NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Tirzepatide 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 tirzepatide in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

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

The evaluation 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?
- There is a requirement for relevant health bodies to comply with the recommendations in this evaluation within 3 months of the date final guidance is published by NICE (see section 4.1). We are aware there may be system challenges that mean an extension to this normal period may be appropriate because tirzepatide cannot be appropriately administered until:
    - training is in place
    - certain health service infrastructure requirements including goods, materials or other facilities are in place
    - other appropriate health services resources, including staff, are in place.

  These challenges may include:
    - commissioning arrangements for weight management services
    - how tirzepatide will fit into the current treatment pathway for weight management

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    - the provision of counselling, psychological support and concomitant behavioural, dietary and physical activity advice
    - titration of tirzepatide and how a stopping rule based on treatment response at 6 months would be implemented
    - capacity in the system.
- Please specify any potential challenges with implementing these recommendations and the associated reasons.
- Please also provide any ways to overcome these potential challenges, any estimate of the time period within which the recommendation can be complied with, and any approaches to phase in funding to manage access to tirzepatide during any potential extended funding variation period.

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

For further details, see NICE’s manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 25 June 2024
- Third evaluation committee meeting: 13 August 2024
- Details of membership of the evaluation committee are given in section 5

1 Recommendations

1.1 Tirzepatide is recommended as an option for managing overweight and obesity, alongside a reduced-calorie diet and increased physical activity, in adults, only if:

- they have an initial body mass index (BMI) of at least 35 kg/m^2, and
- they have at least 1 weight-related comorbidity, and
- the company provides it according to the commercial arrangement (see section 2).

Use lower BMI thresholds (usually reduced by 2.5 kg/m^2) for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean ethnic backgrounds.

1.2 Consider stopping tirzepatide if less than 5% of the initial weight has been lost after 6 months of treatment.

1.3 These recommendations are not intended to affect treatment with tirzepatide 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 healthcare professional consider it appropriate to stop.

Why the committee made these recommendations

Managing overweight and obesity in adults includes diet and exercise support in primary care, but the level of support available varies. Some people may also have semaglutide alongside diet and exercise support if their obesity is managed in a specialist weight management service.

Clinical trial evidence suggests that tirzepatide with diet and exercise support is more effective compared with diet and exercise support alone. Indirect comparisons

suggest it is more effective compared with semaglutide alongside diet and exercise support.

The company proposed that tirzepatide could be used for people with a BMI of at least 30 kg/m^2 and at least 1 weight-related comorbidity. But, the most likely cost-effectiveness estimates for this group are above the range that NICE considers an acceptable use of NHS resources. So, tirzepatide cannot be recommended for this group. The most likely cost-effectiveness estimates for people with an initial BMI of at least 35 kg/m^2 and at least 1 weight-related comorbidity are within the range that NICE considers an acceptable use of NHS resources. So, tirzepatide is recommended for this group.

2 Information about tirzepatide

Marketing authorisation indication

2.1 Tirzepatide (Mounjaro, Eli Lilly) is indicated 'for weight management, including weight loss and weight maintenance as an adjunct to a reduced-calorie diet and increased physical activity in adults with an initial body mass index (BMI) of

- ≥30 kg/m^2 (obesity) or
- ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g. hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus)'.

Dosage in the marketing authorisation

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

Price

2.3 The list prices of tirzepatide (excluding VAT; company communication) for a 4-week supply of pre-filled pen devices for subcutaneous injection are:

- £133.00 for 2.5 mg
- £180.00 for 5 mg
- £255.00 for 7.5 mg and 10 mg
- £330.00 for 12.5 mg and 15 mg.

2.4 The company has a commercial arrangement. This makes tirzepatide available to the NHS at a cost-effective price determined by NICE. The details of this arrangement are commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by Eli Lilly, a review of this submission by the external assessment group (EAG), and submissions from stakeholders. See the committee papers for full details of the evidence.

Clinical need

3.1 Living with overweight or obesity can impact quality of life in a number of ways. It can affect physical functioning, making daily activities more challenging and impacting mental wellbeing because of social stigma associated with the condition. It also increases the risk of developing other conditions such as type 2 diabetes and cardiovascular disease, which may severely impact quality and length of life. The clinical and patient experts explained that obesity is a chronic condition that needs long-term treatment. They explained that other medicines for managing overweight and obesity are only available for a relatively small group of people and access is limited, partly because they are only recommended for use within specialist weight management services (see section 3.2). The patient expert explained that the greatest unmet need was for people with a body mass index (BMI) of at least 35 kg/m^2. But, that all people living with obesity would welcome further treatment options, especially if these were easier to access. The committee understood that people with overweight and obesity have a chronic condition that needs treatment. It concluded that there is an unmet need for a large proportion of people

living with obesity and that tirzepatide would offer a treatment option for these people.

Treatment pathway for overweight and obesity in the NHS

3.2 The management of overweight and obesity in the NHS is delivered by both community-based and secondary care services. NICE's public health guideline on weight management: lifestyle services for overweight or obese adults recommends commissioning of multi-component and integrated lifestyle weight management services. The recommendations suggest that these are:

- multi-component (addressing dietary intake, physical activity levels and behaviour change)
- developed by a multidisciplinary team (MDT) including a dietitian, psychologist and physical activity instructor
- accessed for at least 3 months with weekly or fortnightly sessions.

A clinical expert explained that primary care weight management services are also being delivered. These include advice from GPs, diet and exercise support provided by nurses with specialist interest in obesity and access to dietitians for people with complex needs. The patient expert explained that their experience of care included regular touchpoints with GPs, referral to diet and exercise professionals and access to psychological support. The NHS commissioning expert noted that access to lifestyle weight management services and the level of support provided in primary care services varies across the country. Specialist weight management services provide longer and more comprehensive MDT assessment and interventions. NICE's clinical guideline on obesity: identification, assessment and management defines these as specialist primary, community or secondary care-based MDTs offering a combination of surgical, dietetic, pharmacological and psychological obesity management intervention. They are accessible for a maximum of 2 years. Therefore, the pharmacological treatments recommended for

some people within specialist weight management services in NICE's technology appraisal guidance for semaglutide and NICE's technology appraisal guidance for liraglutide for weight management are only available for up to 2 years. The clinical experts noted that access to specialist weight management services varies across the country, and in some areas they are available for less time. The patient expert also explained that not everyone who needs these services can access them. The committee concluded that diet and exercise support is available for some people with overweight and obesity in primary care and that a limited number of people may also access specialist weight management services. But, the level of support available in primary care and availability of specialist weight management services varies across the country.

