NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Tirzepatide for managing overweight and obesity

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 a lower BMI threshold (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 If less than 5% of the initial weight has been lost after 6 months on the highest tolerated dose, decide whether to continue treatment, taking into account the benefits and risks of treatment for the person.

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.

What this means in practice

Tirzepatide must be funded in the NHS in England to manage overweight and obesity in adults, if it is considered the most suitable treatment option. There is a funding variation for tirzepatide that means it will be introduced in phases. More details are available in the implementation section of this guidance.

NHS England's interim commissioning guidance for NICE's technology appraisal guidance on tirzepatide sets out who may be eligible for tirzepatide over the 3-year period from when this guidance was published.

It says that your eligibility for tirzepatide will depend on your BMI and how many of the following weight-related health conditions you have:

- high blood pressure
- dyslipidaemia (abnormal blood fats)
- obstructive sleep apnoea
- cardiovascular disease (for example, heart disease)
- type 2 diabetes.

You may be eligible now if you have:

- 4 or more of the listed weight-related health conditions and
- a BMI of 40 kg/m^2 or more.

From around June 2026 you may be eligible if you have:

- 4 or more of the listed weight-related health conditions and
- a BMI between 35 kg/m^2 and 39.9 kg/m^2.

From around March 2027 you may be eligible if you have:

- 3 of the listed weight-related health conditions and
- a BMI of 40 kg/m^2 or more.

For people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean ethnic backgrounds, the qualifying BMIs are 2.5 kg/m^2 lower (for example, 37.5 kg/m^2 instead of 40 kg/m^2).

NICE has also produced tools and resources to support the implementation of this guidance.

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 and may change in the future. Some people may also have semaglutide alongside diet and exercise support if their obesity is managed in a specialist weight management service. Tirzepatide can be used in primary care or specialist weight management services.

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 adults 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 adults 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 in the NHS 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, all people living with obesity would welcome further treatment options, especially if they were easier to access. The committee understood that overweight and obesity is a chronic condition that needs treatment. It concluded that there is an unmet need for a large proportion of adults 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 across both primary and secondary care settings. NICE's guideline on overweight and obesity management recommends that interventions provided by overweight and obesity management services should:

- include sustainable ways the person can reduce sedentary behaviour and fit more physical activity into everyday life over the long term
- take any medical conditions the person may have into account when planning any physical activity sessions
- have a qualified activity instructor leading any supervised activity sessions
- last at least 3 months, with weekly or fortnightly sessions
- monitor and review progress toward individual goals throughout the intervention
- be developed by a multidisciplinary team (MDT) that includes healthcare professionals with expertise in overweight and obesity management, nutrition, psychology or physical activity
- be run by staff who are trained in delivering overweight and obesity management interventions and take part in regular professional development sessions.

A clinical expert explained that primary care weight management services are 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 assessments and interventions. NICE's guideline on overweight and obesity management defines these as specialist primary, community or secondary care-based services led by an MDT offering a combination of nutritional, psychological and surgical interventions, and medicines. They are accessible for a maximum of 2 years. So, the pharmacological treatments recommended for some adults within specialist weight management services in NICE's technology appraisal guidance on semaglutide and NICE's technology appraisal guidance on 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 the availability of specialist weight management services varies across the country, and may change in the future.

Treatment setting

3.3 In its submission, the company proposed that tirzepatide could be used in primary or secondary care, and the appropriate diet and exercise support

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 already deliver similar interventions in the NHS (see section 3.8). To support this assumption, it presented evidence from a survey of GPs in England and Wales. It suggested that 78% of the GPs who 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 primary and secondary care would be welcomed. This is because 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 limited. They noted that the setting for tirzepatide delivery should not be restricted. But, they added 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. At draft guidance consultation, stakeholders agreed that diet and exercise interventions needed alongside tirzepatide are not available in primary care consistently across the country. The NHS England clinical adviser explained that obesity services in the NHS are changing rapidly. An example of this is 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. Stakeholders agreed with these implementation challenges. The committee concluded that it would consider tirzepatide in primary and secondary care settings. But it noted that 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 adults 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 adults 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. This included adults with:

- a BMI of 35 kg/m^2 or more with non-diabetic hyperglycaemia and a high risk of cardiovascular disease (the population who are eligible for liraglutide; see section 3.5)
- a BMI of 30 kg/m^2 or more irrespective of comorbidities, and
- a BMI of 35 kg/m^2 or more irrespective of comorbidities.

After the second committee meeting, the company also submitted evidence for adults 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 their risk of complications. The clinical experts explained that people with a higher BMI and comorbidities were generally at higher risk of the consequences of obesity. The committee concluded that the company's target population was appropriate to consider for tirzepatide, but that it would also consider the subgroups presented.

Comparators

3.5 In line with the NICE scope, the company suggested in its submission the appropriate comparators for its target population were:

- semaglutide alongside a reduced-calorie diet and increased physical activity (referred to as diet and exercise support), and
- diet and exercise support alone.

The company also included liraglutide as a comparator for a subgroup of this population who are eligible for this treatment. NICE's technology appraisal guidance on semaglutide for managing overweight and obesity recommends semaglutide alongside diet and exercise for 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
- they have 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 they meet the criteria for referral to specialist weight management services in section 1.11.13 on referring adults to specialist services in NICE's guideline on overweight and obesity management.

