NCPE Assessment

Technical Summary

Tirzepatide (Mounjaro®)

24003

09 February 2026

Applicant: Eli Lilly

Tirzepatide 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; or
- in addition to other medicinal products for the treatment of diabetes.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of tirzepatide (Mounjaro®) for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise (i) as monotherapy when metformin is considered inappropriate due to intolerance or contraindications; (ii) in addition to other medicinal products for the treatment of diabetes.

Following assessment of the Applicant's submission, the NCPE recommends that tirzepatide (Mounjaro®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Eli Lilly) Health Technology Assessment of tirzepatide (Mounjaro®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In April 2025, Eli Lilly submitted a partial dossier on the comparative clinical effectiveness, cost-effectiveness and budget impact of tirzepatide (Mounjaro®) for the treatment of adults with insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise: (i) as monotherapy when metformin is considered inappropriate due to intolerance or contraindications; (ii) in addition to other medicinal products for the treatment of diabetes. However, there was insufficient information for the NCPE Review Group to adequately appraise the economic model provided. A full submission was received in August 2025. This HTA considered adults living with insufficiently controlled T2DM. A separate HTA considered the clinical efficacy, cost-effectiveness and budget impact of tirzepatide in patients living with overweight or obesity, without T2DM (HTA ID: 24024). Approximately 90% of the population with T2DM in Ireland are living with overweight or obesity. Therefore, there is some overlap in the budget impact estimates for the separate indications of tirzepatide for weight management and T2DM. Eli Lilly is seeking reimbursement of tirzepatide on the Community Drugs Scheme (CDS).

Tirzepatide is a long-acting, dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. GIP and GLP-1 are human incretin hormones, which enhance glycaemic control and appetite regulation. Following dose titration, the recommended maintenance doses are 5mg, 10mg, or 15mg once weekly by subcutaneous injection.

T2DM is a chronic, metabolic disease caused by resistance to insulin or impaired insulin production. It is characterised by elevated blood glucose levels (hyperglycaemia). Risk factors include overweight and obesity, lifestyle factors, increasing age and family history. Primary treatment aims are to optimise glycaemic control and prevent disease-related complications. Glycaemic control is monitored though regular measurement of glycated haemoglobin (HbA1c). HbA1c targets are individualised and are determined by patient-specific factors. Diet and exercise are the cornerstones of treatment. Metformin monotherapy is recommended as first-line treatment for patients with no existing co-morbidities. A glucagon-like peptide-1 receptor agonist (GLP-1 RA) or a sodium-glucose

cotransporter 2 (SGLT2) inhibitor, either in combination with metformin or as monotherapy, may be considered first-line for patients with at least one existing co-morbidity (for example, cardiovascular disease, heart failure, overweight and obesity, chronic kidney disease). Insulin-based treatment may be initiated once dual therapy with at least two glucose-reducing agents has failed to achieve glycaemic control.

The Applicant considered three GLP-1 RAs to be relevant comparators to tirzepatide: dulaglutide (Trulicity®), liraglutide (Victoza®) and semaglutide (Ozempic®). The Review Group also considered SGLT2 inhibitors to be relevant comparators; however, these were not included by the Applicant. This omission was considered an important limitation of the health technology assessment (HTA).

In the cost-effectiveness model (CEM), the Applicant divided the full licensed population (for this indication) into three distinct subpopulations (the add-on to one to two oral antidiabetic drugs (OADs) population; the add-on to insulin population; and the monotherapy population). Pair-wise cost-effectiveness results were presented for each strength of tirzepatide (5mg, 10mg and 15mg) versus each strength of comparator across each of the three subpopulations. In total, 24 pairwise comparisons were presented in the Applicant base case. Due to the large volume of results, the Review Group chose to present only results of the comparisons of tirzepatide versus semaglutide (Ozempic®) 1mg once weekly (by subcutaneous injection) in the add-on to one to two OADs population. These were considered the most relevant. This was informed by Clinical Opinion, which indicated that the add-on to one to two OADs population reflected the majority of patients with T2DM in Ireland who might be prescribed tirzepatide. It was also informed by analysis of Primary Care Reimbursement Service (PCRS) data which indicated that semaglutide (Ozempic®) 1mg was the most commonly prescribed GLP-1 RA for T2DM in Ireland.