Treatment setting

3.3 In its submission, the company proposed that tirzepatide could be used either in primary or secondary care, and the appropriate diet and exercise support that should be accessed alongside tirzepatide could be delivered in both settings. During the committee meetings, the company explained that the diet and exercise component of the intervention in its pivotal trial was light-touch and GPs in the NHS are delivering interventions like these in practice (see section 3.9). To support this assumption, it presented evidence from a survey of GPs in England and Wales, suggesting that 78% of the GPs that responded always or very frequently offer specific diet and exercise advice, 67% have access to a dietitian and 80% have access to an exercise professional. A clinical expert noted that diet and exercise support is being delivered in primary care for people with overweight or obesity (see section 3.2). The patient expert explained that access to tirzepatide in both primary and secondary care would be welcomed as access to specialist weight management services, and the pharmacological treatments offered only in these services, is limited. The NHS England clinical adviser explained that services for overweight and obesity are unequal across the country and can be very limited. They

noted that the setting for tirzepatide delivery should not be restricted, but that the long-term diet and exercise support delivered alongside tirzepatide in the company's pivotal trial is not consistently available in primary care. So, for tirzepatide to be delivered in primary care, additional diet and exercise support services would need to be implemented. But they explained that obesity services in the NHS are changing rapidly. They highlighted examples of this including the ongoing NHS England work exploring ways to access obesity management drugs outside hospital settings, and NICE's early value assessment on digital technologies for delivering multidisciplinary weight-management services. The commissioning expert explained that there would be challenges in implementing these additional services given the number of people living with overweight or obesity in England and Wales. The committee concluded that it would consider tirzepatide across both primary and secondary care settings, but there is uncertainty around the level of additional diet and exercise support that would need to be implemented alongside tirzepatide in primary care.

Target population

3.4 The NICE scope for this evaluation and tirzepatide's marketing authorisation includes people with an initial BMI of:

- 30 kg/m^2 or more (obesity) or
- between 27 kg/m^2 and 29.9 kg/m^2 (overweight), who have 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. The company also presented evidence for the full marketing authorisation population and subgroups including the population who are eligible for liraglutide (see section 3.5), people with a BMI of 30 kg/m^2 or more irrespective of comorbidities, and people with a

BMI of 35 kg/m^2 or more irrespective of comorbidities. After the second committee meeting, the company also submitted evidence for people with a BMI of 35 kg/m^2 or more with at least 1 weight-related comorbidity. The company suggested that its target population reflects the group who are most likely to benefit from weight loss, because these people have comorbidities that increase the risk of complications. The clinical experts explained that people with a higher BMI were in general at greater risk of the consequences of obesity. The committee concluded that the company's target population was appropriate to consider for tirzepatide treatment, but that it would also consider the subgroups presented.

Comparators

3.5 In line with the NICE scope, the company suggested in its submission that semaglutide alongside a reduced-calorie diet and increased physical activity (referred to as diet and exercise support), and diet and exercise support alone, were appropriate comparators for its target population. The company also included liraglutide as a comparator for a subgroup of this population who are eligible for this treatment. Semaglutide alongside diet and exercise is recommended in NICE's technology appraisal guidance on semaglutide for managing overweight and obesity, for a maximum of 2 years for adults within a specialist weight management service providing multidisciplinary management of overweight or obesity and with:

- at least 1 weight-related comorbidity, and:
  - a BMI of 35 kg/m^2 or more or
  - a BMI of 30 kg/m^2 to 34.9 kg/m^2 and who meet the criteria for referral to specialist weight management services in NICE's guideline on obesity: identification, assessment and management.

Liraglutide alongside diet and exercise is recommended in NICE's technology appraisal on liraglutide for managing overweight and obesity for adults when it is prescribed in secondary care by a specialist multidisciplinary tier 3 weight management service and with:

- a BMI of 35 kg/m^2 or more, and
- non-diabetic hyperglycaemia, and
- a high risk of cardiovascular disease.

Semaglutide and liraglutide are both recommended at lower BMI thresholds for people from ethnicities known to be at equivalent risk of the consequences of obesity at a lower BMI than people from White ethnicities. The clinical experts explained that liraglutide is less effective than semaglutide. The patient expert highlighted that adherence to semaglutide is likely to be better than to liraglutide, because semaglutide is taken once weekly rather than once daily. So, semaglutide would be the preferred treatment option for most people who are eligible for both semaglutide and liraglutide. The committee agreed that liraglutide is not an appropriate comparator for tirzepatide. The committee noted that semaglutide was recommended only within specialist weight management services, and that not everyone with a BMI of 30 kg/m^2 to 34.9 kg/m^2 with at least 1 weight-related comorbidity is eligible. The committee noted that, if recommended, tirzepatide could be used either within or outside specialist weight management services (see section 3.3). The patient expert explained that not everyone in specialist weight management services would choose to have semaglutide because it needs to be stopped after 2 years and there are concerns around regaining weight lost after stopping and the psychological impact of this. So, some people in these services have diet and exercise support without medicine. The committee concluded that the primary comparator for tirzepatide is diet and exercise support delivered in primary care. It noted that semaglutide is also an appropriate comparator for tirzepatide in people eligible for semaglutide in specialist weight management services.

Clinical evidence

SURMOUNT-1

3.6 The clinical effectiveness evidence for tirzepatide comes from the SURMOUNT-1 clinical trial. SURMOUNT-1 was a randomised, double-blind trial that compared tirzepatide with placebo, both alongside diet and exercise support. It included adults with obesity (BMI of 30.0 kg/m^2 or more) with or without a comorbidity, or with overweight (BMI of 27.0 kg/m^2 to 29.9 kg/m^2) with at least 1 weight-related comorbidity. People with type 2 diabetes or with history of severe psychiatric disorders within the last 2 years were excluded. The trial was done in 9 countries across the world but there were no study sites in the UK. The trial included 4 arms: 3 arms were given tirzepatide at either a 5 mg (n=630), 10 mg (n=636), or 15 mg (n=630) dose and 1 arm was given placebo (n=643). All arms were followed up for 72 weeks. The committee concluded that SURMOUNT-1 was appropriate for decision making.

Generalisability of population comorbidities in SURMOUNT-1

3.7 The company's target population included people with BMI of 30 kg/m^2 or more with at least 1 weight-related comorbidity, which was a subgroup of the full trial population in SURMOUNT-1. The most common comorbidities in the company's target population at baseline in SURMOUNT-1 were hypertension, dyslipidaemia and osteoarthritis, but many other comorbidities were reported that meant someone could be included in the target population. The committee noted that people with type 2 diabetes were not included in SURMOUNT-1. It was aware that tirzepatide is recommended for some people with type 2 diabetes in NICE's technology appraisal on tirzepatide for treating type 2 diabetes. It discussed that, if it was recommended, more people with type 2 diabetes may potentially be eligible for tirzepatide if they meet the criteria for tirzepatide treatment for weight management. SURMOUNT-1 also excluded people with a history of significant active or unstable major depressive disorder or other severe psychiatric disorders within the last 2 years. NHS England commented that the generalisability of the trial should be considered with caution because there is no clinical evidence to show the effectiveness of

tirzepatide in this group of people. The company highlighted that people were only excluded from SURMOUNT-1 if their mental health condition was considered unstable and that 21.6% of people in SURMOUNT-1 reported a pre-existing psychiatric disorder, including but not limited to depression, anxiety, insomnia and major depressive disorder. The committee noted that people with some types of severe psychiatric disorders (such as bipolar or schizoaffective disorder) who may be on antipsychotic medicine did not appear to have been included in SURMOUNT-1. Therefore it was unclear what level of additional psychological support this group of people might need alongside tirzepatide. A clinical expert noted that people with severe psychiatric disorders are already having psychiatric care and that the interventions needed to support the delivery of tirzepatide should be considered separately. The committee concluded that the population in SURMOUNT-1 had a wide range of comorbidities, which made them eligible for inclusion in the target population analysis. It also concluded that by not including people with type 2 diabetes and particular groups with severe mental health disorders, SURMOUNT-1 did not cover the whole population who would potentially be offered tirzepatide in the NHS and who are covered by tirzepatide's marketing authorisation. 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.

