NCPE Assessment

Technical Summary

Tirzepatide (Mounjaro®)

HTA ID: 24024

03 December 2025

Applicant: Eli Lilly

Tirzepatide, as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of

- ≥30kg/m^2 (obesity); **or**
- ≥27kg/m^2 to <30kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of tirzepatide (Mounjaro®) as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of: ≥30kg/m^2, or ≥27kg/m^2 to <30kg/m^2 in the presence of at least one weight-related comorbid condition (WRC).

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 dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of tirzepatide (Mounjaro®) as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) : ≥30kg/m^2, **or** ≥27kg/m^2 to <30kg/m^2 in the presence of at least one WRC (e.g hypertension, dyslipidaemia, obstructive sleep apnoea [OSA], cardiovascular disease [CVD], prediabetes, or type 2 diabetes mellitus [T2DM], as described in the summary of product characteristics (SmPC)). Eli Lilly is seeking reimbursement of tirzepatide on the Community Drug Scheme.

The current standard of care (SoC) for the treatment of overweight and obesity, in Ireland, is outlined in the *HSE Model of Care (MoC) for the Management of Overweight and Obesity* (2020). This MoC describes a step-wise approach, with intensification of care, and addition of pharmacotherapy, based on BMI and WRC-status (e.g presence of hypertension, T2DM, OSA, polycystic ovarian syndrome (PCOS), osteoarthritis, cancer, gastro-oesophageal disease, back pain, depression, and family status of these WRCs). Levels 0 and 1 of the *HSE MoC* recommend the following for patients living with overweight and obesity without WRCs: brief health advice, self-management supports, diet and exercise lifestyle interventions, commercial programmes and primary care team interventions. This care takes place in primary care centres or in general practice. At levels 2 to 4 of the MoC, care is provided in specialist community, ambulatory or hospital settings. Clinical guidelines typically recommend pharmacotherapy in addition to diet and exercise in individuals with a BMI ≥30kg/m^2, **or** ≥27kg/m^2 to <30kg/m^2 with a WRC, where sufficient weight-loss cannot be achieved by means of lifestyle interventions.

Tirzepatide is a long-acting glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor agonist (RA), given subcutaneously (SC) at a starting dose of 2.5 mg once weekly, increased after 4 weeks to 5mg once weekly. If needed, further dose titrations can be made up to a maximum of 15mg once weekly. The recommended maintenance doses are 5mg, 10mg and 15mg once weekly. Liraglutide (Saxenda®) (a GLP-1 RA) is reimbursed for weight management, in Ireland, and is subject to a HSE Managed

Access Protocol (MAP). It is reimbursed in adult patients, as an adjunct to a reduced-calorie diet and increased physical activity for weight management, with an initial body mass index of ≥ 35 kg/m^2 with prediabetes and high-risk of CVD. A HTA of semaglutide for the treatment of overweight and obesity has been submitted to the NCPE and is ongoing (HTA ID: 25024). Other GLP-1 RAs, semaglutide (Ozempic®), dulaglutide (Trulicity®), and liraglutide (Victoza®) are reimbursed, in Ireland, for the management of T2DM under the Long-Term Illness (LTI) scheme. A proportion of patients living with T2DM, with comorbid overweight or obesity, may be in receipt of a GLP-1 RA under the LTI scheme. The comparators of relevance for the HTA of tirzepatide, for the indication under assessment, include diet and exercise interventions and semaglutide. Liraglutide is also a comparator in the subpopulation of patients with an initial body mass index of ≥35 kg/m^2 with prediabetes and high-risk of CVD. The Applicant included diet and exercise, and liraglutide as comparators in the submission, but did not include semaglutide as it is not currently reimbursed for the treatment of overweight and obesity.