1. Comparative effectiveness of tirzepatide

Evidence from the SURPASS clinical trial programme informed the efficacy and safety of tirzepatide in patients with T2DM. Data from six studies (SURPASS-1 to SURPASS-6) were presented. Populations recruited to each of the trials differed with respect to background therapies (ranging from treatment naïve to insulin-experienced) and co-morbidities. Comparators for each trial also varied. They included placebo (SURPASS-1 and SURPASS-5),

semaglutide (SURPASS-2), and different formulations of insulin (SURPASS-3, SURPASS-4 and SURPASS-6). The primary endpoint for each of the SURPASS trials was mean change in HbA1c from baseline to end of study. This was measured at 40 weeks in SURPASS-1, SURPASS-2 and SURPASS-5; it was measured at 52 weeks in SURPASS-3, SURPASS-4 and SURPASS-6. Key secondary endpoints included percentage of patients achieving HbA1c below 53mmol/mol (7.0%) and mean change in bodyweight from baseline to end of study.

SURPASS-2 was considered of most relevance to this assessment. It recruited participants that reflected the add-on to one to two OADs population, and it compared tirzepatide with semaglutide. Evidence from the remaining SURPASS trials was considered supportive, as was data from SURPASS-CVOT, which was published December 2025. This study compared cardiovascular outcomes (including stroke and myocardial infarction) associated with tirzepatide to that of dulaglutide.

SURPASS-2 was a phase III, randomised, open-label trial. A total of 1,878 people were randomised to, and received at least one dose of, study treatment. Eligible participants were adults with T2DM inadequately controlled with metformin. Participants were randomised to receive either tirzepatide 5mg (n=470), tirzepatide 10mg (n=469), tirzepatide 15mg (n=470), or semaglutide 1mg (n=469). All study treatments were administered once-weekly by subcutaneous injection. Doses of tirzepatide were blinded. Participants assigned to tirzepatide initiated treatment in accordance with an established dose-escalation protocol. At baseline, the mean age of participants was 56.6 years, mean HbA1c was 67mmol/mol (8.28%), and more than one third of participants had a baseline HbA1c greater than 69mmol/mol (8.5%). From baseline to Week 40, greater reductions in HbA1c were observed in participants treated with tirzepatide at all doses compared to semaglutide 1mg. The results were statistically significant. Key secondary outcomes were also indicative of improved treatment benefit associated with tirzepatide compared to semaglutide 1mg.

Outcomes from the other five SURPASS trials also favoured tirzepatide. Across each study, tirzepatide demonstrated statistically significant improvements versus the relevant comparator in reducing HbA1c levels, reducing body weight, and facilitating a greater percentage of people to achieve HbA1c less than 53mmol/mol (7.0%). Results from a post-hoc subgroup analysis of SURPASS-4 were supportive of long-term improvement in

glycaemic control (up to 156 weeks). The SURPASS-CVOT trial, with a median follow-up of four years, demonstrated that tirzepatide was non-inferior to dulaglutide with respect to composite risks of death from cardiovascular causes, specifically myocardial infarction or stroke.

Health-related quality of life (HRQoL) was included in all SURPASS trials as a secondary endpoint. There were no significant differences between the tirzepatide arms and the comparators, when measured using the EuroQol® 5-Dimension 5-Level (EQ-5D-5L) questionnaire.

There is limited follow-up data for tirzepatide used in addition to monotherapy, or as an add-on to one to two OADs, beyond 40 weeks. This is of particular relevance to the higher maintenance doses, as participants in the tirzepatide 5mg, 10mg, and 15mg arms spent 36 weeks, 24 weeks, and 16 weeks at their assigned dose, respectively. The impact on clinical efficacy outcomes, where a longer duration of follow up is observed, remains uncertain. Generalisability of the titration protocol in SURPASS-2 to clinical practice in Ireland is also uncertain, as participants were titrated upwards regardless of participant response and dose de-escalation was not permitted.

Direct comparative evidence was available for comparisons of each maintenance dose of tirzepatide versus semaglutide 1mg in the add-on to one to two OADs population only. Indirect evidence, conducted using network meta-analyses (NMAs), was required to inform comparisons between tirzepatide and semaglutide in the add-on to insulin population and in the monotherapy population. It was also required to inform comparisons between tirzepatide and each of the other included comparators (dulaglutide and liraglutide) for each of the three subpopulations. For purposes of this assessment, the add-on to one to two OAD subpopulation network was considered the most relevant to current Irish clinical practice. Due to strict inclusion criteria, no studies informing efficacy for semaglutide qualified for inclusion in the NMA for the add-on to insulin population network. This meant that a comparison of tirzepatide versus semaglutide in the add-on to insulin population could not be conducted. The Review Group considered this omission an important limitation of the Applicant submission.