BMI in SURMOUNT-1

3.8 After the first committee meeting, a comparator company commented that the baseline BMI in SURMOUNT-1 (mean BMI of 38.0 kg/m^2) was higher than the average BMI of people who would potentially be eligible for tirzepatide in primary care. The company presented data from primary care adult weight management services, which showed that 34% of people with overweight or obesity accessing these services between April 2021 and December 2022 have a BMI between 30 kg/m^2 and 34.9 kg/m^2.

It noted that the proportion of people with overweight or obesity with a BMI between 30 kg/m^2 and 34.9 kg/m^2 in SURMOUNT-1 was similar (35.5%). The EAG explained that the BMI distribution in primary care adult weight management services differed to the BMI distribution of people in the general population sourced from the Health Survey for England. This showed that 66% of people with a BMI of at least 30 kg/m^2 have a BMI between 30 kg/m^2 and 34.9 kg/m^2. The EAG explained that the primary care adult weight management services population did not necessarily align with the population who would be eligible to have tirzepatide, because it is sampled from a population where local authority commissioned services are available. The committee discussed that the BMI distribution in SURMOUNT-1 was aligned with people who are in primary care adult weight management services. But, more people from the general population with obesity may potentially access tirzepatide through primary care if it is recommended. So, the committee concluded that the BMI distribution in SURMOUNT-1 was different to the population who would be eligible for tirzepatide in clinical practice and that this could limit the generalisability of the results.

Diet and exercise support in SURMOUNT-1

3.9 People in all arms of SURMOUNT-1 were advised on diet and exercise, to include a diet with a 500-calorie per day deficit and an increase in physical activity by 150 minutes per week. Everyone in the trial also consulted with a dietitian, or equivalently qualified delegate according to local standards, to have diet and exercise management counselling at weeks 0, 4, 8, and 12 during dose escalation, and then at week 24 and then every 12 weeks throughout the trial duration. The EAG highlighted that the trial protocol specified that an individualised diet plan should be developed for each person by a dietitian or another appropriately trained person and reviewed. The protocol also stated that all training for people in the trial should be repeated to ensure adherence. The company explained that the individualised diet plan was a recommendation in the trial protocol and

that the lifestyle modification used in SURMOUNT-1 changed according to which country the trial was being done in. It also explained that the diet and exercise support was intended to be a light-touch approach that was delivered virtually rather than face-to-face in many cases, and not always by a dietitian. Based on this, the company suggested that the diet and exercise support used in SURMOUNT-1 could be replicated in the NHS within primary and secondary care settings. It explained that its target population only included people with a comorbidity and so it expected that diet and exercise support for these people could be incorporated into the ongoing care they have for these comorbidities. A clinical expert explained that although there would be differences in the way the diet and exercise support component of the intervention was delivered in different countries, overall, the trial is generalisable to clinical practice in the NHS. They also explained that there is evidence to suggest that the weight loss seen in the trial would likely be similar without the diet and exercise support provided. The committee noted that the diet and exercise support in SURMOUNT-1 was given for the full 72-week trial duration. It recalled its discussion that although diet and exercise support interventions are being delivered in some areas within primary care, the level of long-term diet and exercise support delivered alongside tirzepatide in SURMOUNT-1 is not consistently available. It also noted that obesity services in the NHS are changing, and it was uncertain exactly what changes to obesity management services would be implemented if tirzepatide was to be delivered in primary care (see section 3.3). So, it concluded that it was uncertain if the diet and exercise support included in SURMOUNT-1 was similar to the obesity weight management services that could be delivered in primary care, especially regarding the length of availability, intensity and consistency across the country.

Dose escalation and dosing in SURMOUNT-1

3.10 The company presented analyses for each arm of SURMOUNT-1, which included 5 mg, 10 mg or 15 mg doses of tirzepatide. The clinical experts

explained that the highest tolerated dose of tirzepatide would likely be used in clinical practice. The company also presented evidence from SURMOUNT-4, a randomised controlled trial in adults with obesity or overweight with at least 1 weight-related comorbidity comparing tirzepatide 10 mg, tirzepatide 15 mg and placebo. This showed that 92.5% of people in the trial were able to titrate to the highest 15 mg dose. SURMOUNT-1 used dose escalation for all arms, with the dose titrated up from 2.5 mg every 4 weeks until people reached the allocated maintenance dose by week 20. There was one chance to de-escalate the dose in the trial, if a person had intolerable gastrointestinal side effects. The committee was aware that the summary of product characteristics for tirzepatide specifies the starting dose of 2.5 mg and dose escalation of 2.5 mg every 4 weeks. The patient expert explained that based on experience with other similar treatments, it is important to titrate the dose of treatment up at the appropriate rate to avoid side effects. The committee concluded that it was likely that the highest tolerated dose of tirzepatide would be used, and for most people this would be 15 mg. The committee also concluded that dose escalation and de-escalation would need appropriate monitoring. How this was done would need to be considered in the implementation of the wraparound obesity management services for delivering tirzepatide.

Tirzepatide's treatment effect compared with placebo

3.11 The company presented clinical effectiveness evidence comparing tirzepatide alongside diet and exercise support with placebo alongside diet and exercise support from SURMOUNT-1. It presented evidence from 72-week follow up for the full trial population (n=2,539), its target population (see section 3.4; n=1,705) and subgroups including people with a BMI of 35 kg/m^2 and at least 1 weight-related comorbidity. The primary outcomes were mean percentage change in body weight and mean percentage of people with 5% or more body weight reduction. Evidence showed that in the full trial population, tirzepatide 15 mg was

associated with a statistically significantly greater reduction in body weight from baseline compared with placebo (mean percentage change difference -20.1%, 95% confidence interval [CI] -21.2 to -19.0%). Evidence also showed that a statistically significantly larger proportion of people on tirzepatide 15 mg lost 5% or more body weight from baseline (96.3%) compared with placebo (27.9%). Similar findings were reported for secondary outcomes in the trial. Evidence on tirzepatide's treatment effect compared with placebo in the company's target population and the subgroup including people with a BMI of 35 kg/m^2 and at least 1 weight-related comorbidity is considered confidential so cannot be reported here, but results are similar to the results for the full trial population. Evidence also showed that tirzepatide was more clinically effective when using the higher dose, across all subgroups presented. The committee noted there was no evidence on tirzepatide's treatment effect compared with placebo beyond 72 weeks. So, it is uncertain what long-term effect tirzepatide would have on morbidity and mortality rates. It concluded that tirzepatide is an effective treatment for overweight and obesity in the full trial population, as well as in the company's target population and presented subgroups at 72-week follow up. But it is uncertain what the effectiveness of tirzepatide is beyond the 72-week period observed in the trial.

Tirzepatide's treatment effect compared with semaglutide

3.12 No head-to-head trial evidence was identified comparing tirzepatide with semaglutide. So, the company also presented network meta-analyses for this comparison for its target population, people with a BMI of 30 kg/m^2 or more with at least 1 weight-related comorbidity. It used data for this population from STEP-1 and SURMOUNT-1. STEP-1 was a randomised controlled trial comparing semaglutide alongside diet and exercise support with placebo alongside diet and exercise support in people with overweight and obesity. The results of the network meta-analyses suggested that tirzepatide 15 mg was statistically significantly more effective than semaglutide 2.4 mg for weight loss and improvement of

high-density lipoprotein levels. They also suggested there was no statistically significant difference between tirzepatide 15 mg and semaglutide 2.4 mg for total cholesterol and systolic blood pressure improvement. The exact data is confidential and cannot be reported here. The committee concluded that the network meta-analysis indicated that tirzepatide 15 mg was at least as effective as semaglutide 2.4 mg across all outcomes reported, and more effective than semaglutide 2.4 mg for weight loss in the target population.

