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 30.0 kg/m² or more) with or without a comorbidity, or with overweight (BMI of 27.0 kg/m² to 29.9 kg/m²) 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/m² to 29.9 kg/m²), 32.8% were categorised as having obesity category 1 (BMI of 30.0 kg/m² to 34.9 kg/m²) and 61.2% were categorised as having obesity categories 2 or 3 (BMI of at least 35.0 kg/m²). 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/m² to 35.0 kg/m² than of at least 35.0 kg/m². The average BMI in the trial was 37.9 kg/m². The clinical experts explained that around 80% of people in tier 3 services have a BMI of 40.0 kg/m² or more and that 1.5% have a BMI of less than 35.0 kg/m² (see section 3.2). The company proposed that people with a BMI of 30.0 kg/m² 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/m² to 34.9 kg/m². So, if semaglutide were to be available for everyone with a comorbidity within this BMI range, as in the company's target population, it is highly likely that the average BMI of the treated population would be lower than the trial population. This is because the prevalence of a BMI of 30 kg/m² to 35 kg/m² in the general population is higher than the prevalence of 35 kg/m² or more. The committee recognised that the highest-risk population should be treated. However, as more people with a lower BMI are included within a treated population, the less well this population would match the trial population. The committee also noted that any large increase in the number of people having treatment 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 were to be accepted. It also needs to be confident 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. This meant it did not reflect the population distribution of overweight and obesity in the general population. 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/m² or more with any weight-related comorbidity) was recommended.

People with type 2 diabetes are not included in STEP 1, although they could have 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 and obesity needs specialist weight management, it would be appropriate for them to have treatment for obesity within a specialist weight management service. 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, a randomised controlled trial of semaglutide compared with placebo in people with overweight or obesity and type 2 diabetes. They noted that people with type 2 diabetes would be likely to have less weight loss than people without type 2 diabetes. But they commented that a small amount of weight loss is associated with greater health gain in a higher risk population such as this. The committee concluded that STEP 1 did not include people with type 2 diabetes, so 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/m² or more) or overweight (BMI of 27 kg/m² to 29.9 kg/m²) with at least 1 weight-related comorbidity. The

post-hoc subgroup analysis (n=1,470) included adults with a BMI of 30 kg/m² 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 a large 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 non-diabetic hyperglycaemia in the full trial population and the post-hoc analysis subgroup.

Semaglutide is more effective than liraglutide for weight loss

3.9 Liraglutide plus weight management support, diet and exercise is the appropriate comparator for people with a BMI of 35 kg/m² 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. The company presented an indirect treatment comparison using individual patient data from STEP 1 and SCALE 1839 to estimate the effectiveness of semaglutide compared with liraglutide in the liraglutide-eligible subgroup. SCALE 1839 was a randomised controlled trial of liraglutide compared with placebo in people with overweight or obesity. 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/m² or more) or overweight (BMI of 27 kg/m² to 29.9 kg/m²) 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 suitable for decision making

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 weight management support, diet and exercise for people with a BMI of 30 kg/m² or more with at least 1 weight-related comorbidity
- compared with liraglutide plus weight management support, diet and exercise for people with a BMI of 35 kg/m² 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 specialist multidisciplinary weight management setting. The model only allowed up to 3 years treatment. 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 3.16) and the model only allowing treatment with semaglutide plus diet and exercise, or diet and exercise alone for up to 3 years. However, it concluded that the perspective of use in specialist weight management services was appropriate and that the model was suitable for decision making.

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 meaningful weight loss, 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. This was in line with the time specified for the decision on continuing treatment in the marketing authorisation.

Semaglutide is limited to 2 years because of restricted time in specialist weight management services and lack of evidence for longer use