1. Comparative effectiveness of tirzepatide

For this HTA, the Applicant considered only those living with overweight and obesity, who do not have T2DM. The Applicant excluded those with T2DM stating that they will be considered in the HTA submission of tirzepatide for patients living with T2DM (HTA ID: 24003). Thus, this HTA (apart from the Budget Impact assessment) does not consider the full licensed population, as patients living with T2DM are excluded. Hereafter, the population considered for this HTA is referred to as 'Full Licence$^{(Ex\text{-}T2DM)'}$).

The main clinical evidence supporting this assessment is sourced from the pivotal *SURMOUNT-1* trial and its three- year extension phase data, as this encompasses the largest and longest-running study in the patients living with overweight and obesity, without T2DM. Other trials in patients without T2DM include *SURMOUNT 3, 4 and 5*. *SURMOUNT-3* assessed the efficacy of tirzepatide in patients who had previously achieved a 5% weight reduction during a 12-week lead-in period of intensive lifestyle intervention, while the aim of *SURMOUNT-4* was to explore the effect of discontinuation of tirzepatide on maintenance of weight reduction following a lead-in phase of open-label tirzepatide. *SURMOUNT-5* provides

the only direct evidence of tirzepatide against an active pharmacological comparator, semaglutide, for this indication.

In *SURMOUNT-1*, participants were randomised 1:1:1:1 to one of three doses of tirzepatide; 5mg (n=630), 10mg (n=636), 15mg (n=630), or placebo (n=643) administered SC once-weekly, as an adjunct to a "diet and exercise" intervention (defined as a 500-calorie deficit and a minimum of 150 minutes of exercise per week). A dose-escalation protocol was applicable to all three doses of tirzepatide, whereby tirzepatide was initiated at a dose of 2.5mg once-weekly, increasing by 2.5mg every four weeks, to reach a pre-assigned maintenance dose. Co-primary end points of the *SURMOUNT-1* trial were the percentage change in body weight, from baseline, at week 72 and the proportion of participants who achieved a ≥ 5% body weight reduction from baseline at week 72. The co-primary endpoints were assessed in the tirzepatide 10mg and 15mg arms, both individually and in a pooled analysis. The same endpoints were assessed in the 5mg arm as a key secondary endpoint. Key secondary endpoints were assessed for all doses. Participants had a baseline mean age of 45 years, 67.5% were women, and 40.6% had prediabetes. Mean BMI at baseline was 38kg/m^2. Overall, tirzepatide at fixed doses of 5mg, 10mg and 15mg (as an adjunct to "diet and exercise") demonstrated statistically significant and clinically meaningful differences versus placebo at 72-weeks in terms of weight-loss, BMI, and waist circumference. The mean percent change in body weight from baseline at week 72 was -16.0% with the 5mg dose of tirzepatide, -21.4% with the 10mg dose and -22.5% with the 15mg dose, compared with -2.4% with placebo ($p<0.001$ for all comparisons with placebo). The percentage of participants who achieved a ≥ 5% body weight reduction from baseline at week 72 was 89.4% with the 5mg dose of tirzepatide, 96.2% with the 10mg dose and 96.3% with the 15mg dose, compared with 27.9% with placebo. Improvements in other metabolic outcomes were also observed, including systolic blood pressure, triglycerides, non-high-density cholesterol (non-HDL-C), HDL-C and fasting insulin. Pooled tirzepatide results, including all three doses, demonstrated a statistically significant and clinically meaningful propensity to delay incident cases of T2DM, with 1.2% of those receiving tirzepatide developing T2DM at the end of the three-year follow-up, compared with 12.06% in those receiving placebo. Greater improvements in health-related quality-of-life (HRQoL), measured using the SF-36 instrument, were also demonstrated. The three-year, open-label

follow-up highlighted the requirement for continuous treatment with tirzepatide to maintain treatment benefits. The Applicant provided results of post-hoc analysis for the subgroup of patients with ≥ 1 WRC, in different BMI categories, including BMI $\geq 30^{(+1\ WRC)}$, BMI $\geq 35^{(+1\ WRC)}$, and BMI $\geq 35^{(liraglutide\text{-}MAP)}$ (i.e. patients eligible for the liraglutide MAP). Results in these subgroups were overall consistent with the Full Licence$^{(Ex\text{-}T2DM)}$ population. Clinical efficacy results were requested for the BMI $\geq 40^{(+1\ WRC)}$ subgroup, but were not provided. Overall, three-year follow-up results indicate a maintenance in tirzepatide treatment effect while on treatment, though continued efficacy beyond this timeframe remains unknown.

