

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Tirzepatide for treating type 2 diabetes

1 Recommendations

1.1 Tirzepatide is recommended for treating type 2 diabetes alongside diet and exercise in adults when it is insufficiently controlled only if:

- triple therapy with metformin and 2 other oral antidiabetic drugs is ineffective, not tolerated or contraindicated, and
- they have a body mass index (BMI) of 35 kg/m² or more, and specific psychological or other medical problems associated with obesity, or
- they have a BMI of less than 35 kg/m², and:
 - insulin therapy would have significant occupational implications, or
 - weight loss would benefit other significant obesity-related complications.

Use lower BMI thresholds (usually reduced by 2.5 kg/m²) for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds.

1.2 This recommendation is not intended to affect treatment with tirzepatide that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Some people with type 2 diabetes have triple therapy with metformin and 2 other oral antidiabetic drugs. When this is ineffective, not tolerated or contraindicated, they may switch one of the antidiabetic drugs for a glucagon-like peptide-1 (GLP-1) receptor agonist (such as semaglutide) or start insulin therapy. For this evaluation, the company asked for tirzepatide to be considered only as an alternative to GLP-1 receptor agonists. This does not include everyone who it is licensed for.

Clinical trial results suggest that tirzepatide reduces blood glucose levels (measured by HbA1c levels) and body weight compared with semaglutide, insulin therapy or placebo. There is only an indirect comparison of tirzepatide with other GLP-1 receptor agonists, which suggests similar benefits, although these results are less certain.

Additional analyses provided by the company after consultation improved confidence in the clinical- and cost-effectiveness evidence. The cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, tirzepatide is recommended for routine use in the NHS.

2 Information about tirzepatide

Marketing authorisation indication

2.1 Tirzepatide (Mounjaro, Eli Lilly) is indicated for ‘the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes’.

Dosage in the marketing authorisation

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

Price

- 2.3 The proposed list price of 4 prefilled disposable injections is commercial in confidence until the guidance is published.

3 Committee discussion

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

Clinical management

Unmet need

- 3.1 Type 2 diabetes is a chronic metabolic condition caused by reduced tissue sensitivity to insulin (known as insulin resistance) and loss of endogenous insulin production. This leads to elevated blood glucose levels (hyperglycaemia). Type 2 diabetes is serious and sometimes progressive condition that can greatly affect the health and wellbeing of people with it. If not managed effectively, it can lead to devastating, life-changing complications. An estimated 90% of adults with type 2 diabetes are living with overweight or obesity at diagnosis. This is linked to difficulties in managing blood glucose levels and to an increased risk of complications. The clinical experts explained that there are 8 different classes of glucose lowering treatments available (in addition to lifestyle interventions; see [section 3.2](#)). But despite this, fewer than 2 in 3 people with type 2 diabetes have HbA1c levels below 53 mmol/mol (7%), highlighting the need for further treatment options. The committee noted the high unmet need for new treatment options in type 2 diabetes.

Treatment options

- 3.2 Treatment options in diabetes are tailored to the individual circumstances of people with type 2 diabetes, such as their HbA1c levels, cardiovascular risk and kidney function. Current first-line treatment options in NHS practice include:

- metformin for people not at high risk of cardiovascular disease
- metformin plus a sodium glucose co-transporter 2 (SGLT2) inhibitor for people at high risk of cardiovascular disease
- a dipeptidyl peptidase-4 (DPP-4) inhibitor, pioglitazone, sulfonylurea or an SGLT2 inhibitor if metformin is contraindicated.

If a person's HbA1c levels are not controlled below an individually agreed threshold, second-line treatment involves switching to or adding a DPP-4 inhibitor, pioglitazone, sulfonylurea or an SGLT2 inhibitor. People can also switch to or add an SGLT2 inhibitor if they develop cardiovascular disease or a high risk of cardiovascular disease. If dual therapy is not adequately controlling HbA1c levels, people can either start triple therapy by adding another oral antidiabetic drug, or start insulin-based treatment (with or without other drugs). If triple therapy with metformin and 2 other oral antidiabetics is ineffective, not tolerated or contraindicated, people can switch one of the drugs for a glucagon-like peptide-1 (GLP-1) receptor agonist (RA) if they:

- have a body mass index (BMI) of 35 kg/m² or more, and specific psychological or other medical problems associated with obesity, or
- have a BMI of less than 35 kg/m², and insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related complications.