3.12 The company included an assumption in the model that people would take semaglutide for a maximum of 2 years. 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. 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. It would give people the opportunity to incorporate more physical activity into their lifestyles, with improved mobility and reduced pain. The committee agreed that treatment for other chronic conditions is not stopped after a certain period when it is tolerated and effective. But it noted that the NHS provides specialist services for obesity that is time limited. The NHS England representative suggested that the psychological impact of stopping semaglutide treatment after 2 years at the same time as being discharged from specialist weight management services could be detrimental. However, the committee agreed that semaglutide should only be used in a specialist weight management service (see section 3.3). The committee noted the clinical experts' statements that specialist weight management services such as tier 3 are usually accessed for up to 2 years. People only very exceptionally stay in tier 3 services for longer. Also, some areas offer these services for shorter periods, and many people are discharged from tier 3 services before 2 years. The committee understood that there are restrictions on time spent in specialist weight management services. It agreed that, for a long-term problem like obesity, this was not ideal (see section 3.2). However, it accepted that the company model was based on a single course of

treatment of no longer than 2 years. This is in line with the clinical trial evidence and is how long, on average, specialist weight management services can be accessed. The ERG highlighted that removing the 2-year stopping rule to model lifelong use, including maintenance of weight loss, was not possible within the company's model. However, increasing the time on treatment to 3 years increased the incremental cost-effectiveness ratio (ICER), suggesting that longer use is less likely to be cost effective. The company highlighted that the longest treatment duration studied in a clinical trial was 2 years in the STEP 5 trial (a randomised controlled trial of 2-year treatment with semaglutide compared with placebo for people with overweight or obesity). There is no evidence for longer-term use of semaglutide available, including evidence for maintenance treatment. However, longer-term evidence may be available in the future. The ERG noted that the results of the STEP 5 trial were comparable to the results from the STEP 1 trial used in the model, supporting the efficacy of semaglutide use for up to 2 years. The committee concluded that the assumption that treatment would be stopped at 2 years was reasonable in the context of NHS specialist weight management services, which are time limited. Such services are the only appropriate setting for semaglutide treatment given the marketing authorisation and clinical evidence base. However, when further evidence becomes available, it might be possible to consider long-term use in other settings if the evidence suggests that long-term or lifetime use is clinically and cost effective.

The assumptions for weight gain are uncertain

- 3.13 The company included an assumption that 3 years after stopping semaglutide (with a 2-year treatment period), the weight advantage with semaglutide would be lost. This means the average weight for people taking semaglutide would be in line with what it would be in the average population in the diet and exercise treatment arm after 5 years. The company also assumed that people whose glucose tolerance became normal on treatment would revert to having non-diabetic hyperglycaemia

3 years after treatment stopped. In response to consultation, the committee noted the suggestion that the SCALE 1839 trial showed rapid weight gain in the first 12 weeks after stopping liraglutide. It was also suggested that the SCALE 1839 trial showed that weight would return to baseline weight following liraglutide treatment after 6 to 12 months, and that similar would be expected for semaglutide. The NHS England representative also noted evidence from a pharmacokinetic modelling study of liraglutide that showed weight returned to close to baseline by 29 weeks after stopping treatment following 56 weeks of liraglutide. The clinical experts noted that the assumptions around the rate of weight gain after treatment were very uncertain. They suggested that, on average, it would be expected that the weight advantage gained with semaglutide would be lost around 2 to 3 years after stopping treatment. But they explained that some people would maintain clinically relevant weight loss for longer. A committee member with experience of using semaglutide and liraglutide for treating diabetes explained that liraglutide is a less active and less effective treatment. Therefore, less weight would be expected to be lost with liraglutide than semaglutide (see section 3.9). Because of the expected greater weight loss with semaglutide the time to regain the weight following semaglutide treatment would be longer than the time to regain the weight following liraglutide treatment. The ERG explained that the STEP 4 clinical trial provided some evidence that not all weight lost is regained 1 year after stopping semaglutide. STEP 4 was a randomised trial that included a treatment arm including semaglutide treatment for 20 weeks, followed by placebo for 48 weeks for people with overweight or obesity. A 20-week treatment duration is less than the time in the marketing authorisation specified for reassessment of benefit (see section 3.11). Therefore, initial weight loss in STEP 4 was expected to be less than that with 2 years of semaglutide treatment in clinical practice. If initial weight loss were lower because of a shorter treatment duration, it would be expected that the time to lose the weight advantage associated with semaglutide would be shorter than if semaglutide was given for 2 years. The ERG agreed that the assumption of the loss of weight

advantage over 3 years was reasonable. It also provided a scenario analysis showing a modest effect on the cost-effectiveness results when an assumption of a loss of weight advantage over 2 years was included in the model. The committee concluded that this was an area of uncertainty. It accepted that there is not yet any long-term evidence to show the true average time to lose the weight advantage after semaglutide treatment. However, it noted that including an assumption in the model of loss of weight advantage at the lower end of the clinical expert's estimation (2 years) did not have a major effect on the cost-effectiveness estimate.