NICE's technology appraisal on liraglutide for managing overweight and obesity recommends liraglutide alongside diet and exercise only if it is prescribed in secondary care by a specialist multidisciplinary tier 3 weight management service and only for adults 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 adults 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. This is because it needs to be stopped after 2 years and there are concerns around regaining weight 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 adults 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 of the following weight-related comorbidities: hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular

disease. People with type 2 diabetes were excluded, but people with prediabetes were not. People with history of significant active, unstable major depressive disorder, or other severe psychiatric disorders within the last 2 years were also excluded. The trial was done in 9 countries 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 adults with a BMI of 30 kg/m^2 or more with at least 1 weight-related comorbidity. This 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 people 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. If recommended, more people with type 2 diabetes may be eligible for tirzepatide if they meet the criteria for tirzepatide treatment for weight management. At consultation, stakeholders raised concerns that SURMOUNT-1 excluded people with type 2 diabetes and so there is no clinical-effectiveness data on tirzepatide for managing obesity for these people. During the third committee meeting a clinical expert explained that there may be greater health gains in people with type 2 diabetes than people without. This is because tirzepatide affects blood glucose levels as well as weight loss. They explained that although evidence suggests there is less weight loss for people with type 2 diabetes than for people without, tirzepatide's impact on blood glucose levels is greater. The EAG also highlighted evidence that suggested that natural history weight gain is slower in people with diabetes. So, it is possible that people with type 2 diabetes

would have a slower rate of weight regain after stopping tirzepatide (see section 3.17). A patient expert explained that there is often an overlap of people living with obesity and living with type 2 diabetes. Separating access to tirzepatide for the 2 populations could create confusion and worsen existing stigma. 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. 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. This included but was 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. So, it was unclear what level of additional psychological support these adults 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 because SURMOUNT-1 did not include people with type 2 diabetes or with certain mental health disorders, it did not cover the whole licensed population. It also did not cover the whole population who would potentially have tirzepatide in the NHS. But, the committee noted that the health benefit gained with tirzepatide seen in SURMOUNT-1 was likely to be generalisable to people with type 2 diabetes. This is because for people with type 2 diabetes, tirzepatide would be more likely to have other health benefits in addition to weight loss (for example, its greater effect on blood glucose levels). The committee also noted that natural history weight regain is likely to be slower after stopping tirzepatide. The

committee concluded that there was some uncertainty about the generalisability of the clinical-effectiveness results in SURMOUNT-1 to the population who would potentially be offered tirzepatide, but this was acceptable.

Diet and exercise support in SURMOUNT-1

3.8 People in all arms of SURMOUNT-1 were advised on diet and exercise. This included a diet with a 500-calorie per day deficit and to increase their weekly physical activity by 150 minutes. People in the trial also saw a dietitian (or equivalently qualified delegate according to local standards) for diet and exercise management counselling at weeks 0, 4, 8, and 12 during dose escalation. They then saw them again at week 24 and then every 12 weeks throughout the trial. 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 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 in many cases was delivered virtually rather than face-to-face, 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 primary and secondary care in the NHS. It explained that its target population only included people with a comorbidity. 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 noted that there would be differences in how the diet and exercise support is delivered in different countries. But they explained that, overall, the trial is generalisable to clinical practice in the NHS. They also explained that they would anticipate that the weight loss seen in the trial may be similar without the diet and exercise support provided. This is because diet and exercise contributes less to weight loss in combination with a treatment like tirzepatide. But, they noted that diet and exercise was an important component of the overall intervention. The

committee noted that the diet and exercise support in SURMOUNT-1 was given for the full 72-week trial duration. It recalled that diet and exercise support interventions are being delivered in some areas within primary care. But it noted that 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). 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. There was particular uncertainty regarding the length of availability, intensity and consistency across the country. So, the committee concluded that it would need to consider tirzepatide in the context of a range of weight management services.

Dose escalation and dosing in SURMOUNT-1

3.9 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. It compared a maximum tolerated dose of tirzepatide (either 10 mg or 15 mg) and placebo. This showed that 92.5% of people in the trial were able to tolerate a maximum dose of 15 mg. 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 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

3.10 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 (n=1,705; see section 3.4), and subgroups including adults 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 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 adults 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

3.11 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, adults 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 adults 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

3.12 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 3.8). 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 3.9). 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

3.13 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 they 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 3.12), 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 SURMOUNT-1, 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 clinical trial evidence (from SURMOUNT-2 and SURPASS) suggests that people with type 2 diabetes do show improved glycaemic control and therefore additional health benefits with tirzepatide (see section 3.12). Clinical experts agreed that there are likely to be additional health gains with tirzepatide for people with type 2 diabetes (see section 3.7) and that this is not reflected in the economic model. The EAG agreed that the economic model is not set up to model people with type 2 diabetes. This is because one of the key drivers of the model is the avoidance or delay of type 2 diabetes, which does not apply to people who already have it. It did not include a proportion of people with type 2 diabetes in the baseline model population. So people who have type 2 diabetes at baseline are not represented in the model. 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 support 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's baseline population not including people with type 2 diabetes. But if this population were included in the model the benefits of tirzepatide would likely be underestimated. It concluded that it was appropriate to include people with type 2 diabetes within any population for which tirzepatide was recommended for weight management.

BMI distribution

3.14 The company estimated the BMI distribution of people included in the model from a gamma distribution fitted to the SURMOUNT-1 target population. The EAG raised concerns that the gamma distribution does not include enough people at the lower end of the BMI range. A comparator company also 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. In response to draft guidance consultation, the company provided detailed graduation of the BMI distribution of people with a BMI of 30 kg/m^2 and higher with at least 1 comorbidity in SURMOUNT-1. Based on this, the EAG noted that a relatively high proportion of people in SURMOUNT-1 had a BMI of 30 kg/m^2 to 31 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. So, by not including enough people at the lower end of the BMI range, the cost-effectiveness estimates would be biased in favour of tirzepatide. The company presented data on BMI distribution from primary care adult weight management services. It suggested that this represented people who were incentivised to seek treatment and so would represent people who would be likely to use tirzepatide. The data showed that 34% of people with overweight or obesity accessing primary care adult weight management services between April 2021 and December 2022 had a BMI between 30 kg/m^2 and 34.9 kg/m^2. The company 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 the target population of SURMOUNT-1 was similar (35.5%). The EAG used a log-normal distribution fitted to Health Survey for England data on BMI distribution collected in the general population in its base case. 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 suggested that the general population better reflects the population who would be given tirzepatide, because it was plausible that anyone from the general population eligible for tirzepatide may start treatment. The patient expert explained that it was likely that many people with a BMI between 30 kg/m^2 and 34.9 kg/m^2 would want to take tirzepatide if it was available.