Generalisability of the tirzepatide dose-escalation protocol in *SURMOUNT-1* to clinical practice in Ireland is uncertain, as patients' doses were titrated upwards until the pre-assigned dose was achieved. In practice, a proportion of patients may be maintained on a lower dose where they have demonstrated a sufficient response. The generalisability of the "diet and exercise" therapy (i.e a 500 calorie deficit per day and at least 150 minutes of physical activity per week)in the *SURMOUNT-1* trials to clinical practice is also unclear. The magnitude of benefit in the absence of the "diet and exercise" intervention has not been demonstrated. The SmPC does not define a specific diet and exercise regimen. Where the intensity of a "diet and exercise" intervention in clinical practice in Ireland is less than what was applied in the *SURMOUNT-1* trial, the treatment effect may be overestimated

Results from the *SURMOUNT-3* and *SURMOUNT-4* trials were supportive of a clinical benefit for tirzepatide. The *SURMOUNT-2* trial included participants with T2DM, and also generated supportive results, though the magnitude of improvement in outcomes with tirzepatide, including weight-loss, was lower across most parameters, compared to the *SURMOUNT-1, -3 and -4* trials. The *SURMOUNT-5* trial, which compared tirzepatide (10mg or 15mg) to semaglutide (1.7mg or 2.4mg) in patients without T2DM, demonstrated significantly greater reductions in weight with tirzepatide. The Review Group requested the inclusion of semaglutide as a comparator in the submission, but this was not provided by the Applicant.

An indirect treatment comparison (ITC) was conducted by the Applicant to assess the comparative effectiveness of tirzepatide versus liraglutide in a population eligible for the liraglutide MAP. The ITC included two studies: the *SURMOUNT-1* trial and the phase III,

double-blind, randomised, placebo-controlled trial for liraglutide 3mg once daily SC, the *SCALE Obesity and Prediabetes* trial. The Review Group considered both studies to be eligible for inclusion in an ITC. Both have broadly comparable baseline clinical characteristics, with some differences in demographic characteristics and inconsistency across the "diet and exercise" support provided. Despite these differences, change from baseline in weight in the placebo arm was similar in both trials. Outcomes in *SCALE* were measured at 56 weeks, while outcomes in *SURMOUNT-1* were measured at 72 weeks due to the longer titration schedule for tirzepatide. The Review Group considers that this time difference is unlikely to introduce significant bias to the results of the ITC for weight reduction, but this is less certain for other outcomes. The results of the ITC, showed a statistically significant improvement in weight reduction for all three doses of tirzepatide, compared with liraglutide 3mg once daily. For other outcomes assessed, the differences were not statistically significant. A comparative-effectiveness analysis of tirzepatide, including semaglutide in addition to liraglutide in a network meta-analysis, was requested by the Review Group, but was not provided by the Applicant.

2. Safety of tirzepatide

Safety results were presented from the *SURMOUNT-1* trial and included all randomised patients who received at least one dose of the study drug (n=2,359). The number of participants experiencing serious adverse events (SAEs) were similar between the tirzepatide arms and the placebo arms, ranging from 5.1% to 6.3% in the tirzepatide arms, versus 6.8% in the placebo arm. Rates of SAEs after three years remained comparable across arms, ranging from 12.6% to 13.4% in the tirzepatide arms, versus 11.9% in the placebo arm. Just over half of treatment related adverse events (TRAEs) were gastrointestinal (GI) in nature, and GI-related symptoms were more common in the tirzepatide arms compared with the placebo arm. Most GI TRAEs were transient, mild to moderate in severity, and occurred primarily during the dose-escalation period. Treatment discontinuations occurred at a comparable frequency with the 10mg and the 15mg tirzepatide dose, and fewer patients on tirzepatide 5mg discontinued treatment.