Retreatment might be appropriate for some people meeting the eligibility criteria for a rereferral to a specialist weight management service

3.14 The company's model 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 have it again. They also noted that rereferral into specialist weight management services is not usual but does happen occasionally. The committee discussed that the cost effectiveness of retreatment with semaglutide after weight regain was unknown because this was not included in the trial or the model. However, it acknowledged that retreatment might be appropriate for some people who have lost and regained weight and who become eligible for treatment again according to the same starting criteria.

The model assumes that all people with non-diabetic hyperglycaemia develop type 2 diabetes after a cardiovascular event

3.15 The company included a simplifying assumption in the model that all people with non-diabetic hyperglycaemia who have a cardiovascular event develop type 2 diabetes within the following year. The clinical experts explained that people with non-diabetic hyperglycaemia 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 with non-diabetic hyperglycaemia 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 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 with non-diabetic hyperglycaemia who had a cardiovascular event.

Risk equations are the only available method for modelling long-term health outcomes

3.16 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. In response to consultation comments that disagreed with using risk equations to predict long-term cardiovascular disease outcomes, the ERG conducted scenario analyses excluding the

cardiovascular disease benefits alone, or in combination with diabetes outcomes from the model. These showed that excluding cardiovascular disease benefits from the model had a small upward effect on the cost-effectiveness estimate. However, excluding diabetes benefits had a larger effect. 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 other risk parameters seen with semaglutide in STEP 1 would have some benefit. It noted, though, that this was difficult to quantify. The company explained that there would be further evidence on the long-term cardiovascular outcomes with semaglutide from the SELECT trial. This is a randomised controlled trial comparing semaglutide with placebo for up to 5 years in people with overweight or obesity and cardiovascular disease. The committee noted that the benefits seen in STEP 1 for shifting diabetic status from non-diabetic hyperglycaemic to normoglycaemic were both striking and important (see section 3.8). This suggested that the time spent without diabetes could be increased for people taking semaglutide. The committee agreed that prolonging time without diabetes was an important and highly beneficial outcome, even if this was limited in duration. It noted that removing diabetic benefits from the model had a much greater upward effect on the ICER than removing cardiovascular benefits, which only modestly increased the ICER. Despite the uncertainties associated with using risk equations, the committee concluded that they were the only method available. This was because it had not been presented with an alternative method for estimating long-term health outcomes.

Cost-effectiveness estimate

Because of uncertainty, there needs to be a high level of confidence that the ICER is around £20,000 per quality-adjusted life year gained

3.17 [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 3.16)
- the possible implications for NHS delivery of services.

Based on these uncertainties, the committee agreed that it needed a high level of confidence that the ICER was at the lower end of the range for acceptable cost effectiveness (£20,000 to £30,000 per QALY gained).

The ERG's and company's assumptions are reasonable

3.18 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)
- a loss of the weight advantage gained with semaglutide, and a return to the original glycaemic state 3 years after stopping treatment (see section 3.13)
- no retreatment throughout the full time horizon of the model (see section 3.14)
- that 100% of people with non-diabetic hyperglycaemia develop type 2 diabetes after a cardiovascular event (see section 3.15).

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

- people with non-diabetic hyperglycaemia do not automatically develop type 2 diabetes after a cardiovascular event (see section 3.15)
- 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 £274 (compared with the company's assumption of £1,081).

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

3.19 For the population who were eligible for liraglutide (people with a BMI of 35 kg/m² 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.

A restricted version of the company's original target population is appropriate

3.20 The company presented cost-effectiveness estimates for semaglutide in comparison with diet plus exercise for people with a BMI of 30 kg/m² 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 at least 35.0 kg/m² and 33% had a BMI of 30.0 kg/m² to

34.9 kg/m², and the average BMI was 37.9 kg/m² (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/m² and 34.9 kg/m² far exceeded that of a BMI of at least 35.0 kg/m². 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/m², the ICER increased from the base case of £16,337 per QALY gained (including a mean starting BMI of 38.7 kg/m²) 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 time to losing the weight advantage associated with semaglutide (see section 3.13), and the percentage of people with type 2 diabetes who would have treatment in practice (see section 3.7). The ERG's scenario analysis assuming a loss of weight advantage over 2 years rather than 3 years increased the ICER to £21,060 per QALY gained. The company's 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 concern about the reliability of using risk equations to predict cardiovascular events. It noted that these were predictions alone and not based on clinical evidence (see section 3.16). However, although this remained an uncertainty, semaglutide was still cost effective if these benefits were not included in the model. 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 specialist weight management services for people with a BMI of less than 35.0 kg/m² is only made in specific circumstances. Also, according to