Lower BMI thresholds (usually reduced by 2.5 kg/m²) should be used for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds. The committee concluded that the treatment pathway for type 2 diabetes is complex. It also concluded that, when triple therapy is ineffective, not tolerated or contraindicated, there are limited treatment options.

Positioning of tirzepatide

3.3 The NICE scope defined the relevant patient population as the same as that in tirzepatide's marketing authorisation (see [section 2.1](#)). But, in its

submission, the company positioned tirzepatide in a narrower population, that is, as an alternative to GLP-1 RAs in adults with type 2 diabetes inadequately controlled with 3 or more antidiabetic drugs. It explained that this is because this is where it expects tirzepatide is to be used in NHS practice (with 2 oral antidiabetic agents). It also noted that this population has the highest unmet need. The clinical experts explained that, internationally, tirzepatide is used earlier in the treatment pathway. But they agreed that it would likely be used as an alternative to GLP-1 RAs in NHS practice. They noted that all GLP-1 RAs have broad licences, ranging from for people who have not had treatment for type 2 diabetes to people who have had insulin. But their use in the NHS is limited to third or fourth line. The clinical experts also explained that treatments administered by injection, such as tirzepatide and most GLP-1 RAs are less easily adopted in primary care than oral tablets. They are also more expensive than most oral treatments, so they would be reserved for further lines of treatment in the NHS. The EAG noted that the criteria for using GLP-1 RAs in NHS practice are not only defined by previous treatment (see [section 3.2](#)). The committee would have preferred to have assessed tirzepatide in the broader population aligned with the NICE scope. But it was not presented with any evidence to do so. It acknowledged that the company's positioning of tirzepatide as an alternative to GLP-1 RAs was reasonable. But it noted that this would mean that it could only consider tirzepatide for people:

- with a BMI of 35 kg/m² or more, and specific psychological or other medical problems associated with obesity, or
- with a BMI of less than 35 kg/m², and when insulin therapy would have significant occupational implications or when weight loss would benefit other significant obesity-related complications.

Lower BMI thresholds (usually reduced by 2.5 kg/m²) should be used for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds.

Relevant comparators

3.4 The company submission included the following GLP-1 RAs as relevant comparators: dulaglutide, liraglutide and semaglutide (oral and injectable formulations). The company noted that the GLP-1 RAs lixisenatide and exenatide (standard and modified-release) were excluded because of limited market share in the UK. The clinical experts confirmed that lixisenatide and exenatide are less commonly used in clinical practice. The committee agreed that GLP-1 RAs are relevant comparators, considering the company's positioning of tirzepatide as an alternative to them. It agreed that the GLP-1 RAs chosen by the company represented those that would be used in NHS practice.

Clinical evidence

Clinical-effectiveness evidence: SURPASS trials

3.5 The clinical-effectiveness evidence for tirzepatide came from 4 trials, SURPASS-2 to -5. These were multinational multicentre randomised phase 3 studies. They assessed tirzepatide 5 mg, 10 mg and 15 mg against:

- semaglutide in adults with type 2 diabetes who had inadequate glycaemic control with metformin (1,500 mg/day or more; SURPASS-2) alone
- insulin degludec in adults with type 2 diabetes who had inadequate glycaemic control on stable doses of metformin with or without an SGLT2 inhibitor (SURPASS-3)
- insulin glargine in adults with type 2 diabetes with a high risk of cardiovascular disease, and inadequate glycaemic control on stable doses of at least 1 and no more than 3 oral antidiabetic drugs, including metformin, an SGLT2 inhibitor or sulfonylureas (SURPASS-4)
- placebo in adults with type 2 diabetes and on insulin glargine with or without metformin (SURPASS-5).