So, if tirzepatide was available for this population it is likely that the proportion of people with a BMI between 30 kg/m^2 and 34.9 kg/m^2 accessing primary care adult weight management services would increase. In response to draft guidance consultation, the company suggested data could be considered from the IMPACT-O study, which collected BMI data on people from UK primary care clinics between January 2018 and September 2022. The company suggested that the data lies between the Health Survey for England data and the community weight management service data. The committee noted 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 access tirzepatide through primary care if it is recommended. The committee considered that the BMI distributions in SURMOUNT-1, primary care adult weight management services and IMPACT-O were likely to be different to the population who would access tirzepatide in clinical practice. So, it concluded that the EAG's base case using the log-normal distribution of the Health Survey for England data to model BMI distribution was most appropriate. But, the BMI distribution was uncertain, so the committee would also like to have seen scenarios using the BMI distribution from IMPACT-O.

Assumptions in the economic model

Costs of obesity management services

3.15 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
- injection training for patients
- monitoring appointments during dose titration

- diet and exercise counselling every 12 weeks
- a medicines review
- an additional MDT 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, because these services were given for the entire duration tirzepatide was given in SURMOUNT-1. 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. It also suggested 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 MDT 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 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 noted that it is not clear what these services will include. The EAG estimated the resource use for obesity management services according to NHS England's proposals. This reflected the interventions used in the trial for tirzepatide for as long as the person was on tirzepatide, and 2 years of 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. It 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 its 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

3.16 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 those having tirzepatide and those having diet and exercise support alone. This was 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. This was in line with natural progression due to 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 relative 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 in the long term because data from SURMOUNT-1 was only available for 72 weeks. In response to the draft guidance consultation, stakeholders were concerned about the lack of long-term treatment effect data. 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 included in the company's model. It did this by applying the same natural progressive increase in weight by age to the tirzepatide arm after 72 weeks, in line with the end of trial follow up. The company highlighted that by 72 weeks, the treatment effect for tirzepatide was constant. It 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 (Heerspink et al. 2022; including a population with type 2 diabetes and measuring kidney outcomes), showed no treatment effect waning for people having tirzepatide over that period. In response to draft guidance consultation, the company suggested that the data from SCALE was likely to include people who had stopped treatment. So it was not useful data to indicate what the absolute treatment effect for people on tirzepatide might be over time. It also highlighted that liraglutide is less effective than tirzepatide and so the applicability of findings from SCALE to indicate the treatment effect for tirzepatide is limited. The company also presented extension phase data from the SELECT study in semaglutide showing that there was no loss of

absolute treatment effect over 221 weeks. The company stated that this is more representative of tirzepatide, but there is no data beyond 221 weeks. The clinical experts supported the notion that weight seemed to stabilise on treatment with GLP-1 analogs (including semaglutide and tirzepatide) until they are stopped, but there is no long-term data. They explained that it is unlikely weight would be regained while on tirzepatide because of its mechanism of action. But they also explained that there is no observed data to show that people having the diet and exercise intervention in SURMOUNT-1 would have an increase in weight over time. The clinical experts explained that in the SCALE study, the weight gain seen in the liraglutide arm could be because of a reduction in lifestyle interventions in combination with liraglutide. They added that diet and exercise contributes less to the overall treatment effect when more effective pharmacological treatments are used. So, the same level of loss of effect from a reduction in lifestyle intervention would not be expected for tirzepatide. The EAG also explained that the natural history weight gain parameter the company used from Ara et al. (2012) only included people without type 2 diabetes. It suggested that it was appropriate to use a combined weight gain parameter that also included people with type 2 diabetes to reflect the population eligible for tirzepatide. The committee considered 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 effect difference between the tirzepatide and diet and exercise arms increases over time. It agreed that without long-term evidence this was highly uncertain. So, it concluded that it would consider multiple scenarios that assumed a constant relative treatment effect between the tirzepatide and diet and exercise arms in decision making. These include:

- applying natural history weight gain from 72 weeks in both the tirzepatide and diet and exercise arms based on weight gain parameters for people with and people without diabetes from Ara et al. (2012)

- applying no natural history weight gain in either the tirzepatide or the diet and exercise arm.

Weight regain after stopping treatment

3.17 In its submission, the company's model assumed 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 3.11) 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. Some other 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. In response to draft guidance consultation, the company also updated its model to assume that weight would be regained in 2 years after stopping tirzepatide. 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

3.18 The EAG highlighted that in the diet and exercise arm in the model, people who had prediabetes (also known as non-diabetic hyperglycaemia) at baseline that was reversed as a result of weight loss, had it 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, in line with when weight was regained in the company's original model. 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 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 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 is not possible to exactly replicate the approach to loss of prediabetes reversal in the diet and exercise arm that was used in the tirzepatide arm. But, the company presented a scenario in which the time points at which prediabetes reversal is lost and average weight returns to baseline are aligned in the diet and exercise arm 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. At the second committee meeting, 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. In response to draft guidance consultation, the EAG and company

both updated their base-case assumptions to reflect the committee's preferred assumption. The committee concluded that the changes to the model made by the EAG and the company meant that prediabetes reversal loss had been appropriately incorporated into the model.

Long-term impact of obesity

3.19 After the first committee meeting, the EAG highlighted that the model did not account for non-reversible long-term impacts on health outcomes from previously having a higher BMI. This is because the model assumes that someone with a high baseline BMI that decreases during the model's time horizon has equal health risks as someone with a consistently lower BMI. The EAG suggested that this might not be appropriate. For example, someone with long-term insulin resistance caused by their obesity is unlikely to have similar long-term cardiovascular outcomes to someone who had never had insulin resistance. The patient expert explained that the long-term impact of a previous higher BMI does affect some domains of health, including a long-term psychological impact for some people. The clinical experts explained that there is a lot of variation in the ongoing long-term adverse effects of having had a higher BMI, but it will impact some 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 direct 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 that suggested what impact the residual risk of previously having had a higher BMI could have, as indicated by the results in Haase et al. It acknowledged that the scenarios presented reflected an arbitrary