1 clinical expert, the population of people with a BMI of less than 35.0 kg/m² 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, the committee agreed that it was appropriate to consider a population at the highest risk for the adverse effects of obesity and likely to gain the most benefit from semaglutide. This would increase 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 this was only if they also meet the criteria for treatment in specialist weight management services in line with the criteria in NICE's clinical guideline on obesity.

Other factors

There are likely to be uncounted benefits not included in the QALY calculation

3.21 The committee considered whether there were further benefits associated with semaglutide treatment that had not been captured by the QALY calculation. It discussed that, while the long-term benefits of weight loss were modelled, some long-term benefits such as reduced risk of liver disease may not have been captured in the model. It also discussed that weight loss may have other benefits that may not have been captured in the model. Examples could include:

- a decreased risk of adverse events associated with respiratory infections such as COVID-19
- a reduction in social isolation and stigma associated with obesity, and related improvement in career prospects (see section 3.1),
- improvement in fertility or success rate for in vitro fertilisation.

The committee noted that there was some uncertainty around the assumptions in the model. However, it concluded that it was also important to consider these uncounted benefits, which may positively affect the cost-effectiveness estimates if they were to be modelled.

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

3.22 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.

Specialist weight management services are not equally accessible throughout England

3.23 The committee noted that specialist weight management services are not equally available throughout the country (see section 3.2). It discussed that the uneven distribution of specialist weight management services produces a postcode lottery for access to these services. It also considered comments from consultees that access to specialist weight management services is restricted for some people with severe mental illness. Because of these issues, the committee discussed whether semaglutide should be offered in different settings, such as tier 2 or mental health services. However, it considered that specialist weight management services (with a suitable duration of care) are the only appropriate setting for semaglutide treatment. This is because they can provide the necessary multidisciplinary specialist weight management interventions needed to provide semaglutide as a package of care. This is in line with the marketing authorisation for semaglutide, which specifies

that it is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management. It is also in line with advice from the clinical experts that semaglutide is not a stand-alone treatment. They explained that semaglutide should only be given alongside a suitably sustained programme of lifestyle interventions with multidisciplinary input, and in line with the trial design (see section 3.3). The committee noted a consultation comment that some secondary care mental health services provide advice on and management of physical health. This includes lifestyle advice for weight management alongside treatment for mental health issues. However, the committee agreed that this is not equivalent to the setting in the trial, which included weight-loss orientated multidisciplinary treatment. It also agreed that there was no evidence that semaglutide would be effective outside this setting. The committee noted comments that even intensive diet and lifestyle interventions are ineffective in people with severe mental illness. This means that pharmacological management of obesity might be particularly important in this group. However, the committee understood that semaglutide is licensed only as an adjunct to diet and exercise, and it could not make a recommendation that was not in line with either the marketing authorisation or the evidence base for semaglutide. The committee agreed that specialist weight management services should be accessible to anyone who is eligible and able to engage with the interventions provided, regardless of comorbidities. The committee concluded that the system for obesity management is not ideal. It suggested that this system, including the referral criteria for people with severe mental illness, should be reconsidered. It welcomed any review of NHS services for overweight and obesity, which is not uniform.

Conclusion

Semaglutide is recommended for some people living with obesity

3.24 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 3.20). 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 adults:

- with at least 1 weight-related comorbidity and:
 - a BMI of at least 35.0 kg/m², or
 - a BMI of 30.0 kg/m² to 34.9 kg/m² and they meet the criteria for referral to specialist weight management services in [NICE's clinical guideline on obesity: identification, assessment and management](#).

They noted that lower BMI thresholds (usually reduced by 2.5 kg/m²) should be used for people from south Asian, Chinese, and Black African or Caribbean family backgrounds. Whether semaglutide should be stopped if less than 5% of the initial weight has been lost after 6 months of the maintenance dose should be considered.

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

The guidance on this technology will be considered for review 3 years after publication. 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
June 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

ISBN: [to be added at publication]