The NMA was conducted in a Bayesian Mixed Treatment Comparisons framework.

Tirzepatide demonstrated a statistically significant improvement with respect to reductions in HbA1c, weight, and body mass index (BMI). The Applicant assumed that outcomes analysed for tirzepatide at Week 40 ± 4 weeks were comparable to outcomes at Week 26 ± 4 weeks in comparator studies, due to the longer periods required to titrate to the tirzepatide 10mg and 15mg maintenance doses. The Review Group considered this could bias the treatment effect in favour of tirzepatide, given that participants will have had a longer overall treatment period with tirzepatide, inclusive of the titration period. The estimand, which defines the treatment effect a trial aims to measure while accounting for intercurrent events, used for many of the comparator trials may have differed to the estimand used for the SURPASS trials. Participants taking rescue medication were censored in the SURPASS trials; however, this may not have been the case in the comparator trials, which is likely to have biased in favour of tirzepatide.

2. Safety of tirzepatide

Safety and tolerability of tirzepatide, in patients with T2DM, was informed by data from the SURPASS-1 to SURPASS-5 trials, and from two phase III studies conducted in a Japanese population (SURPASS-J-Mono and SURPASS-J-Combo). Approximately 70% of people treated with tirzepatide reported an adverse event (AE). The most commonly reported AEs were gastrointestinal-related. Nausea and diarrhoea were most common. Other gastrointestinal-related AEs included decreased appetite, dyspepsia, vomiting and constipation.

Tirzepatide should be used with caution in people with a history of pancreatitis, in those with severe gastrointestinal disease, and in those with diabetic retinopathy. Tirzepatide is not recommended during pregnancy.

3. Cost effectiveness of tirzepatide

Methods

Cost-effectiveness was assessed, from the perspective of the HSE, using the PRIME Type 2 Diabetes (PRIME T2D) model. This was an individual patient simulation model that was purpose-built to model cost-effectiveness of interventions for T2DM. It was programmed in Java and was accessible using an online interface. The model had a lifetime horizon and a one-year cycle length. The population being considered was the full licensed population for tirzepatide for this indication. However, this was subdivided into three distinct

subpopulations in the CEM, as previously described. The modelled intervention was tirzepatide (5mg, 10mg and 15mg). The modelled comparators were dulaglutide, liraglutide and semaglutide.

The Review Group encountered several challenges with the PRIME T2D model including: computational burden, inabilities to validate all parameters and codes, and concerns about inputting commercially sensitive information into an on-line platform.

Cost-effectiveness results generated by the PRIME T2D model were considered to be highly uncertain. For a subset of analyses, the Applicant provided comparative results generated by the validated Core Diabetes model. The incremental cost-effectiveness ratios (ICERs) produced by the PRIME T2D model were generally lower than those produced by the Core Diabetes model. Additionally, the cost-effectiveness estimates provided by the PRIME T2D model were unstable, suggesting that the sample size used to run the model was too small.

Upon entry to the PRIME T2D model, all patients were assumed to have been prescribed either tirzepatide or one of the GLP-1 RA comparators. The model used surrogate outcomes to model T2DM progression. T2DM-related disease complications were also included (for example, cardiovascular complications). There was limited data on the risk of developing complications as this was not measured directly in the trials. Therefore, risk equations were used to inform the risk of developing T2DM-related complications. Relative treatment effects for tirzepatide versus semaglutide 1mg were informed by direct comparative evidence provided by SURPASS-2. Relative treatment effects for tirzepatide versus all other comparisons, were informed by outcomes from the NMA. After 40 weeks on treatment, it was assumed that all surrogate outcomes remained constant until treatment discontinuation, with the exception of HbA1c progression. Upon treatment discontinuation, it was assumed that all surrogate outcomes returned to baseline values. One of the key risk equations informing the PRIME T2D model used data which was based on a study conducted in the UK more than 20 years ago. The study predated introduction of GLP-1 RAs, which have improved the management of T2DM. Therefore, the Review Group considered that the risk of T2DM related disease complications may be overestimated in the PRIME T2D model.