Company's economic model

3.13 The company submitted an individual patient simulation model using a 4-week cycle length for the first 2 years followed by an annual cycle length for the rest of the lifetime time horizon. Having proposed that tirzepatide could be used in both primary and secondary care, the company presented 2 base cases. The first compared tirzepatide 5 mg, 10 mg, and 15 mg (each alongside diet and exercise support) with diet and exercise support alone (see section 3.9). The second compared tirzepatide 5 mg, 10 mg, and 15 mg (each alongside diet and exercise support) with semaglutide alongside diet and exercise support. The committee focused its discussion on the analysis of tirzepatide 15 mg (see section 3.10). The model used risk equations, which used surrogate outcomes including BMI to estimate the risk of an event in the model happening. The committee noted that using risk equations to estimate long-term outcomes, rather than trial data for those outcomes, contributed to the uncertainty around the treatment benefits in the model. The model included 10 different clinical events, including events with ongoing effects (such as temporary reversal of prediabetes, stroke or obstructive sleep apnoea) and one-off events such as knee replacement. The committee noted that other clinical events such as cancer may be influenced by BMI, and these had not been captured in the model. It concluded that although there were some uncertainties associated with the company's model, it was suitable for decision making.

Baseline characteristics

3.14 People entering the model in the company's base case had a BMI of 30 kg/m^2 or more with at least 1 weight-related comorbidity, in line with its target population. People entered the model in a normal glucose tolerance state or with prediabetes but did not have any of the other complications or comorbidities at baseline that were later included as possible events in the model. Risk equations were used to estimate the probability of the 10 clinical events in the model (see section 3.13), and death, occurring. The treatment effects on the predictors informing these risk equations were taken from the company's network meta-analyses and directly from clinical trial data. The EAG noted that not including any of the later modelled complications or comorbidities for people entering the model was not in line with the baseline data from SURMOUNT-1, in which a proportion of people had baseline comorbidities such as previous myocardial infarction, obstructive sleep apnoea and non-alcoholic fatty liver disease. It explained that this was likely to bias the cost-effectiveness results in favour of tirzepatide. After the first committee meeting, the EAG updated its base case to include a proportion of people entering the model with previous myocardial infarction, obstructive sleep apnoea and non-alcoholic fatty liver disease. The EAG highlighted that no-one enters the model with type 2 diabetes. The company explained that it was inappropriate to include a proportion of people entering the model with type 2 diabetes because no benefits from improved glycaemic control would be modelled for these people. But evidence from clinical trials of tirzepatide in people with type 2 diabetes (SURMOUNT-2 and SURPASS) suggests that people with type 2 diabetes do show improved glycaemic control and therefore additional health benefits with tirzepatide. The EAG agreed that it was only appropriate to show the cost effectiveness of tirzepatide in people with type 2 diabetes in a model designed for that population. It did not include a proportion of people with type 2 diabetes in the baseline model population. But it explained that this meant that people who have type 2 diabetes at baseline are not represented in the model

and that this introduces uncertainty into the model because the results are driven by the cost offsets and utility gains from avoiding type 2 diabetes. The committee noted that NICE's technology appraisal guidance on tirzepatide for treating type 2 diabetes recommends tirzepatide alongside diet and exercise for some people with type 2 diabetes (see section 3.7). This indicates that tirzepatide is cost effective for some people with type 2 diabetes and so reduced the uncertainty associated with not including this population in the model at baseline. The committee concluded that it was appropriate to include people in the baseline population who have the modelled complications and comorbidities. It also concluded that there was some uncertainty associated with the model baseline population not including people with type 2 diabetes.

BMI distribution

3.15 The EAG explained that the company's model assumes that BMI follows a gamma distribution, but it was unclear how well this matches the actual distribution of people in the target population in SURMOUNT-1, because a detailed graduation of the BMI distribution was not presented. The EAG raised concerns that the assumed distribution in the model may not be representative of people who would have tirzepatide with a BMI at the lower end of the BMI range (for example someone with a BMI between 30 kg/m^2 to 35 kg/m^2). It explained that people with a lower BMI have relatively fewer quality-adjusted life year (QALY) gains from tirzepatide than people with a higher BMI. Therefore, by not sampling enough people at the lower end of the BMI range, the cost-effectiveness estimates would be biased in favour of tirzepatide. The EAG explained that the data on BMI distribution presented by the company from primary care adult weight management services and from the general population both show a distribution of BMI that includes more people with a BMI at the lower end of the BMI range than included in the SURMOUNT-1 target population. This difference is greater when comparing SURMOUNT-1 with the general population. The EAG presented a scenario analysis that applied

the Health Survey for England general population BMI distribution to the model, assuming a truncated normal distribution. The patient expert explained that in general, people with a BMI of at least 30 kg/m^2 who would potentially be eligible for tirzepatide would want to access this treatment, and it was not the case that only people with a higher BMI would be motivated to start treatment. The committee discussed that further analysis on the BMI distribution is needed. It requested that the detailed graduation of the BMI distribution in SURMOUNT-1 is presented to better understand how well the BMI distribution in the SURMOUNT-1 trial matches the distribution in clinical practice. It concluded that it is appropriate to include an adjustment for BMI distribution in the model to better reflect the population who would be potentially eligible to have tirzepatide in clinical practice.

Assumptions in the economic model

Costs of obesity management services

3.16 After the first committee meeting, the committee requested further information on the potential composition and costs of obesity management services needed to deliver tirzepatide. NHS England submitted estimates of the potential resource use needed for obesity management services, which reflected the protocol in the SURMOUNT-1 trial. This included appointments for initial assessment, education on diet and exercise, patient injection training, monitoring appointments during dose titration, ongoing diet and exercise counselling every 12 weeks, a medicines review, an additional multidisciplinary team patient review and psychological support for a third of people. NHS England suggested that the proposed services should be available for as long as tirzepatide is being used. It highlighted that the resource estimates had been developed with clinical expert input and reflected the wraparound support that had been provided in SURMOUNT-1. It also suggested that it is not appropriate to include these costs in the diet and exercise arm in the model because the services needed are not yet available. The company

suggested that NHS England had overestimated the time and regularity needed for each appointment and that other healthcare professionals may be able to provide some of the services that NHS England suggested would be delivered by GPs or dietitians. The company explained that the diet and exercise support provided in SURMOUNT-1 was not necessarily provided by dietitians and that nurses were qualified to manage dose titration. The company proposed that the diet and exercise arm of the model should also include appointments for diet and exercise counselling. It proposed that the obesity management services that were unique to tirzepatide and so should be accounted for only in the tirzepatide arm of the model were:

- starting treatment, including injection training, which could be nurse-led
- 5 dose titration appointments, which could be nurse-led, and
- an annual multidisciplinary team review, which could be done by a GP by reviewing notes.