In SURPASS-2, -3 and -5, people had to have HbA1c levels of 53 mmol/mol (7.0%) or more to 91 mmol/mol (10.5%) or less. In SURPASS-4, the levels had to be 58 mmol/mol (7.5%) or more to 91 mmol/mol (10.5%) or less. People also had to have had a stable weight for 3 months, and a BMI of 25 kg/m² or more in SURPASS-2, -3 and -4, and a BMI of 23 kg/m² or more in SURPASS-5. The committee noted that, in the SURPASS trials, mean BMI was less than 35 kg/m², and the mean duration of diabetes was between 8 years and 14 years. It noted that SURPASS-2, -3 and -5 excluded people who were on triple therapy. Previous triple therapy (metformin plus a sulfonylurea and an SGLT2 inhibitor) was only allowed in SURPASS-4. But only a very small proportion of people had it (the exact proportion is considered confidential by the company and cannot be reported here). The committee noted that they were the population that most closely aligned with the company's proposed positioning of tirzepatide in the treatment pathway (see [section 3.3](#)). The clinical experts explained that people who start injectable treatments have usually had diabetes for many years because they try more convenient oral treatments first. They noted that baseline characteristics from the SURPASS trials represented what they see in NHS practice, specifically for BMI. The committee concluded that the populations of the SURPASS trials were generally similar to the population seen in the NHS, except that the NHS population will have had more lines of previous treatment. This is because people would have to have a triple therapy before becoming eligible for tirzepatide under the company's proposed positioning of tirzepatide in the treatment pathway.

Clinical-effectiveness evidence: SURMOUNT trials

In its second meeting, the committee considered whether SURMOUNT-2 and the SURMOUNT-CN trials should have been included in the company's submission. The company noted that the SURMOUNT trials focused on a different indication (weight loss) and were not relevant to this appraisal. Only SURMOUNT-2 included people with type 2 diabetes, but it would not have been included in the company's network meta-analysis

(NMA) for the current appraisal. This was because the definition of background therapies allowed was not directly relevant to the current appraisal's decision problem. The EAG noted substantial differences between SURMOUNT-2 and the SURPASS-2, -3, -4 and -5 trials, and that direct comparison was not advisable. A key difference was that people in SURMOUNT-2 were allowed to change concomitant antidiabetic treatment during the trial, which was not allowed in SURPASS -2, -3, -4 and -5. Also, people in SURMOUNT-2 did not need to have inadequate glycaemic control while on metformin monotherapy (with or without other antidiabetic medication) when entering the study. In SURPASS-2, -3 and -4, they did. The committee was content with the SURMOUNT trials being excluded from the company submission.

Effect on HbA1c and body weight

3.6 The committee noted that tirzepatide (all doses) showed statistically significant reductions in HbA1c levels and weight compared with comparators in all SURPASS trials. But weight reduction was more pronounced with higher doses of tirzepatide, while the effect on HbA1c seemed less dose-dependent. The company noted that the dose response curve may have appeared flat for HbA1c reduction from baseline. But the actual baseline HbA1c was not particularly high in the SURPASS trials. The company highlighted that, importantly, 81% to 97% people reached HbA1c levels of less than 53 mmol/mol (7%) across all trials, which was statistically significantly more than with any comparator. The clinical experts noted that fairly flat dose response curves for HbA1c mean that people can have good glucose control with lower doses of tirzepatide. They noted that people may still wish to increase their doses to have the additional benefit of further weight loss. The committee concluded that tirzepatide (all doses) showed statistically significant reductions in HbA1c and body weight compared with all comparators in SURPASS trials. It also concluded that higher tirzepatide doses give higher weight reductions.

Adverse effects of tirzepatide

3.7 Overall, tirzepatide was reasonably well tolerated in the SURPASS trials, with the most common adverse effects being nausea, dyspepsia and vomiting. The clinical experts explained that the adverse effects are consistent with those of GLP-1 RAs. They explained that a way to minimise the risk of these adverse effects is to slowly up titrate the dose. This is currently done in the NHS with the GLP-1 RAs. The clinical experts noted that titration of tirzepatide will be much slower than it is with GLP-1 RAs, so more resource-intensive. The clinical experts further explained that, in clinical practice, if someone has any gastrointestinal problems, dose increases may be delayed, or they may remain on their current dose. In contrast, the option for slower titration is generally unavailable in clinical trials. The committee acknowledged that the adverse effects of tirzepatide are aligned with those of GLP-1 RAs, and expected them to be manageable in clinical practice.