reduction in loss of effect based on the evidence that there is residual risk for some outcomes. But, that the scenarios provided a way of exploring 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. It raised further limitations with Haase et al., including that the weight loss from baseline in Haase et al. was lower than the weight loss seen with tirzepatide in SURMOUNT-1. The company highlighted a study by Khunti et al. (2023). This was an extension of the Haase et al. study that looked at the change in the risk of complications associated with weight loss. This study showed that the weight loss benefit on obesity-related complications depended on the amount of weight loss. The company highlighted the data indicating residual impacts from previously having had a higher BMI. It suggested that this shows there are important benefits associated with treating obesity early, before BMI progresses to later disease stages. Analysis based on Haase et al. and Khunti et al. was only incorporated into scenarios to show decision risk and not included in either of the company's or EAG's base cases. The EAG provided a scenario reducing the effect of type 2 diabetes on the model outputs to match the data from Khunti et al., which increased the ICER. There were potential biases with the Haase et al. data. But the committee considered that this data, and Khunti et al., showed it is reasonable to assume some long-term impact on some outcomes from having previously had a higher BMI. This was supported by the clinical experts. The committee felt that if the residual impact of a previously higher BMI was not included in the model, the QALY gain was likely to be overestimated. It noted that this was the case with the company and EAG base cases. So it concluded that there was uncertainty introduced into the model because it did not account for the residual impact of a previously higher BMI. It concluded that if any reduction in effect from this was taken into account, the base-case ICERs presented were likely to be higher.

Stopping because of non-response

3.20 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 having the 15 mg dose 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. In response to draft guidance consultation, the company updated its approach to estimating the number of people stopping treatment 6 months after titrating to the highest dose. To do this, it used data from the target population in SURMOUNT-1 at 48 weeks. 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 data from the target population in SURMOUNT-1 at 48 weeks. This is because this was the closest available data on this outcome. 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

3.21 The company did not include a long-term stopping rule for tirzepatide in any of its analyses. This was 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. This was because semaglutide is only available in specialist weight management services and they are only accessible for a maximum of 2 years. In response to draft guidance consultation, some stakeholders suggested that it was appropriate to not include a long-term stopping rule because obesity is a chronic condition that needs long-term management. Other stakeholders raised that NICE's technology appraisal guidance on semaglutide recommends it with a 2-year stopping rule. They suggested that it may be appropriate to also include a long-term stopping rule for tirzepatide, in line with recommendations for semaglutide. In NICE's technology appraisal guidance on semaglutide, the company proposed that semaglutide was used for up to 2 years and submitted a model reflecting this. The committee concluded that it was not appropriate to include a long-term stopping rule for tirzepatide. It also 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

3.22 The risk equations in the company's model estimate the risk of events occurring (such as development of type 2 diabetes) over multiple years, based on a person'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. So 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

3.23 In its submission, the company sourced the cost of type 2 diabetes from NHS reference costs from 2021 to 2022, 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. The EAG 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 non-inpatient costs represented a total cost per year for someone with type 2 diabetes without complications, and not the net cost compared with someone with obesity. So, it likely overestimates the costs associated specifically with type 2 diabetes in people who also have obesity. In calculating the costs for type 2 diabetes, the EAG therefore applied a net cost that removed the ongoing costs for obesity included in the model. The EAG also applied drug costs 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. This is in line with recommendations in NICE's guideline on type 2 diabetes in adults: management. The company considered the EAG's approach to be overly conservative. It stated that the EAG's approach:

- excludes inpatient costs not otherwise captured by the model
- underestimates drug costs, and
- does not account for people with advanced disease who need more intensive treatment.

In response to draft guidance consultation, the company updated its base case to use the UKPDS costs. But it used the gross cost, which included obesity costs, rather than the net cost used by the EAG. It also included drug costs from Capehorn et al. (2021). The company also disagreed with the EAG's method of cost inflation, which used the NHS Cost Inflation Index. It preferred to use the Personal Social Services pay and prices index to inflate the costs of 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.

This was 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. No one enters the model with type 2 diabetes (see section 3.13). So the committee considered it reasonable to use a cost estimate that more closely reflected people with recently diagnosed type 2 diabetes. It was therefore appropriate to use the UKPDS non-inpatient costs that did not include more expensive items of care. This was because they are likely to be more often associated with more advanced type 2 diabetes. It also considered the EAG's drug costs to be most appropriate. This was because the estimates from Capehorn et al. used by the company were based on people who had been diagnosed with type 2 diabetes for an average of 7 years. The committee agreed that the EAG's approach using the net costs for type 2 diabetes were appropriate. This was because this more accurately represented the costs associated specifically with type 2 diabetes in people who also have obesity. It also agreed that the EAG's methods for inflation using the NHS Cost Inflation Index was standard practice in health technology assessment and the NICE technology assessment manual permits both methods. So, overall, the committee concluded that it preferred the EAG's approach for estimating the costs of type 2 diabetes.

Cost effectiveness

Acceptable ICER

3.24 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 around:

- the long-term treatment effects of tirzepatide (see section 3.16), and
- the impact of a previously higher BMI on long-term outcomes (see section 3.19).

The committee discussed that, as well as the high levels of parameter uncertainty, there is also high decision risk given the potential population size eligible for tirzepatide if it is recommended. The committee noted that the acceptable ICER was £20,000 per QALY gained in the appraisal of semaglutide and other similar previous appraisals. It was aware that this was because of the uncertainties in the modelling assumptions, including the long-term treatment benefits. The committee also acknowledged the added decision risk of a new setting of care for tirzepatide. Because of the uncertainties the committee agreed that an acceptable ICER would not be greater that £20,000 per QALY gained.

Company and EAG model assumptions

3.25 After the draft guidance consultation, the company's base-case model assumptions included:

- BMI distribution estimated using a gamma distribution fitted to the SURMOUNT-1 target population (see section 3.14)
- background resource costs for GP and nurse visits and for blood tests for both arms (see section 3.15)
- no decrease in absolute tirzepatide treatment effect while on treatment, and therefore a relative increase in tirzepatide treatment effect compared with diet and exercise over time (see section 3.16)
- weight regained during the 2 years after stopping treatment (see section 3.17)
- prediabetes reversal benefit lost in the tirzepatide and diet and exercise arms aligned to when weight is regained in those arms (see section 3.18)
- tirzepatide stopping rates because of non-response at 6 months after titration to the highest dose based on the proportion of people

remaining on treatment at 48 weeks in the SURMOUNT-1 target population (see section 3.20)

- semaglutide stopping rates (10%) at 6 months after titration because of non-response based on clinical expert opinion (see section 3.20)
- no long-term stopping rule for tirzepatide (see section 3.21)
- event risks estimated by risk equations, estimating the annual rate of events from multi-year event risks (see section 3.22)
- gross costs for type 2 diabetes taken from UKPDS, inflated using the Personal Social Services pay and prices index and drug costs from Capehorn et al. 2021 (see section 3.23)
- a modelled cohort size of 1,000.