The company presented a range of scenarios that showed the impact on the incremental cost-effectiveness ratio (ICER) of including its or NHS England's obesity management service proposals. But it did not apply any of these to its base case. The resource used in the company's base case included 4 GP visits, 8 nurse visits and 1 blood test per year, in all arms for the full time horizon of the model. The EAG amended its base-case assumptions after the first committee meeting to include the resource use proposed by NHS England for obesity management services. It applied all the proposed resource to the tirzepatide arm for the duration of tirzepatide treatment and assumed no resource costs for the diet and exercise arm. The EAG also amended the proportion of people having psychological support to align with the proportion of people in SURMOUNT-1 with current or historic psychiatric problems. The committee discussed that primary care obesity management services would likely need to adapt to deliver

tirzepatide alongside the diet and exercise support also needed (see section 3.3), but it is not clear what these services will include. The EAG's approach to estimating obesity management service resource use according to NHS England's proposals reflected the interventions used in the trial for tirzepatide and no service use for people having diet and exercise support alone. The committee noted that primary care weight management services are being delivered, although access and level of support varies across the country (see section 3.2). The committee discussed that of all the proposals it had seen, NHS England's were likely to represent the highest cost impact for obesity management services needed for delivering tirzepatide. The committee concluded that given the uncertainty around the weight management support needed for the tirzepatide and diet and exercise arms, it would consider a range of obesity management service scenarios in decision making. It noted that it is likely that scenarios using NHS England's proposals would result in the highest likely cost-effectiveness estimates.

Tirzepatide treatment effect over time

3.17 The company's model assumed that for the period of time that clinical trial data was available (72-weeks based on SURMOUNT-1 data), weight decreased for both those having treatment with tirzepatide and those having diet and exercise support alone, in line with the weight loss seen in each arm in the trial. After this point, for people having diet and exercise support alone, weight increase was assumed in line with natural progression because of age, based on data from Ara et al. (2012). For tirzepatide, the weight lost because of the treatment and its associated benefits was assumed to continue indefinitely until treatment was stopped. The EAG explained that this meant that the treatment effect between the tirzepatide treatment arms (which assumed a constant weight) and the diet and exercise arm (where weight increased steadily in line with natural history) increased over time. The EAG highlighted that there was no

evidence that this assumption was correct, because data from SURMOUNT-1 was only available for 72 weeks. The clinical experts suggested that it is likely that, over time, people on tirzepatide would regain weight even while on treatment. This is because, on average, weight is gained as people get older because of more sedentary lifestyles and increased chance of disability. But, they noted that this is uncertain because there is no long-term evidence for tirzepatide. The EAG highlighted evidence from the SCALE study in liraglutide that suggested weight is regained over time while still on treatment. It explained that a similar reduction in absolute treatment effect over time is plausible for tirzepatide. The EAG removed the increasing difference in treatment benefit between arms by applying the same natural progressive increase in weight according to age to the tirzepatide arm after 72 weeks, in line with the end of trial follow up. The company explained that there is no evidence to suggest that the absolute treatment benefit of tirzepatide is lost over time and there is no biological rationale to support that assumption. It explained that a trial for tirzepatide with follow up of 102 weeks, SURPASS-4 (including a type 2 diabetes population and measuring kidney outcomes), showed no treatment effect waning over that period. The committee discussed that the rate of weight gain while on tirzepatide and when this would start was uncertain without long-term clinical data. But it had not been presented with any evidence that showed that the relative treatment difference between tirzepatide and diet and exercise arms increases over time. The committee concluded that it was likely that the impact of age-related natural increase in weight would, to some extent, also impact someone taking tirzepatide over the time horizon of the model. So, it preferred the EAG's assumption that applied the natural progressive increase in weight to both arms.

Weight regain after stopping treatment

3.18 The company assumed in its model that after stopping tirzepatide, the weight that had been lost was regained at a steady rate over 3 years. At

3 years after stopping treatment, weight was aligned with where it would have been had treatment not started (in line with the diet and exercise support arm endpoints). The EAG explained that the rate of weight regain seen after stopping semaglutide treatment in STEP-1 (see section 3.12) suggested that the time it takes for the treatment effect to be lost is closer to 2 years. The clinical experts explained that STEP-1 provided relevant data to estimate the time that treatment benefits would be lost after stopping tirzepatide. They explained that for semaglutide, around two thirds of the weight lost while on treatment is regained within the first year after stopping and that the benefits gained such as reduced blood pressure are also lost by this time. But they noted that there is no long-term data for what happens to weight after stopping tirzepatide. After the first committee meeting, the EAG updated its model to assume that weight would be regained in 2 years after stopping tirzepatide. The EAG noted that assuming either 2 or 3 years for time to weight regain did not have a meaningful impact on the ICER. The committee concluded that it was uncertain how quickly the benefits associated with tirzepatide would be lost after stopping treatment. But it preferred to assume that weight would be regained in 2 years after stopping in line with the evidence for semaglutide.

Prediabetes reversal loss

3.19 The EAG highlighted that in the diet and exercise support arm in the model, people who had prediabetes (also known as non-diabetic hyperglycaemia) at baseline who had this prediabetes reversed as a result of weight loss, had prediabetes return at 2 years. It explained that this was different from how prediabetes reversal was modelled in the active treatment arms. It explained that for people on tirzepatide, prediabetes reversal was lost 3 years after stopping treatment. The company explained that this was because prediabetic status cannot be gradually reversed in the individual patient simulation model. The EAG explained that handling the loss of prediabetes reversal differently in the

diet and exercise support arm and the active treatment arms biases the cost-effectiveness results, favouring active treatment. The EAG explained that it could not directly amend the model so that the diet and exercise support and active treatment arms were aligned in how prediabetes reversal was handled. But, it advised that analyses to mimic this suggested that this could have a large effect on the cost-effectiveness results. The company explained that it is not possible to stop diet and exercise because ongoing diet and exercise support should always be available for people managing obesity. So, it's not possible to exactly replicate the approach to loss of prediabetes reversal in the diet and exercise arm that is used in the tirzepatide arm. But, it presented a scenario where the time point for loss of prediabetes reversal in the diet and exercise arm aligns to the time point at which the diet and exercise arm average weight returns to baseline in the model. This aligned more with the approach in the tirzepatide arm where prediabetes reversal occurs 3 years after treatment is stopped and weight that was lost has been regained. The company noted that there is no data to support the glycaemic improvements modelled in the diet and exercise arm and so this scenario is likely to overstate the duration of prediabetes reversal in that arm. The clinical experts explained that prediabetes reversal loss is likely to be slower after stopping tirzepatide than in people who have lost weight through diet and exercise alone. But they also explained that the rate of prediabetes reversal loss is primarily driven by the person's weight rather than whether they have had tirzepatide. The committee concluded that prediabetes reversal loss was likely to be driven by weight regain. So, it concluded that it was appropriate for prediabetes reversal loss in both the tirzepatide and diet and exercise arms to align with when weight was regained in those arms.