Tirzepatide administration

3.8 The committee noted that the marketing authorisation for tirzepatide states that it should be titrated as needed to recommended maintenance doses of 5 mg, 10 mg or 15 mg. In contrast, in the SURPASS trials, people were randomised to their maximum dose of tirzepatide. The company acknowledged there was a mismatch between dosing of tirzepatide in clinical practice and the clinical trials, but noted the same issue applies to all comparator trials. The clinical experts explained that, in NHS practice, the focus is on blood glucose levels, so if the target HbA1c is met, people would stay at the current dose of tirzepatide. The committee recalled that people may also stay at their current (lower than maximum) dose when they have adverse effects (see [section 3.7](#)). The committee concluded that the way in which tirzepatide was used in the clinical trials, and so the NMA, did not match how it would be used in clinical practice. But it acknowledged that this was the best evidence available.

NMA misalignment and decision problem

3.9 Because of a lack of direct evidence from clinical trials, the company did an NMA to assess the relative efficacy and safety of tirzepatide compared with all GLP-RAs available in NHS practice. The network was defined to align with SURPASS-2 and -3, and included studies in people on 1 or 2 oral antidiabetic drugs. The EAG was concerned that these criteria did not match the company's target population (people on triple therapy; see [section 3.3](#)). The company explained that an NMA criteria of 1 or 2 oral antidiabetic drugs referred to a background treatment of up to 2 oral antidiabetic drugs. Once tirzepatide or GLP-1 RAs were added, people would be having double or triple therapy. The EAG highlighted that previous and background treatments are 2 separate issues. In the NHS, people would have to have a triple therapy before becoming eligible for GLP1-RAs, while the company's NMA excluded studies in people on triple therapy. One of the clinical experts explained that treatment effect is not expected to be affected very much by previous treatment. Treatment effect is mostly dependent on a person's initial glycaemic control level, with lower responses for people whose HbA1c levels are close to their targets. They noted that GLP-1 RAs were shown to be equally effective across different lines of treatment. The company explained that it had done a subgroup analysis of SURPASS-4, NMA meta-regression analyses and NMA sensitivity analyses to assess the effect of differences in background treatment on the clinical-effectiveness results. All results were consistent with the main results, supporting their generalisability regardless of baseline treatment. The EAG noted that:

- the subgroup analysis of SURPASS-4 showed a statistically significant difference in HbA1c level depending on the number of previous treatments
- the company's meta-regression analysis was limited to comparing 1 previous treatment with 2 previous treatments
- the NMA sensitivity analysis included only a small number of studies in which people had triple therapy

- neither analysis addressed the differences in the type of treatment used, rather than the number of treatments.

The EAG also explained that the validity of the NMA was based on the assumption that all the studies included in the network were similar in all factors that may have affected the relative effects (that is, condition and patient characteristics). But it noted that the studies included in the NMA varied greatly in terms of previous treatments and baseline characteristics that may potentially modify treatment effects. These included mean baseline HbA1c values ranging from 57 mmol/mol (7.4%) to 89 mmol/mol (10.3%), and baseline diabetes duration ranging from 0.6 years to 10.1 years. The EAG further explained that the tirzepatide data was analysed at 40 weeks for SURPASS-2, -3 and -5 and at 42 weeks for SURPASS-4 (with up to 20 weeks of dose escalation). The comparator data was analysed at 22 weeks to 30 weeks (with up to 12 weeks of dose escalation). This further added to variability between the studies in the NMA. The EAG thought that the extent of the differences between the studies meant that the NMA was at high risk of bias in an unknown direction. But it acknowledged that additional sensitivity analyses excluding all trials with high heterogeneity between them (for the same direct comparison) seemed to make little difference to the main analysis. The committee noted the problems with the NMA. But it further noted that a direct comparison was possible, based on SURPASS-2 results, at least with semaglutide. This scenario analysis was provided by the company during consultation (see [section 3.18](#)). The committee concluded that, although misaligned with the company's decision problem, this scenario analysis improved confidence in clinical-effectiveness results.