In the PRIME T2D model, it was assumed that patients intensified treatment when HbA1c increased above 53mmol/mol (7.0%). Patients could experience a maximum of two

treatment intensification episodes. Treatment intensification was the only mechanism by which patients could discontinue tirzepatide or GLP-1 RA treatment. The Review Group considered these assumptions to be oversimplifications. In clinical practice, HbA1c goals are individualised according to patient characteristics. Furthermore, the HbA1c threshold chosen for triggering treatment intensification was considered by the Review Group to be too low for many patients. For example, the National Institute for Health and Care Excellence (NICE) recommend treatment intensification if HbA1c levels rise to 58 mmol/mol (7.5%) or higher. Additionally, in practice, patients would discontinue tirzepatide or GLP-1 RA treatment for other reasons, for example due to AEs. However, the model did not incorporate this functionality. A number of regression models were available to inform the effect that the addition of insulin had on change in HbA1c. The Review Group considered there to be limitations associated with the regression model chosen by the Applicant and that an alternative regression model was more appropriate.

A systematic literature review was conducted to identify HRQoL data to inform utility values in the model. Each simulated patient was assigned a baseline utility value. Disutilities associated with AEs and T2DM-related complications were applied. A utility gain associated with weight loss was assumed in Year One. From Year Two onwards, a utility decrement was applied for each unit of BMI above 25kg/m^2. The Review Group considered that there were a number of limitations with the assumptions relating to utilities. These included double counting and the use of utility attributed to weight change at the end of Year One rather than an average value over the year.

Costs included in the model were drug acquisition costs, T2DM-related complication costs, and AE costs. The Applicant stated that costs for administration, resource use, and monitoring while on tirzepatide are expected to be similar to that of other GLP-1 RAs. The Review Group considered that tirzepatide would be subject to additional monitoring, based on clinical opinion. However, functionality was not available to explore this assumption in the model.

Results

As described previously, important limitations of the PRIME T2D model were identified by the Review Group. As some substantial limitations could not be addressed, the Review

Group considered the NCPE adjusted base case to be exploratory.

Three changes were made to inform the NCPE exploratory base case. The HbA1c threshold for treatment intensification was increased from 53mmol/mol (7.0%) to 58mmol/mol (7.5%). A BMI-based approach to change in utility in Year One was used as an alternative to the Applicant's weight-based approach. A different regression model was chosen to inform the treatment effect of insulin on change in HbA1c. The input value assigned to the study duration covariate in the regression model was changed to a value the Review Group considered to be more accurate.

Results of the Applicant and NCPE-exploratory base case deterministic cost-effectiveness analyses are presented in Tables 1 and 2, respectively. To address concerns regarding instability of cost-effectiveness results, the Review Group increased the sample size. Results of the NCPE exploratory base case reflect the average ICER. To improve the stability of the Applicant's base case results, the Review Group also increased the sample size of the Applicant's base case results. These results are also presented in Table 1.

Table 1: Applicant base case incremental cost-effectiveness results [a, b,]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Applicant base case as presented by the Applicant [c]					
Semaglutide 1mg	68,993	7.235	-	-	-
Tirzepatide 5mg	78,853	7.265	9,860	0.030	331,168
Tirzepatide 10mg	80,165	7.323	11,172	0.088	126,592
Tirzepatide 15mg	80,173	7.345	11,181	0.110	101,384
Applicant base case averaged across five simulations [d]					
Semaglutide 1mg	68,952	7.234	-	-	-
Tirzepatide 5mg	78,851	7.271	9,899	0.037	268,249
Tirzepatide 10mg	80,116	7.314	11,164	0.080	139,466
Tirzepatide 15mg	80,137	7.344	11,185	0.110	101,451

ICER: incremental cost-effectiveness ratio; **mg:** milligram; **OAD:** oral antidiabetic drugs; **QALY:** quality adjusted life year

[a] Comparison of tirzepatide versus semaglutide 1mg in the add-on to one to two OADs population

[b] Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes

[c] The Applicant performed one simulation run using a sample size of 400,000 patients

[d] The Review Group conducted five simulation runs of the Applicant's base case, using five different seed numbers (the same seed numbers used for the NCPE exploratory base case). Each simulation run used a same sample size of 400,000 patients. The averaged results are presented in this table.