Long-term impact of obesity

3.20 After the first committee meeting, the EAG highlighted that the model assumes that the health risks for someone with a high BMI at baseline

that decreases during the time horizon of the model are equal to the health risks for someone who consistently had the same lower BMI. In other words, the model did not account for any non-reversible long-term impact on health outcomes from having previously had a higher BMI. The EAG suggested that this might not be appropriate. For example, if someone had been insulin resistant for a long time because of their obesity, the long-term impact on cardiovascular outcomes is unlikely to be similar to someone who had never been insulin resistant. The patient expert explained that the long-term impact of previous higher BMI does affect some domains of health, including a long-term psychological impact for some people. The clinical experts explained that there are high levels of variation in what the ongoing long-term adverse effects are from having had a higher BMI, but that this will impact a proportion of people. The EAG presented evidence from Haase et al. (2021), a retrospective study of UK databases that estimated the effect of intentional weight loss on the risks of various weight-related complications. The EAG acknowledged that there were limitations to Haase et al., but that it indicated it may be unreasonable to assume there is no long-term impact from having previously had a higher BMI. It also highlighted that Haase et al. did not include a measure of the increased risk of mortality, so there was no evidence to indicate if previous higher BMI was associated with increased mortality risk. The EAG suggested that the model may overestimate the effect of weight loss on obesity-related complications and potentially mortality risk, although the latter was less clear. The EAG presented scenario analyses. These reduced the effect of weight loss on particular outcomes in the model by 25% or 50% if the data in Haase et al. indicated that there was a residual risk of that outcome occurring from having previously had a higher BMI. It applied these scenarios to subgroups according to BMI in line with the data presented by BMI subgroups in Haase et al. For the subgroup of people with a BMI of 30 kg/m^2 to 35 kg/m^2, it also presented a scenario where it combined a 50% loss of effect in the outcomes shown to have residual effect from having

previously had a higher BMI with a 25% loss of effect on mortality from weight loss applied in the model. The EAG acknowledged that the scenarios presented reflected an arbitrary reduction in loss of effect based on the evidence that there is residual risk for those outcomes. But, that the scenarios provided a way of showing the impact on the ICER if the long-term impacts of obesity were taken into account. The company raised concerns around the implementation of these scenarios and explained that it is well understood that losing weight has an overall benefit on long-term outcomes. The committee discussed that although there were potential biases with the Haase et al. data, it showed it is reasonable to assume that there will be some long-term impact on some outcomes from having previously had a higher BMI. This was also supported by the clinical experts. The committee discussed that if the residual impact of having previously had a higher BMI was not included in the model, as was the case with the company and EAG base cases, the QALY gain is likely to be overestimated. It concluded that there was uncertainty introduced into the model because it did not account for this. It concluded that the base-case ICERs presented were likely to be higher if any reduction in effect from a residual impact of having previously had a higher BMI was taken into account.

Stopping because of non-response

3.21 The summary of product characteristics for tirzepatide states that a decision should be made on whether to stop treatment if less than 5% of initial body weight is not lost 6 months after titrating to the highest tolerated dose (non-responders). The patient experts explained that having this decision point was important to help identify people whose condition does not respond to tirzepatide and for whom treatment should be stopped. This is because these people will not gain the benefits from treatment but will continue to have the risk of side effects. The clinical experts agreed that stopping treatment after 6 months without a response at the highest tolerated dose was appropriate. The company originally

estimated the number of people who would stop tirzepatide at 46 weeks in the model (6 months after titrating to the 15 mg dose) from the proportion of non-responders after 72 weeks in the full trial population in SURMOUNT-1. After the first committee meeting, the company used data from the full trial population at 48 weeks to inform the proportion of non-responders. The EAG highlighted that data is available from SURMOUNT-1 for the proportion of non-responders at 48 weeks in the target population, but this had not been supplied. It suggested that using this to estimate the number of people stopping treatment at 46 weeks would be more appropriate, because it aligns closely with the recommendation to assess treatment response at 46 weeks for those on the 15 mg dose of tirzepatide. It also noted that using the SURMOUNT-1 data for non-responders at 6 months in the applicable subgroup, rather than the full trial population, is appropriate. After the first committee meeting, the EAG used the company's original approach estimating the number of people who would stop tirzepatide at 46 weeks in the model from the proportion of non-responders after 72 weeks in the full trial population in SURMOUNT-1. This was because it had not been supplied with the relevant 48-week data for each subgroup. The company assumed that 10% of people on semaglutide would stop treatment after 6 months because of non-response, based on clinical expert opinion. The clinical experts in the committee meeting suggested that they would expect a higher proportion of people to stop semaglutide because of a lack of response. After the first committee meeting, a comparator company submitted evidence to show the proportion of people who stopped semaglutide because of non-response at 6 months in a trial of semaglutide for weight loss. The committee concluded that to estimate the proportion of people stopping tirzepatide because of lack of response after 46 weeks, it was appropriate to use the closest available data on this outcome from SURMOUNT-1 for the company's target population, which was at 48 weeks. It further concluded that it was appropriate to include the

available trial data for semaglutide to estimate the response rate at 6 months.

Long-term stopping rules

3.22 The company did not include a long-term stopping rule for tirzepatide in any of its analyses, because it suggested that tirzepatide could be used either within or outside specialist weight management services and so was not restricted by its time limitations (see section 3.2). The patient expert explained that obesity is a chronic condition that needs long-term treatment. The EAG explained that SURMOUNT-4 data suggests that after stopping tirzepatide, weight is regained over time. The clinical experts explained that this was also supported by longer-term evidence for semaglutide from STEP-1. At the first committee meeting, the EAG provided 2 base cases including and not including a 2-year stopping rule for tirzepatide. After the first committee meeting, it updated its base case to not include a 2-year stopping rule for tirzepatide. Both the company and the EAG included a 2-year stopping rule for semaglutide because it is only available in specialist weight management services, which are accessible for a maximum of 2 years. The committee concluded that it was not appropriate to include a long-term stopping rule for tirzepatide. It further concluded that for the comparison with semaglutide, it was appropriate to apply a 2-year stopping rule for semaglutide.

Annualisation of multi-year event risks

3.23 The risk equations used in the company's model estimate the risk of the event occurring (such as development of type 2 diabetes) over multiple years, based on an individual's risk factors. The EAG explained that the risk of an event occurring is annualised from this value and it is applied in the model in an annual cycle. The EAG noted that it is unlikely that the risk of an event occurring is constant over a given time and that annualising the event risk may lead to estimating that events occur too early in the model. This would lead to bias because people would be

assumed to have events for too long. It also explained that the model re-estimates the risk of each event annually, based on the updated health outcomes of the person in the model. This leads to some people in the model having increased risk of an event every year over the same time in which the risk equation estimates an initial risk of an event. The EAG explained that this leads to overestimation in the incidence of events in all arms. But because of the improved outcomes for people in the active treatment arms, the bias would favour those arms. The EAG provided analysis that estimated the amount of overestimation of the risk of events for an average person in the model. It presented scenario analyses that included adjustments to the 10-year risk functions to account for these overestimations. It noted that these scenarios were illustrative and given the model structure it was not possible to quantify the exact impact of the potential compounding of the risk of events over time. The company also presented scenarios to show the impact on its base case if the risk of developing type 2 diabetes was reduced by 25% and 50% in all arms. The committee considered both the company's and the EAG's scenario analyses, noting that the EAG's adjustments especially had a limited impact on the ICER. It concluded that the compounding of the risk of events remained an uncertainty in the model, but it was reassured by the EAG's scenario analysis that showed this uncertainty did not have a large impact on the cost-effectiveness estimates.