The company's economic model

Company model compared with other recognised diabetes models

3.10 The company described its PRIME type 2 diabetes model (PRIME T2D), which was developed in JAVA, as a discrete-time event, patient-level simulation model. It explained that the model type and structure was

similar to the CORE Diabetes Model and the UK Prospective Diabetes Study (UKPDS) model. JAVA was used for its computational efficiency, which was needed to run complex patient simulations. These captured treatment algorithms and risk factor progression, and projected the cumulative incidence of micro- and macrovascular complications, and hypoglycaemic events. The company highlighted that pre-existing type 2 diabetes models used risk equations based on population with low-risk complications. In comparison, PRIME T2D used a model averaging approach, in which the risk predictions from 3 models are combined. This considered patient characteristics over time and was shown to better predict micro- and macrovascular complications (see [section 3.11](#)). Also, it used data exclusively from populations with type 2 diabetes, while older models used data from mixed type 1 and type 2 diabetes. The EAG noted that the company's model was very complex and done in a software that is not standard for health economic evaluation. So, it was very challenging for the EAG to scrutinise the model. After consultation, the company provided additional analyses to improve committee confidence in the economic model. These included:

- one-way sensitivity analyses for key model inputs for tirzepatide 10 mg compared with semaglutide 1.0 mg
- validation of the PRIME T2D model against other diabetes models and published studies
- cost-effectiveness results run in the CORE Diabetes Model.

The EAG noted that the results of these analyses supported credibility of the PRIME T2D model, despite noting some limitations. The committee concluded that the additional analyses provided by the company had improved its confidence in the cost-effectiveness results from PRIME T2D.

Approach to estimate risk of micro- and macrovascular complications

3.11 No comparative data on micro- and macrovascular complications of diabetes, including cardiovascular outcomes, was available. Instead,

these outcomes needed to be modelled. The company noted that current diabetes models were shown to poorly predict cardiovascular outcomes, as shown in the Ninth Mount Hood Diabetes Challenge. To better predict these outcomes, they need to be calibrated with hazard ratios from cardiovascular outcomes' trials, which can be challenging. PRIME T2D uses an alternative approach and estimated the rates of micro- and macrovascular complications using model averaging. This drew on 3 different risk models:

- UKPDS OM2, better suited for people with a low-risk profile and short duration of disease
- BRAVO model, better suited to people with more advanced disease and a higher risk profile (derived from the ACCORD trial population, which was at high risk of cardiovascular complications)
- Hong Kong Diabetes Registry, applicable to South-east Asian populations (not influential in predicting the risk of micro- and macrovascular complications).

The company highlighted that using just 1 cohort (a low-risk cohort) did not take into consideration what was going to happen to the person being simulated in the future. It emphasised that the model averaging approach estimated the risk in a range of simulation populations, combining risk equations, and automatically weighing the risk equations for different populations. It also emphasised that PRIME T2D, using model averaging, validated well against several cardiovascular outcomes' trials, as shown in the PRIME T2D technical report. After consultation, the company provided a scenario analysis using only UKPDS risk equations to predict the risk of micro- and macrovascular complications. This showed minimal impact on the cost-effectiveness estimates. It also provided information on risk-equation weighting over time. The EAG noted that the company's rationale for using the model averaging approach was credible. It acknowledged that, theoretically, model averaging may be a better approach than using single-risk equations. The EAG was reassured that the scenario analysis using only the UKPDS OM2 equations had minimal

impact on the cost-effectiveness estimates. But it commented that, ideally, it would like to see a scenario analysis using only the BRAVO risk equations too. The EAG also noted that the company did not present a comparison between the Ninth Mount Hood Diabetes Challenge results and the current implementation of PRIME T2D. But it did acknowledge that PRIME T2D, using model averaging, seemed to predict the risk of micro- and macrovascular complications well compared with the published studies (see [section 3.10](#)). The committee accepted the company's approach to estimating the risk of micro- and macrovascular complications.

