NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Tirzepatide for treating type 2 diabetes

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

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

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

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

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

After consultation:

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using tirzepatide in the NHS in England.

For further details, see [NICE's manual on health technology evaluation](#).

The key dates for this evaluation are:

- Closing date for comments: 18 July 2023

- Second evaluation committee meeting: 1 August 2023

- Details of the evaluation committee are given in [section 4](#)

1 Recommendations

1.1 Tirzepatide is not recommended, within its marketing authorisation, for treating type 2 diabetes alongside diet and exercise in adults when it is insufficiently controlled:

- alone when metformin cannot be taken because of intolerance or contraindications, or
- with other antidiabetic drugs.

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 not effective, 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. But the results are uncertain.

In addition to the uncertainties in the clinical evidence, there are issues with the company's economic model. These include that:

- the external assessment group was unable to fully scrutinise it

- it is unclear how accurately it predicts the long-term health outcomes with tirzepatide and GPL-1 receptor agonists

- there is no evidence showing how the model results compare with other economic models for diabetes.

So, the cost-effectiveness estimates are uncertain, and tirzepatide is not 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

- alone 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 and cannot be reported here.

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 devasting, 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 level is 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 not effective, not tolerated or contraindicated, people can swich 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/m^2 or more (adjusted accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or
- who have a BMI of less than 35 kg/m^2 but for whom insulin therapy would have significant occupational implications or when weight loss would benefit other significant obesity related complications.

The committee noted that the treatment pathway for type 2 diabetes is complex. It concluded that, when triple therapy is not effective, 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 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/m^2 or more (adjusted accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or
- with a BMI of less than 35 kg/m^2 but for whom insulin therapy would have significant occupational implications or when weight loss would benefit other significant obesity related complications.

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 GLP-1 RAs chosen by the company represent those that would be used in NHS practice.

Clinical evidence

Clinical effectiveness evidence

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 alone (1,500 mg/day or more; SURPASS-2)
- insulin degludec in adults with type 2 diabetes who had inadequate glycaemic control on stable doses of metformin with or without a 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 people with type 2 diabetes and on insulin glargine with or without metformin (SURPASS-5).

In SURPASS-2, -3 and -5, people had to have an HbA1c level of 53 mmol/mol (7.0%) or more to 91 mmol/mol (10.5%) or less. In SURPASS-4 it was 58 mmol/mol (7.5%) or more to 91 mmol/mol (10.5%) or less. They also had to have had a stable weight for 3 months and a BMI of 25 kg/m² or more in SURPASS-2 to -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/m^2, 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 population of the SURPASS trials were generally similar to the population seen in the NHS, except the population have had previous treatment. This is because people would have to have a triple therapy before becoming eligible for tirzepatide under company's proposed positioning of tirzepatide in the treatment pathway.

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 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 network meta-analysis (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 the SURPASS-2 and -3 trials, 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 level is 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. 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 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 heterogeneity 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 further noted that a direct comparison was possible, based on SURPASS-2 results, at least with semaglutide. It concluded that a scenario analysis based on this data might be useful for its decision making, despite its misalignment with company's decision problem.

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 macrovascular and microvascular 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. 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 non-standard software. So, it was very challenging for the EAG to scrutinise the model. The company explained that it did everything it could to be transparent about its model. It had shared the model source code, Javascript object notation files, technical report, peer-reviewed manuscript and the 2020 PRIMA report on the model with the EAG. The EAG confirmed that it was able to reproduce the company's base-case results locally (that is, without the web interface). But it noted this is usually a starting point to an EAG's critique of the model. The EAG noted that the company did not provide a checklist for model validation nor the full one-way sensitivity analyses requested, which could have helped it scrutinise the model. The EAG highlighted that it preferred to use the CORE Diabetes Model or UKPDS outcomes model (UKPDS OM2) for comparability with previous NICE technology appraisals and NICE's guideline on managing type 2 diabetes in adults. The committee acknowledged that, hypothetically, the PRIME T2D model might be an improvement compared with other diabetes models. It also acknowledged that the EAG was not able to scrutinise the model to the usual rigorous standard because of the model complexity and non-standard software. It concluded that it could not be confident that the cost-effectiveness results presented by the company were accurate. The committee noted that it would like to see the results of the deterministic one-way sensitivity analyses on the full set of model parameters. It noted that its confidence in the model results may be further increased by comparison with a cost-

effectiveness analysis run in the CORE Diabetes Model or UKPDS outcomes model (UKPDS OM2).