Table 2: NCPE exploratory base case incremental cost-effectiveness results [a, b, c]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Semaglutide 1mg	67,770	7.25	-	-	-
Tirzepatide 5mg	82,372	7.28	14,601	0.032	449,326

Tirzepatide 10mg	84,059	7.33	16,288	0.081	201,798
Tirzepatide 15mg	84,023	7.37	16,252	0.115	140,886

ICER: incremental cost-effectiveness ratio; **mg:** milligram; **NCPE:** National Centre for Pharmacoeconomics; **OAD:** oral antidiabetic drugs; **QALY:** quality adjusted life year

[a] Comparison of tirzepatide versus semaglutide 1mg in the add-on to one to two OADs population
[b] Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes.
[c] For the NCPE exploratory base case, the Review Group ran five simulations, using five different seed numbers. Each simulation run used a same sample size of 400,000 patients. The averaged results are presented in this table.

Sensitivity analysis

Due to the structure of the PRIME T2D model, the Review Group did not consider it feasible to conduct a reliable deterministic one-way sensitivity analysis or probabilistic sensitivity analysis. As discussed previously, the Review Group were limited in their ability to conduct scenario analyses.

A Price-ICER analysis was conducted by the Review Group. However, due to computational burden associated with the PRIME T2D model, calculated percentage reductions were calculated via linear interpolation. When compared to semaglutide 1mg, and using NCPE exploratory base case assumptions, reductions in the prices to wholesaler of approximately 77%, 67%, and 59% (inclusive of the Framework Agreement rebate) for the 5mg, 10mg, and 15mg strengths, respectively, would be required for tirzepatide to demonstrate cost-effectiveness at the €45,000 per quality-adjusted life year (QALY) cost-effectiveness threshold. Reductions in the prices to wholesaler of approximately 81%, 76%, and 71%, for the 5mg, 10mg, and 15mg strengths, respectively, would be required for tirzepatide to demonstrate cost-effectiveness at the €20,000 per QALY threshold.

4. Budget impact of tirzepatide

Each pack of tirzepatide contains four pre-filled pens, which provides a 28-day supply. The prices to wholesaler per pack of tirzepatide 2.5mg and per pack of tirzepatide 5mg are €324.37 and €337.22, respectively. The price to wholesaler per pack of tirzepatide for each of the other strengths (7.5mg, 10mg, 12.5mg and 15mg) is €365.31. The estimated annual cost of tirzepatide per patient to the HSE ranges from €5,742 to €6,214 (including value-added tax [VAT], inclusive of the 9% Framework Agreement Rebate, and pharmacy dispensing fee), depending on the maintenance dose prescribed (that is, 5 mg once-weekly to 15 mg once-weekly). The Applicant submitted a budget impact model, estimating the gross and net drug-budget impact associated with tirzepatide over the next five years. There

were several uncertainties associated with the Applicant's budget impact estimates. The Review Group addressed some limitations by including an incident population, and adjusting the proportion of patients assumed to be eligible for treatment with a GLP-1 RA to align with data from the PCRS data analysis. Market share estimates were also updated to align with the current use pattern from PCRS data in Ireland. An annual discontinuation rate was applied for all treatments, as informed by a large UK retrospective cohort study conducted in patients with T2DM initiating GLP-1 RA therapy. Applying this assumption resulted in similar estimates for annual expenditure on comparators as observed in the PCRS analysis.

The Applicant's five-year net drug-budget impact was estimated as €166.4 million (including VAT). The NCPE-adjusted five-year net drug-budget impact was estimated at €452.6 million (including VAT).

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment

6. Conclusion

The NCPE recommends that tirzepatide, for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise (i) as monotherapy when metformin is considered inappropriate due to intolerance or contraindications; (ii) in addition to other medicinal products for the treatment of diabetes, be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

Tirzepatide has demonstrated clinically meaningful benefits in terms of reduction in HbA1c and other metabolic outcomes. Continued efficacy in the long-term is still uncertain. Cost-effectiveness estimates are subject to substantial uncertainty, due to limitations with the Applicant's chosen model. While the budget impact associated with reimbursement of tirzepatide for patients with T2DM may overlap with that for chronic weight management, it remains substantial. Some long-term cost offsets associated with a reduction in healthcare costs are likely, but the magnitude of these offsets is uncertain.

* *This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.*