Modelling of long-term treatment effectiveness

3.12 In line with the EAG's recommendations, the company's revised base-case model used UKPDS OM2 risk factor progressions for:

- all risk factors while on insulin therapy
- HbA1c, low-density lipoprotein, high-density lipoprotein, estimated glomerular filtration rate, white blood cells count, heart rate and haemoglobin levels while on tirzepatide or comparator treatments.

For systolic blood pressure (SBP) and BMI, the company's model assumed no change while people were on tirzepatide and GLP-1 RAs. This was based on studies for cardiovascular outcomes with GLP-1 RAs that showed body weight and SBP remained stable while on treatment. The EAG noted that the company provided a rationale for assuming no change in SBP and BMI, and applied UKPDS OM2 risk factor progressions for other risk factors, as requested. The committee accepted the company's approach to the modelling of long-term risk factor progression.

Treatment intensification criteria

3.13 In PRIME T2D, people were assumed to intensify treatment, that is, stop initial treatment and switch to basal insulin therapy, when their HbA1c levels rose above 59 mmol/mol (7.5%). In the model, there were no other

causes for stopping treatment. The clinical experts explained that, in clinical practice, when HbA1c levels rise above agreed targets, people usually have insulin added on to an existing GLP-1 RA, rather than the GLP-1 RA being stopped. The committee noted that [NICE's guideline on managing type 2 diabetes in adults](#) states that GLP-1 RAs should only be continued if the person with type 2 diabetes has had a beneficial metabolic response (that is, a reduction of at least 11 mmol/mol [1.0%] in HbA1c and weight loss of at least 3% of initial body weight in 6 months). But it acknowledged clinical advice that use in clinical practice may deviate from this recommendation. After consultation, the company provided a scenario analysis that assumed treatment is intensified by adding insulin to tirzepatide and GLP-1 RAs when people's HbA1c targets are not met. The results showed limited impact on the cost-effectiveness estimates. The committee accepted the company's modelling of treatment intensification.

Company's modelling of adverse events

3.14 The company's revised base-case model only included nausea rates for tirzepatide and comparators. Severe and non-severe hypoglycaemic rates were only included for basal insulin therapy. The EAG preferred to include both nausea and vomiting. The clinical experts highlighted that vomiting is less common than nausea, and in clinical practice you can avoid it by a very gradual up titration ([see section 3.7](#)). They noted that vomiting is the potential outcome of nausea, so there is a risk of double-counting if both are included. After consultation, the company provided a scenario analysis incorporating diarrhoea as an adverse event. The EAG noted that this had only a minor impact on the cost-effectiveness estimates. The committee concluded that the company's inclusion of this adverse event was acceptable.

Company's baseline utility value for type 2 diabetes

3.15 The company's revised base-case model adjusted utility values for aging, in line with the EAG's suggestion. But the EAG noted that the company's

baseline utility value for people with type 2 diabetes (0.815) was still higher than the utility score for the general population at the same age (0.804). It noted that a recent meta-analysis of 19 studies reported an average utility of 0.772 for people with type 2 diabetes ([Redenz et al. 2023](#)). The company emphasised that it used a baseline value from [NICE's guideline on managing type 2 diabetes in adults](#) to align with it as closely as possible. It also noted that the study by Redenz et al. was published after its submission. After consultation, the company provided 2 scenario analyses using lower baseline utilities for people with type 2 diabetes: 0.785 from [Clarke et al. \(2002\)](#) and 0.772 from Redenz et al. The EAG noted that both scenario analyses resulted in cost-effectiveness estimates slightly lower than the company's base-case results. The committee concluded that it preferred to use the lower baseline utility value identified by the EAG. But it acknowledged that changing the value had limited impact on the cost-effectiveness estimates.