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)

The company highlighted that using just 1 cohort (a low-risk cohort) did not take into consideration what was going to happen 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. The EAG acknowledged that, theoretically, model averaging may be a better approach than using single-risk equations. But it noted that the company did not present a comparison between Ninth Mount Hood Diabetes Challenge results and the current

implementation of PRIME T2D. Also, the company did not present any scenario analyses examining the effect of its approach, such as selecting a single predictive model. Without such evidence, it is not clear whether PRIME T2D better predicts cardiovascular complications than existing diabetes models. The committee noted that risk equations are designed to predict the risk that someone with a set of characteristics has over time. They are not designed to show how that risk might change if those characteristics change over time because of treatment. But this is how the company implemented them in the model. The committee accepted that, hypothetically, the company's approach may be better than drawing on a single-risk equation but remained uncertain about this. It concluded that sensitivity analyses in which a single-risk prediction is selected would help it understand how these approaches compare and the impact on cost-effectiveness estimates.

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 on tirzepatide and GLP-1 RAs. This was based on studies for cardiovascular outcomes with GLP-1 RAs, and showing that body weight and SBP remain 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%). It noted that no other causes for stopping treatment were included. 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. A scenario analysis assuming treatment is intensified by adding insulin to tirzepatide and GLP-1 RAs when people's HbA1c targets are not met would allow it to explore the impact of this deviation on cost-effectiveness estimates.

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. The committee concluded that the company's inclusion of adverse events 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. 2022). 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. The committee acknowledged that the baseline utility for type 2 diabetes was higher than that for the general population at the same age. It concluded that it preferred to use the lower baseline utility value identified by the EAG.

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. In addition, 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. The committee noted that the multiplicative method is a preferred approach to combine disutilities, in line with the NICE health technology evaluations: the manual. It noted that the company had not provided a clear rationale for why the multiplicative approach was not appropriate. It also noted that previous technology appraisals to which it referred had been published before the new methods manual applied. The committee concluded that the updated manual should have been followed.

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 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 incremental cost-effectiveness ratios (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 quality-adjusted life year gained for tirzepatide (all doses) against all comparators. But the committee recalled uncertainty in the NMA (see section 3.9) and the economic model (see section 3.10), and the lack of sufficient sensitivity analyses (see section 3.10). The committee concluded that the following additional analyses could help resolve its concerns:

- a scenario analysis based on direct head-to-head results against semaglutide from SURPASS-2; the committee noted previous treatment in SURPASS-2 did not align with company target population, but that risk of bias would be minimised (see section 3.9)
- cost-effectiveness results when analysis is run in CORE Diabetes Model and/or UKPDS OM2 (see section 3.10)
- one-way sensitivity analyses for all inputs in PRIME T2D (tornado diagram; see section 3.10)
- sensitivity analyses around the model averaging approach used to predict the risk of micro- and macrovascular complications (see section 3.11)
- scenario analysis in which GLP-1 RAs and tirzepatide are continued (while adding insulin) when intensifying treatment (see section 3.13)
- using a baseline utility value that is lower than the utility score for the general population at the same age (see section 3.15)

- using the multiplicative method to combine disutilities in the base case or provide a rationale for why a multiplicative approach is not appropriate (see [section 3.16](#)).

Other factors

Equality

3.19   The committee noted that people of South Asian, 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 not recommended

3.21   The committee's concerns about the clinical evidence and cost-effectiveness model meant that it was not confident about the results. The committee agreed that further analyses were needed to address this uncertainty. So, tirzepatide is not recommended for treating type 2 diabetes in adults.

4 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.

Chair

Radha Todd

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

Technical lead

Ewa Rupniewska

Technical adviser

Thomas Feist

Project manager

ISBN: [to be added at publication]