The following differences from the company's model were included in the EAG's base case:

- BMI distribution estimated using a log-normal distribution fitted to Health Survey for England data (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 (see section 3.15)
- applying NHS England's proposed costs minus titration appointments for the diet and exercise arm for 2 years (see section 3.15)
- removing the net increase in tirzepatide treatment effect by applying a natural progressive increase in weight by age to the tirzepatide arm after 72 weeks, based on a parameter for people without type 2 diabetes from Ara et al. 2012 (see section 3.17)
- using the net costs for type 2 diabetes from UKPDS, inflated using the NHS Cost Inflation Index and drug costs associated with newly diagnosed type 2 diabetes, based on NICE clinical guidelines and drug tariff prices (see section 3.23)
- removing mortality modifiers applied in the company's model for cardiovascular disease and non-alcoholic fatty liver disease because the increased death from these events is covered by the BMI mortality modifier

- a model cohort size of 20,000.

The EAG also presented a second base case including the above assumptions but using the Ara et al. (2012) natural history weight gain parameter for people with and without type 2 diabetes (see section 3.17).

The committee's preferred assumptions

3.26 The committee's preferred assumptions mostly aligned with the assumptions in the EAG's base case (see section 3.25). It concluded that there were uncertainties remaining around the long-term treatment effect (see section 3.16) and the BMI distribution in the model (see section 3.14). So, the committee requested to see additional scenarios with its preferred assumptions exploring the following:

- constant relative long-term treatment effect in the tirzepatide arm and diet and exercise arm after 72 weeks, by:
  - applying natural history weight gain in both the tirzepatide and diet and exercise arms based on weight gain parameters for people with and without type 2 diabetes from Ara et al. (2012) from 72 weeks (included in the EAG's second base case; see section 3.16)
  - applying no natural history weight gain in either the tirzepatide or diet and exercise arm
- the BMI distribution from the IMPACT-O trial data, sampled directly from the graduated BMI data
- both of these scenarios with a range of obesity management service interventions.

Incremental cost-effectiveness ratios

EAG's subgroup analyses

3.27 The EAG presented 5 base-case analyses covering different populations of adults with:

- a BMI of at least 30 kg/m^2 and at least 1 weight-related comorbidity (the company's target population)
- a BMI of at least 30 kg/m^2 and less than 35 kg/m^2 and at least 1 weight-related comorbidity
- a BMI of at least 35 kg/m^2 and at least 1 weight-related comorbidity
- a BMI of at least 35 kg/m^2, prediabetes and a high risk of cardiovascular disease
- 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 and a high risk of cardiovascular disease.

Having concluded that its preferred assumptions aligned closely with the EAG's base case, the committee focused its decision making on ICERs generated from these EAG subgroup analyses.

Subgroup with a BMI of at least 30 kg/m^2 and at least 1 weight-related comorbidity

3.28 For the company's target population (adults with a BMI of at least 30 kg/m^2 and at least 1 weight-related comorbidity), the EAG's base-case ICERs were £28,697 and £29,810 per QALY gained. The committee considered that these ICERs were not sufficiently close to the acceptable ICER threshold of £20,000 per QALY gained to be considered cost effective. But, it had requested to see ICERs for the company's target population that included all its preferred assumptions and scenarios, assuming a constant relative treatment effect in the tirzepatide and diet and exercise arms and a scenario with the BMI distribution matched to that of the data from IMPACT-O (see section 3.14). Including the IMPACT-O BMI distribution in the model had a minor impact, lowering the EAG's base-case ICER in the company's target population. The committee noted that the EAG's second base case already included the first requested scenario of a constant relative treatment effect by applying natural history weight gain in both arms based on weight gain parameters for people with and without diabetes. When the EAG applied the second requested scenario of no natural history weight gain, the ICER increased

to £35,325 per QALY gained. This scenario included no natural history weight gain for people in the model while on tirzepatide, but an increase in weight to align with the weight in the diet and exercise arm when tirzepatide was stopped. This was in line with the committee's preferred assumptions on weight regain after stopping treatment (see section 3.17). People in the diet and exercise arm had no increase in weight over the model time horizon. This resulted in a constant treatment effect in the model for people while they were on treatment only, after week 72. The company proposed an alternative scenario to show no natural history weight gain in both arms, where no weight regain was included for people who stopped tirzepatide. This resulted in a constant treatment effect in the model for the entire time horizon after week 72. The ICER for the company's scenario of no natural weight gain in both arms was £29,151. The committee considered ICERs from a range of scenarios on these analyses for different obesity management service assumptions. The scenarios it requested were:

- no costs of obesity management services or effects for the diet and exercise arm, and
- using NHS England's proposed obesity management service costs but not including routine management costs for obesity.

The EAG also proposed a scenario using a combination of both of these assumptions, which the company also presented. The ICERs for the EAG's second base case with these scenarios included were all above £20,000 per QALY gained (ranging from £22,247 to £26,230 per QALY gained). When considering these scenarios for obesity management service costs in combination with the EAG's implementation of the scenario for no natural weight gain in either the tirzepatide or the diet and exercise arm while on treatment (ICER of £35,325 per QALY gained), the ICERs decreased, ranging from £23,816 to £31,183 per QALY gained. The ICERs for the company's implementation of the scenario for no natural weight gain in either the tirzepatide or the diet and exercise arm for the entire time horizon

(£29,151 per QALY gained) also decreased when different assumptions for obesity management service costs were included. These ranged from £18,982 to £25,710 per QALY gained. The committee concluded that all of the ICERs it had requested to see in scenario analyses for the company's target population were above £20,000 per QALY gained. The only scenario presented that was under £20,000 per QALY gained was the company's implementation of no natural weight gain plus the scenario proposed by the EAG using a combination of assumptions for obesity management service costs. This included no costs of obesity management services or effects for the diet and exercise arm and using NHS England's proposed obesity management service costs but not including routine management costs for obesity in the tirzepatide arm. The committee noted that this included assumptions of no weight regain for people who stop tirzepatide, which was not in line with the committee's preferred assumptions. It also noted the costs for obesity management services used in this scenario were unlikely to represent the costs incurred for tirzepatide in the NHS. The EAG's base-case ICERs, which aligned with the committee's preferred assumptions, were substantially above £20,000 per QALY gained. So, the committee concluded that tirzepatide was not considered a cost-effective use of NHS resources for the company's target population.