Cost of type 2 diabetes

3.24 The company sourced the cost of type 2 diabetes from NHS reference costs from 2021, covering diabetes-related hospital attendance across 74,041 people. The EAG suggested that this was not representative of the around 4 million people in the UK with type 2 diabetes and it was not clear how the company had estimated its costs. It preferred to use the UK Prospective Diabetes Study (UKPDS) data, which estimated the cost of consultations, visits, admissions and procedures associated with diabetes-related complications between 1997 and 2007. The UKPDS data

did not take into account expensive items of care for end-stage renal disease, dialysis and transplant. But the EAG suggested that because people in the model have newly developed type 2 diabetes, they were less likely to experience these more expensive items of care in the near future. The EAG explained that the resulting annual inpatient and non-hospital costs represented a total cost for a person with type 2 diabetes and no other comorbidities, and not the net cost compared with a person with obesity. So, it likely overestimates the costs associated specifically to type 2 diabetes in people who also have obesity. So, the EAG used the UKPDS non-hospital costs in its base case to account for this difference. The company considered the EAG's approach to be overly conservative, stating that: it does not include drug costs for type 2 diabetes; that it excludes inpatient costs not otherwise captured by the model, and, that it doesn't account for people with advanced disease who need more intensive treatment. It presented scenarios that used costs sourced from Capehorn et al. (2021) for the costs of microvascular complications and the drug treatments associated with type 2 diabetes. The EAG questioned the appropriateness of using data from Capehorn et al. to estimate the costs associated with newly diagnosed type 2 diabetes, because the average duration since diagnosis of type 2 diabetes in Capehorn et al. was 7 years. It suggested that the costs associated with type 2 diabetes are likely to be greater for people who have had the disease for longer. After the first committee meeting, the EAG updated its base-case assumptions to use the UKPDS costs as well as an estimate for the drug costs associated with type 2 diabetes based on drug tariff prices. This estimate takes into account the sequential treatment options that would be offered to someone with newly diagnosed type 2 diabetes, in line with recommendations in NICE's guideline on type 2 diabetes in adults: management. The committee discussed that no-one enters the model with type 2 diabetes (see section 3.14) and so it is reasonable to estimate the costs associated with recently diagnosed type 2 diabetes. It considered that the company's NHS reference cost estimates, which only covered

hospital attendance-related costs, were likely overestimated. The committee concluded that the EAG's approach, which included UKPDS non-hospital costs in addition to drug costs, was most appropriate to include in decision making.

Cost-effectiveness

Acceptable ICER

3.25 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically that:

- There are high levels of uncertainty around the long-term treatment effects of tirzepatide (see section 3.17).
- There are high levels of uncertainty around the impact of a previously higher BMI on long-term outcomes (see section 3.20).

The committee discussed that, as well as the high levels of uncertainty, there is also high decision risk given the potential population size eligible for tirzepatide if it was recommended. Taking both factors into account, the committee concluded that an acceptable ICER would be around £20,000 per QALY gained.

Company and EAG model assumptions

3.26 The company's base-case model assumptions included:

- background resource costs for GP and nurse visits and blood tests for both arms (see section 3.16)

- no decrease in tirzepatide treatment effect while on treatment and a net increase in tirzepatide treatment effect over time (see section 3.17)
- weight regained over 3 years after stopping treatment (see section 3.18)
- prediabetes reversal benefit lost in the diet and exercise support arm after 2 years in the model and 3 years after stopping active treatment in the tirzepatide arm (see section 3.19)
- tirzepatide stopping rates at 6 months because of non-response based on the proportion of people remaining on treatment at 6 months in the full trial population (see section 3.21)
- semaglutide stopping rates (10%) at 6 months because of non-response based on clinical expert opinion (see section 3.21)
- no long-term stopping rule for tirzepatide (see section 3.22)
- event risks estimated by risk equations, estimating the annual rate of events from multi-year event risks (see section 3.23)
- costs for type 2 diabetes taken from NHS reference costs 2021 (see section 3.24).

The following amendments were made by the EAG and included in its base case:

- including a proportion of people at baseline with previous myocardial infarction, obstructive sleep apnoea and non-alcoholic fatty liver disease (see section 3.14)
- applying the resource use proposed by NHS England for obesity management services to the tirzepatide arm for the duration of tirzepatide treatment and no resource use to the diet and exercise arm (see section 3.16)
- removing the net increase in tirzepatide treatment effect by applying natural progressive increase in weight according to age to the tirzepatide arm after 72-weeks (see section 3.17)

- assuming weight is regained over 2 years after stopping treatment (see section 3.18)
- assuming tirzepatide stopping rates at 6 months because of non-response based on the proportion of non-responders after 72 weeks in the full trial population in SURMOUNT-1 (see section 3.21)
- using the costs for type 2 diabetes from UKPDS plus an estimate of drug costs associated with type 2 diabetes based on drug tariff prices (see section 3.24)
- removing mortality modifiers applied in the company's model for history of angina, myocardial infarction and stroke because the increased risk of death from these events is covered by the BMI mortality modifier
- amending the adverse event-related treatment stopping rate from annually applying the stopping rate because of adverse events from SURMOUNT-1 at 72 weeks (the company's assumption), to mainly applying stopping because of adverse events in the first year of the model, followed by an annual 1% stopping rate
- halving the non-alcoholic fatty liver disease incidence rate to adjust for differences in hazard ratios observed across the 2 studies used by the company to estimate incidence rate and hazard ratios for the development of non-alcoholic fatty liver disease, because the hazard ratios were around double in the study used to source these than in the study used to source incidence rate
- increasing the prevalence of obstructive sleep apnoea for people with a BMI between 30 kg/m^2 and 35 kg/m^2 (2.85% sourced from the UK Clinical Practice Research Datalink database) compared with the company's assumption that this population has equal risk of obstructive sleep apnoea to the general population
- amending the quality-of-life functions used by the company to compensate for effects of the function where quality of life starts to improve as BMI increases beyond 39.0 kg/m^2 for men and 46.5 kg/m^2 for women

- removes disutilities included by the company for obesity-related complications that are already covered by the quality-of-life functions
- other minor model amendments that cumulatively had a negligible impact on the cost-effectiveness estimates.

The committee's preferred assumptions

3.27 The committee's preferred assumptions mostly aligned with the assumptions in the EAG's base case (see section 3.26). Its preferred assumptions that differed from the EAG's base case were:

- prediabetes reversal loss modelled so that it aligns with the approximate time in the model that baseline weight is regained in all arms (see section 3.19)
- an adjustment for BMI distribution in the model to reflect the population who would be potentially eligible to have tirzepatide in the general population (see section 3.15) and
- assuming tirzepatide stopping rates at 6 months because of non-response based on the proportion of non-responders at 48 weeks in the target population in SURMOUNT-1 (see section 3.21).

It also agreed that it would like to see further analysis including all its preferred assumptions and:

- different assumptions for obesity management service resource use for all arms (see section 3.16)
- analysis of the long-term impact on outcomes from previously having had a higher BMI (see section 3.20).

Incremental cost-effectiveness ratios

3.28 The EAG presented 5 base-case analyses covering different populations:

- People with a BMI of at least 30 kg/m^2 and at least 1 weight-related comorbidity (the company's target population).

- People with a BMI of at least 30 kg/m^2 and less than 35 kg/m^2 and at least 1 weight-related comorbidity.
- People with a BMI of at least 35 kg/m^2 and at least 1 weight-related comorbidity.
- People with a BMI of at least 35 kg/m^2, prediabetes and a high risk of cardiovascular disease.
- People with a BMI of at least 30 kg/m^2 and less than 35 kg/m^2 and at least 1 weight-related comorbidity, or with a BMI of at least 35 kg/m^2 without prediabetes or a high risk of cardiovascular disease, or without prediabetes and high risk of cardiovascular disease.