Multiplicative approach to combining disutilities

3.16 The company's revised base-case model applied disutility for complications, adverse events and overweight to the baseline utility value for type 2 diabetes using an additive approach. It highlighted that source publications reported all disutilities as additive values. Also, previous NICE technology appraisals guidance adopted an additive approach to combine disutilities. The company emphasised that using the multiplicative approach may underestimate the effect of diabetes-related complications on people's health-related quality of life (HRQoL). After consultation, the company highlighted evidence from [Gough et al. \(2009\)](#). This concluded that HRQoL decrements associated with type 2 diabetes and obesity showed no significant interaction, so could be assumed to be additive. Also, studies by [Sullivan et al. \(2011\)](#) and [Hayes et al. \(2016\)](#) considered it reasonable to treat comorbidities for diabetes as independent and add utility decrements. The company also provided a scenario analysis using a multiplicative approach for combining disutilities. The EAG noted cost-effectiveness estimates increased with the

multiplicative approach compared with the company's base-case results. But the incremental cost-effectiveness ratios (ICERs) remained below £20,000 per quality-adjusted life year (QALY) gained. The committee noted that [NICE health technology evaluations: the manual](#) states that the multiplicative method is a preferred approach for combining disutilities. But it acknowledged that the evidence provided by the company supported using an additive approach. The committee concluded that an additive approach for combining disutilities was acceptable for this appraisal.

Probabilistic sensitivity analysis

3.17 The company explained that the probabilistic sensitivity analysis in PRIME T2D aimed to capture uncertainty around all aspects of simulation, not only uncertainty around model parameters. It also stated that it followed the methods used in the CORE Diabetes Model. The EAG explained the company's approach was not standard, and that the estimated mean results might have been correct but distribution around results was likely distorted and uncertainty underestimated. The committee concluded that the company's probabilistic sensitivity analysis may have underestimated the uncertainty around the ICERs. But it thought that the mean results were likely to be appropriately estimated.

Cost effectiveness

Cost-effectiveness estimates

3.18 The company's revised base-case ICERs were less than £20,000 per QALY gained for tirzepatide (all doses) against all comparators. Additional analyses provided by the company after consultation improved confidence in the clinical-effectiveness results (see [section 3.9](#)) and the economic model (see [section 3.10](#)). Scenario analyses included:

- using head-to-head comparison between tirzepatide and semaglutide based on SURPASS-2 results

- using only UKPDS risk equations to predict the risk of micro- and macrovascular complications
- assuming a GLP-1 RA or tirzepatide are continued after starting basal insulin (instead of switching to basal insulin)
- incorporating diarrhoea as an adverse event
- using lower baseline utility values (0.785 and 0.772) for people with type 2 diabetes
- using a multiplicative method for combining disutilities.

All ICERs produced in the scenario analyses were less than £20,000 per QALY gained for tirzepatide. So, the committee considered tirzepatide to be a cost-effective use of NHS resources. It recommended tirzepatide in line with the company's positioning, that is, as an alternative to GLP-1 RAs in the type 2 diabetes treatment pathway.

Other factors

Equality

3.19 The committee noted that people of Black Caribbean, Black African and South Asian family background are at a higher risk of being diagnosed with type 2 diabetes, and at a younger age. It acknowledged that there is a higher prevalence of the condition among people in more deprived areas and they have poorer care, leading to poorer outcomes. It noted that a high proportion of people with type 2 diabetes have excess weight. It also noted that people who experience weight stigma are less likely to have good care and to seek help from a healthcare professional to support weight loss. The committee noted these concerns, but concluded that they had no effect on its recommendations.

Innovation

3.20 The committee noted that tirzepatide is a first in class dual GLP-1 and GIP RA. But it did not identify additional benefits of tirzepatide not captured in the economic modelling. So, the committee concluded that all the additional benefits of tirzepatide had already been considered.

Conclusion

Tirzepatide is recommended

- 3.21 The committee concluded that all ICERs for tirzepatide (all doses) against all comparators were within what NICE considers a cost-effective use of NHS resources. Because of tirzepatide's positioning as an alternative to GLP-1 RAs, it is recommended in a narrower population than its marketing authorisation.

4 Implementation

- 4.1 [Section 7 of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has type 2 diabetes and the doctor responsible for their care thinks that tirzepatide is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee A](#).

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.

Chairs

Radha Todd and James Fotheringham

Chair and vice chair, technology appraisal committee A

NICE project team

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

Janet Boadu and Giacomo De Guisa

Technical leads

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Project manager

ISBN: [to be added at publication]