Subgroup with a BMI of at least 35 kg/m^2 and at least 1 weight-related comorbidity

3.29 The EAG's ICER for the subgroup of adults with a BMI of at least 35 kg/m^2 and at least 1 weight-related comorbidity was £21,372 per QALY gained. When including the Ara et al. (2012) weight gain parameter for people with diabetes, this ICER increased to £22,076 per QALY gained. The committee recalled that it would consider scenarios around the cost of obesity management services in decision making (see section 3.15). The EAG's base-case ICERs for the same population with no costs for obesity management services included in either arm were £17,171 and £17,735 per QALY gained. When no costs of obesity management services or

effects for the diet and exercise arm were included in the model, the EAG's base-case ICERs for this population were £19,129 and £19,904 per QALY gained. 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 considered that the EAG's base case included a conservative assumption for long-term treatment effect, and it preferred this assumption because of the high level of uncertainty around this. But, if tirzepatide did have a better long-term relative treatment effect compared with diet and exercise, it would lower the ICER. The committee agreed that given this, the EAG's base-case ICER for this population was sufficiently close to the acceptable ICER of £20,000 per QALY gained to be likely for tirzepatide to be considered cost effective. It also considered the scenarios presented for obesity management services, which were below the committee's acceptable ICER of £20,000 per QALY gained. Considering both these points, the committee agreed that for adults with a BMI of at least 35 kg/m^2 and at least 1 weight-related comorbidity, tirzepatide is a cost-effective use of NHS resources. Other subgroups presented by the EAG included adults with a BMI of at least 35 kg/m^2 and with prediabetes, or with prediabetes and high cardiovascular disease risk. These resulted in ICERs lower than for the population of adults with a BMI of at least 35 kg/m^2 and at least 1 weight-related comorbidity. These populations are included within the subgroup of adults with a BMI of at least 35 kg/m^2 and at least 1 weight-related comorbidity. The committee concluded that tirzepatide is cost-effective for adults with a BMI of at least 35 kg/m^2 with at least 1 weight-related comorbidity.

Other factors

Equality

3.30 The committee was aware that people with mental health disorders, especially those having atypical antipsychotics, may have increased risk of developing obesity. But it acknowledged that access to specialist weight management services may be limited for these people. The

committee discussed that it would consider tirzepatide in primary and secondary care settings. So, 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 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 considered comments from stakeholders that there are health inequalities associated with the inequitable access to nutritional food in these communities. There were stakeholder concerns that recommendations for a restricted calorie diet did not take into account the nutritional value of people's diet. The committee noted that it was expected that tirzepatide would be used alongside a diet and exercise intervention, including healthcare professionals who could advise on a healthy diet. But, the implementation of this could not be covered by a technology appraisal. The committee 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. So the cost effectiveness of tirzepatide has been assessed across a range of service designs. 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. It 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 guideline on overweight and obesity management recommends using lower BMI thresholds for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean ethnic backgrounds as a practical measure of overweight and obesity. The committee agreed that a similar adjustment to the BMI thresholds is suitable for tirzepatide.

Use in practice

3.31 The committee considered that there are likely to be challenges with implementing tirzepatide in primary care. So a funding variation to allow a longer implementation period than usual to comply with the recommendation has been included in this guidance (see section 4). This is because a large number of people would potentially be eligible for tirzepatide and the resources needed for its delivery, such as diet and exercise support, are not available equitably across the country (see sections 3.2 and 3.3). It is not within the remit of the committee to make recommendations for the funding variation. But it discussed if there were any groups of people who could be prioritised for tirzepatide, to help inform priority cohorts set out in the interim commissioning policy as part of the funding variation (see section 4.11). 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 who have multiple weight-related comorbidities, may particularly benefit from tirzepatide. The clinical expert also explained that stratifying the eligible population based on risk should not be done only using BMI. This is because the presence of comorbidities is often a better indicator for the risk associated with overweight and obesity. The clinical expert explained that evidence-based recommendations assessing clinical risk would be more useful to identify those with highest risk. They highlighted the joint position statement by the Society for Endocrinology and Obesity Management Collaborative UK (PDF only), which provided guidance for the phased introduction of new medical therapies for weight management. This includes 4 cohorts,

grouped by the various risk factors that indicate the level of risk people have from living with overweight or obesity. The committee concluded that the groups highlighted by the joint position statement may be useful to inform prioritisation as part of the funding variation. But, it was outside its remit to make recommendations for this. The summary of product characteristics for tirzepatide states that it is not recommended during pregnancy and in women of childbearing potential not using contraception. It also advises using a non-oral or barrier method of contraception for 4 weeks after starting tirzepatide, and after each dose escalation. These issues cannot be addressed in a technology appraisal, but they may be considered as part of an implementation strategy for tirzepatide. The committee concluded that although it was aware of the potential implementation challenges, its remit is to evaluate the clinical and cost effectiveness of tirzepatide. So it could not consider implementation issues further in its decision making.

Conclusion

Recommendation

3.32 For the company's target population, the ICERs that include all of the committee's preferred assumptions and relevant scenarios for tirzepatide compared with diet and exercise and with semaglutide were above the acceptable ICER. The ICERs for tirzepatide in adults with a BMI of at least 35 kg/m^2 and at least 1 weight-related comorbidity may be below or around the acceptable ICER. So, 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 BMI of at least 35 kg/m^2 and
- at least 1 weight-related comorbidity.

A lower BMI threshold (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 Regulation 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 NICE to specify a time period within which integrated care boards (ICBs), NHS England and, with respect to their public health functions, local authorities must comply with the recommendations in this evaluation. Ordinarily, this time period is within 3 months of the date of final guidance publication.