At the second committee meeting, none of the company's or EAG's analyses included all the committee's preferred assumptions. The EAG noted that the subgroup analyses included the subgroup-specific baseline characteristics but applied the clinical effect estimates from the target population. The committee discussed that it would prefer to include the relevant efficacy data for each subgroup. After the second committee meeting, the company presented analyses with all the committee's preferred assumptions, including subgroup-specific efficacy data, for the following subgroups:

- People with a BMI of at least 35 kg/m^2 and at least 1 weight-related comorbidity.
- People with a BMI of at least 35 kg/m^2, prediabetes and a high risk of cardiovascular disease.

For the population with a BMI of at least 35 kg/m^2 and at least 1 weight-related comorbidity, the company presented a range of scenarios on these analyses. This included different resource use for obesity management services, in line with the committee's preference to use a range of scenarios in decision making (see section 3.16). The ICERs presented compared with diet and exercise ranged from £15,355 to £18,559 per QALY gained. The EAG commented that the resource use

included in the company's scenario analyses, including the NHS England proposed resource use, was not in line with the figures provided by NHS England. So, the EAG also presented 2 additional scenarios including NHS England's proposed resource use on a base case including the committee's preferred assumptions for the population with a BMI of at least 35 kg/m^2 and at least 1 weight-related comorbidity. The first included the NHS England proposed resource use applied only to the tirzepatide arm, with no resource use included in the diet and exercise arm (£19,535 per QALY gained). The second included the NHS England proposed resource use applied to the tirzepatide arm and the same resource use, minus the titration appointments needed for tirzepatide applied to the diet and exercise arm (£18,850 per QALY gained). The committee also considered the scenarios on a base case including the committee's preferred assumptions presented by the EAG, adjusting for the long-term impact on outcomes from previously having had a higher BMI (see section 3.20). It noted that the impact on the ICER from including this analysis was limited and so was unlikely to influence decision making. The committee concluded that all the scenarios it had been presented with, including its preferred assumptions for people with a BMI of at least 35 kg/m^2 and at least 1 weight-related comorbidity, were below £20,000 per QALY gained.

The committee noted that although none of the analyses presented for people with a BMI of at least 30 kg/m^2 and at least 1 weight-related comorbidity (the company's target population) included all its preferred assumptions, the EAG's base case most closely reflected these. It noted that in the EAG's base case, the company's target population compared with diet and exercise resulted in an ICER of £24,735 per QALY. The ICERs for the comparison with semaglutide include a confidential comparator discount and so cannot be reported here, but they were within a similar range as the ICERs for the comparison with diet and exercise. The committee discussed that it would like to see ICERs including all its preferred assumptions and the relevant subgroup efficacy data for the

company's target population and for people with a BMI of at least 30 kg/m^2 and less than 35 kg/m^2 and at least 1 weight-related comorbidity who may be at particularly high risk. The committee concluded that the ICERs for the subgroups of people with a BMI of at least 35 kg/m^2 including all its preferred assumptions were below £20,000 per QALY gained. It further concluded that it had not been presented with ICERs for the company's target population that included all its preferred assumptions, but that the analysis that most closely reflected this resulted in an ICER over £20,000 per QALY gained.

Other factors

Equality

3.29 The committee was aware that people with mental health disorders, especially those having atypical antipsychotics may have increased risk of developing obesity, but that the ability to access specialist weight management services may be limited for these people. The committee discussed that it would consider tirzepatide across both primary and secondary care settings. Therefore, eligibility for tirzepatide will not be restricted by access to specialist weight management services. The committee was also aware that SURMOUNT-1 did not include people with a history of significant active or unstable major depressive disorder or other severe psychiatric disorders within the last 2 years. So, there was no evidence for the treatment effect of tirzepatide in this population or any evidence for how much additional psychological support might be needed. But, despite the increased level of uncertainty this introduced into the model, the committee agreed that populations excluded from SURMOUNT-1 should not be excluded from the recommendations for tirzepatide. The committee was also aware that overweight and obesity disproportionately affects socioeconomically disadvantaged communities and that this is likely to contribute to health inequalities. It understood that services for overweight and obesity are unequal across the country and can be very limited, and they are not necessarily available in the areas of

the country with the greatest need (see section 3.3). There is uncertainty around the level of additional diet and exercise support that will need to be implemented alongside tirzepatide. But, the NHS England clinical adviser explained that obesity services are changing rapidly. The committee concluded that it was not within its remit to make recommendations about obesity management services but tirzepatide should be accompanied by diet and exercise support services. The committee noted that people from some ethnicities are at an equivalent risk of the consequences of obesity at a lower BMI than people from White ethnicities. NICE's clinical guideline on obesity: identification, assessment and management recommends using lower BMI thresholds for people with a South Asian, Chinese, other Asian, Middle Eastern, and Black African or African-Caribbean ethnicity as a practical measure of overweight and obesity. The committee agreed that a similar adjustment to the BMI thresholds are suitable for tirzepatide.

Use in practice

3.30 The committee discussed that there are likely to be challenges with implementing tirzepatide in primary care and that a longer implementation period to comply with the recommendation may be required. This is because the number of people who would potentially be eligible for tirzepatide is large and the resource needed for its delivery, including the accompanying diet and exercise support, is not available equitably across the country (see sections 3.2 and 3.3). It was aware that the company may provide further evidence and analyses in support of a broader recommendation for other populations after the draft guidance consultation. The committee discussed if there were any groups of people who could be prioritised for tirzepatide if a funding variation was required. The patient expert explained that the greatest unmet need was for people with a BMI of at least 35 kg/m^2 (see section 3.1) and for people who lose and gain weight regularly. The clinical experts explained that people who need to lose weight before they can have surgery or fertility treatment, or

who have 3 or more weight-related comorbidities may particularly benefit from tirzepatide treatment. The committee concluded that the groups highlighted by the patient and clinical experts may be appropriate for prioritisation if needed. It further concluded that although it was aware of the potential implementation challenges, its remit is to evaluate the clinical and cost effectiveness of tirzepatide and so it could not consider implementation issues further in decision making.

Conclusion

Recommendation

3.31 The committee concluded that the ICERs for tirzepatide compared with both diet and exercise and semaglutide for the company's target population were likely to be above the acceptable ICER when all its preferred assumptions were taken into account. It further concluded that the ICER for tirzepatide compared with diet and exercise for people with a BMI of at least 35 kg/m^2 and at least 1 weight-related comorbidity is likely below the acceptable ICER. So, tirzepatide is recommended for a subgroup of people as an option for managing overweight and obesity, alongside a reduced-calorie diet and increased physical activity, in adults, only if they have:

- an initial BMI of at least 35 kg/m^2 and
- at least 1 weight-related comorbidity.

Lower BMI thresholds (usually reduced by 2.5 kg/m^2) should be used for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean ethnic 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 integrated care boards,

NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of final guidance publication. There may be system challenges that mean an extension to this normal period may be appropriate (see section 3.30 and the request for consultation comments at the start of this draft guidance). If a funding variation request is submitted and accepted by NICE, a consultation with stakeholders will be undertaken on the proposals.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has overweight or obesity and the healthcare professional responsible for their care thinks that tirzepatide is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

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

Chair

James Fotheringham

Vice chair, technology appraisal committee A

NICE project team

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

Albany Chandler

Technical lead

Yelan Guo, Sally Doss

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