4.2 Under Regulation 7(5), if NICE considers it appropriate, NICE must specify a longer period if the health technology cannot be appropriately administered until training, additional health service infrastructure requirements and or other health services resources including staff are in place. The NICE manual on health technology evaluations states that NHS England may request a longer time to implement technologies when the potential net budget impact is expected to exceed £20 million per year in any of the first 3 financial years of its use in the NHS.

NHS England funding variation request

4.3 NHS England submitted a funding variation request, on behalf of NHS providers and ICBs, to extend the time needed to comply with the recommendations.

4.4 NHS England's funding variation request includes the following justification:

- **Availability of services:** Weight management services are not routinely commissioned in primary care. Therefore, time is needed to develop coordinated and sustainable service models.
- **Clinical capacity:** The recommendation cannot be safely implemented within 3 months because there is insufficient capacity to deliver tirzepatide in primary care. To meet this resource need, healthcare professionals will require training.

- **Inequity of access:** In the absence of an extension to the time required to comply with the recommendations, it is likely that:
  - there would be inconsistent access to tirzepatide, leading to inequality of access and patient outcomes
  - services that already exist would need to be decommissioned to provide the resources required to deliver tirzepatide.
- **Budget impact:** The anticipated costs of implementing the recommendation exceed the budget impact test of £20 million in each of the first 3 years.

4.5 NICE's Guidance Executive considered NHS England's funding variation request, informed by responses to a formal process of stakeholder consultation. NHS England, with those on whose behalf it makes the funding variation request, has responsibility for implementing the service changes necessitated by this recommendation. NICE should be cautious and sure of its judgement before requiring the provision of services that NHS England does not consider can be provided safely and equitably. NHS England has indicated that it does not yet have in place the arrangements that it considers necessary to provide tirzepatide to the full extent recommended in this guidance within the usual 3-month timeframe. NHS England's position, in setting out what it believes it needs to do to put the necessary arrangements in place, and the timescale for doing so, has credibility.

4.6 NICE fully understands the concerns put forward by consultees who object to the considerably extended implementation period. Any additional delay in accessing recommended treatments is, of course, undesirable. However, NHS England's plans to put in place new service delivery models reflect compelling evidence presented by NHS England that the current arrangements expose the service and its patients to the risks associated with inadequate resources. In addition, it is apparent from its initial proposal and response to consultation that NHS England is making a considerable effort to ensure that patients for whom a delay in access to tirzepatide represents the greatest risk will have access to it under the

planned interim commissioning policy. NHS England has now published their interim commissioning guidance for NICE's technology appraisal guidance on tirzepatide.

Amendments and clarifications to implementation proposals

4.7 NICE's Guidance Executive accepted that a funding variation is justified. However, NICE has made the following amendments and clarifications to NHS England's implementation proposals (outlined in sections 4.8 to 4.13).

Duration

4.8 NHS England proposed a total guidance implementation period of 12 years, in 3 parts:

- **A**: an additional 90 days before any requirement on ICBs to fund tirzepatide, providing a 180-day implementation period
- **B**: after the 180 days, a period of 3 years in which eligibility will increase in stages to around 220,000 patients, selected based on health need and clinical benefit, and
- **C**: after this, up to a maximum of a further 9 years, dependent upon maturation of the obesity treatment pathway in primary care.

NICE is required by its legal obligations to specify a maximum period for implementation. In the circumstances, NICE accepts that a maximum period of 12 years may be necessary, and, accordingly, specifies that period. However, NICE also considers that there is substantial uncertainty in this estimate, and there is likely to be scope to complete implementation within a significantly shorter period. Accordingly, NICE recommends an initial implementation period of not more than 3 years for a subset of the eligible population, using this period to test and make the necessary arrangements to safely and efficiently scale a variety of implementation service models including digital support for patients.

NICE will evaluate relevant evidence generated during the initial guidance implementation period of up to 3 years and review the effectiveness of the service delivery pilots. NICE may then set a revised timeline for the second phase of the guidance implementation period. A review conducted within the first 3 years will provide evidence on the most clinically and cost-effective service delivery models which could be used to shorten the total guidance implementation timeframe.

Timing

4.9 NHS England requested a delay of 6 months to the funding requirement for all eligible patients. Considering the responses from the consultation, NICE recommends mandated funding of tirzepatide:

- within 3 months from final guidance publication for all patients accessing specialist weight management services at that time and subsequently, since these services and the associated wraparound care is already established
- must be made available from 6 months of final guidance publication for a phased introduction of delivery to eligible cohorts, at a minimum, in line with NHS England's interim commissioning policy, since NICE accepts that it will take time for commissioners to establish effective services in primary care.

Eligible population

4.10 The qualifying comorbidities specified by NHS England in its implementation proposal do not align with the population eligible for tirzepatide as recommended in section 1 of this guidance. NHS England's interim commissioning policy, that will manage access to tirzepatide during the extended funding variation period, must ensure that tirzepatide is delivered to the full eligible population within the maximum period of 12 years, based on cohort prioritisation led by clinical need. The marketing authorisation for tirzepatide states that adults with a BMI between 27 kg/m^2 and less than 30 kg/m^2 must have at least 1 weight-related comorbidity. It gives the following examples of weight-related

comorbidities, however this list is not exhaustive: hypertension; dyslipidaemia; obstructive sleep apnoea; cardiovascular disease; prediabetes; type 2 diabetes mellitus. Non-alcoholic fatty liver disease was also included as a modelled complication in the economic model that was accepted and used by the committee in its decision making to establish tirzepatide's cost effectiveness. The eligible population within NICE's guidance includes adults with a body mass index (BMI) of at least 35 kg/m^2 (or a lower threshold, 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) and at least 1 weight-related comorbidity. The comorbidities listed in the marketing authorisation and used as baseline characteristics in the model (listed above) are the key weight-related comorbidities that should be considered within NHS England's interim commissioning policy. However, other important comorbidities, for example learning disabilities and severe and enduring mental illness, should also be considered in the interim commissioning guidance and prioritisation statement. NICE estimates that the total eligible population is 3.4 million people, and expects that the interim commissioning guidance and prioritisation statement led by clinical need will identify at least 220,000 people eligible for tirzepatide to be funded within the first 3 years of implementation.

Prioritisation

4.11 NHS England proposed prioritising patients according to BMI and the number of qualifying comorbidities. Based on responses to the funding variation consultation and the evaluation committee discussion, NICE recommends a modified approach to clinical prioritisation of the eligible population that is more closely aligned with expert opinion, an example of which is the joint position statement by the Society for Endocrinology and Obesity Management Collaborative UK on phased introduction for new medical therapies for weight management (PDF only). In line with the NICE manual on health technology evaluations, NHS England is developing an interim commissioning policy that will apply to phase-in funding and that will manage access to tirzepatide during the extended

funding variation period, describing how patient cohorts will be prioritised in line with these recommendations. To support this, NHS England will produce a new prioritisation statement with relevant clinical experts, considering both referral prioritisation in specialist weight management services and priority cohorts in other settings (including primary care-based services).

Review at 3 years

4.12 NICE will conduct a formal review to be completed within 3 years from the date of final guidance publication. This will consider:

- characterisation and quantification of the cohorts prescribed tirzepatide, including the common comorbidities for adults with a BMI of at least 35 kg/m^2 (or a lower threshold, 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)
- real-world evidence on service implementation, associated costs and service uptake
- a comparison of the different service models trialled, including their feasibility and relative clinical and cost effectiveness, and
- whether any changes to the recommendations in section 1 are appropriate.

Service models

4.13 Information on the proposed service delivery models was redacted from the funding variation documentation NICE consulted on, and there is very limited detail with which these can be assessed. While it is not NICE's role to specify service delivery models, it is essential that a range of approaches is tested and evaluated, including the use of digital technologies. Comments received from stakeholders during consultation suggested that NHS England's proposals rely very heavily on general practice and overestimate the activity that would be required in this service. Therefore, data describing the models adopted by NHS England or ICBs, and their implementation, outcomes and costs, will be further

considered at the review point described above. To inform this review with relevance to the whole eligible population recommended in the guidance, it will be important to ensure that service delivery models are tested in populations with a range of eligible BMIs and comorbidities.

What this means for commissioners

- The eligible population for tirzepatide is described in this guidance, and can be summarised as adults with a BMI of at least 35 kg/m^2 (or a lower threshold, 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) and at least 1 weight-related comorbidity. NICE estimates that the total eligible population is 3.4 million people, and expects that an interim commissioning policy will identify at least 220,000 people in England eligible for tirzepatide to be funded within the first 3 years of implementation.
- Prioritisation of cohorts for treatment will be based on a prioritisation statement led by clinical need and produced by NHS England that considers both referral prioritisation in specialist weight management services and priority cohorts in other settings, including primary care-based services.
- ICBs are required to fund tirzepatide:
  - within 3 months for all patients accessing specialist weight management services at that time, and subsequently
  - from 6 months to support a phased introduction of delivery to other eligible cohorts.
- NHS England will make available to ICBs an interim commissioning policy outlining how patient cohorts should be prioritised and the service models that are recommended during this initial implementation within 4 weeks of final guidance publication.
- NICE will evaluate data collected during the first phase of guidance implementation, within the first 3 years. It will consider whether to revise the maximum total 12-year implementation period and whether NHS England should produce an updated interim commissioning policy for the remaining implementation period.

4.14 This variation of the implementation period is made under Section 7(5) of the Regulations.

4.15 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. The All-Wales Weight Management Pathway sets out that weight management medication will only be prescribed within a specialist service, where clinically indicated, and only in combination with a behavioural (lifestyle) intervention that includes a reduced-calorie diet and increased physical activity. Tirzepatide will be available for Local Health Boards in Wales to prescribe should they wish to use it within those specialist services from the publication of NICE's final guidance. However, further work will be undertaken to determine whether it is appropriate to make tirzepatide available through arrangements other than specialist weight management services, and if so the nature of those arrangements. Welsh Ministers will make a decision regarding any extended use of tirzepatide in due course. At such a time and when a decision is taken about when, how and whether tirzepatide is made available for use outside the current arrangements set out within the All-Wales Weight Management Pathway, Welsh Ministers will write to NICE outlining those arrangements.

4.16 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, the funding variation request, and NHS England's and NHS Wales' strategies for implementation.

Evidence generation to support implementation

4.17 NICE will complete a review no later than 3 years from the date of the final guidance publication, and sooner if possible. This will consider real-world evidence on service implementation, associated costs and service uptake. Sections 4.18 to 4.23 provide additional detail on the evidence that should be collected to address areas of uncertainty.

4.18 Further characterisation and quantification of the cohort prescribed tirzepatide should be collected during this 3-year period. This should describe the common comorbidities for adults with a BMI of at least 35 kg/m^2 (or a lower threshold, 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), and which of these may change if there is a reduction in BMI.

4.19 In addition to the direct costs of tirzepatide, data should be collected on costs associated with the implementation of services including the costs of service delivery, upskilling and education materials.

4.20 To keep the burden of data collection to a minimum, real-world evidence should be generated from routine data collections. Most of the real-world evidence is expected to be available from existing primary care sources.

4.21 Real-world evidence could be generated from routine data assets such as Clinical Practice Research Datalink (CPRD), which contains the largest cohort of primary care data in the UK. Other routes to accessing primary care data include the OpenSAFELY platform and federated analysis from subnational secure data environments.

4.22 Real-world evidence that is generated directly from weight management services should be collected within the Community Services Data Set. Real-world evidence that is generated from secondary care services should be captured in Hospital Episode Statistics.

4.23 NICE will work with NHS England to further specify the data to be collected in the full evidence generation plan.

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), technical advisers and project managers.

Emma Bajela
Technical lead

Albany Chandler and Yelan Guo
Technical advisers

Thomas Feist and Jennifer Upton
Project managers

Janet Robertson
Associate director

Jacoline Bouvy
Programme director

Update information

Minor changes since publication

August 2025: Eligibility criteria from NHS England's interim commissioning guidance added to what this means in practice box.

June 2025: What this means in practice box added to the recommendations section with details of NHS England's interim commissioning guidance.

ISBN: 978-1-4731-6697-4