Of note, an abnormally high mean night-time diastolic blood pressure was observed in the tirzepatide 15mg arm. The clinical significance of this is unknown. A cardiovascular (CV)

meta-analysis submitted by the Applicant to the Committee for Medicinal Products for Human Use does not suggest any increased CV-related risk associated with tirzepatide, however, further data are awaited from the *SURMOUNT-MMO* study to arrive at reliable conclusions regarding CV events. An increased risk of hypoglycaemia may occur in patients receiving tirzepatide in combination with insulin or an insulin secretagogue, potentially requiring a dose-reduction of the insulin or insulin secretagogue. In the direct comparison of tirzepatide versus semaglutide in *SURMOUNT-5*, the overall rates of AEs occurring in greater than 5% of participants were similar between the two arms. A greater proportion of participants in the tirzepatide arm experienced SAEs, however a greater proportion of participants in the semaglutide arm discontinued treatment due to AEs.

3. Cost effectiveness of tirzepatide

The Applicant submitted cost-effectiveness analyses, comparing tirzepatide, as an adjunct to "diet and exercise", to "diet and exercise" alone, in the Full licence$^{(Ex\text{-}T2DM)}$ population, and the BMI ≥30$^{(+1\ WRC)}$ and BMI ≥35$^{(+1\ WRC)}$ subpopulations. A comparison of tirzepatide with liraglutide (both as an adjunct to "diet and exercise") in the BMI ≥35$^{(liraglutide\text{-}MAP)}$ subpopulation was also submitted. In all analyses, patients living with T2DM were excluded. An analysis in the BMI ≥40$^{(+1\ WRC)}$ subpopulation was requested by the Review Group but was not submitted. Given the poor clinical outcomes associated with increasing BMI, the omission of the BMI ≥40$^{(+1\ WRC)}$ subpopulation from the Applicant's submission is a significant limitation.

Methods

An individual patient simulation (IPS) model used a lifetime horizon and a cycle length of four weeks for the first two years, and one year thereafter. In the model, baseline patient characteristics and surrogate outcomes are used as inputs for risk equations, which determine the per-cycle risk of experiencing clinical events including T2DM, cardiovascular events, sleep apnoea, non-alcoholic fatty liver disease, knee replacement and death. For each patient, these clinical events are simulated to occur per cycle and are associated with costs, disutilities and changes in risk of future events. A small proportion of patients are also assumed to undergo bariatric surgery each cycle. The key surrogate outcomes determining

clinical events include weight, HbA1c (which determines the proportion of patients experiencing prediabetes reversal), SBP, HDL and total cholesterol. Key efficacy inputs, for the surrogate outcomes, were derived from pre-specified analyses (full licence$^{(Ex\text{-}T2DM)}$) or post-hoc analyses (all other subpopulations) of *SURMOUNT-1*. For the comparison with liraglutide, efficacy inputs were derived from the ITC. Change in weight (%) is the main driver of clinical effectiveness. Data on the risk of death associated with increased BMI and other co-morbidities were obtained from the literature.

After 72 weeks, it is assumed that weight, cholesterol and SBP surrogate endpoints remain constant until treatment discontinuation. This is based on three-year follow up of the *SURMOUNT-1* study, supported by 4.25-year data available for another GLP-1 also indicated for the treatment of overweight and obesity. For patients treated with "diet and exercise" alone, weight is assumed to increase over time in line with natural BMI progression. As a result of these two assumptions, the relative effect of pharmacological treatment is assumed to increase over time, as patients' weight is assumed to remain constant while on treatment. While the evidence for tirzepatide is supportive of maintained efficacy up to the time points analysed, evidence of a longer-term efficacy is lacking. A further limitation of the model is the use of surrogate outcomes to predict clinical events. This is a significant limitation of the available evidence and a major source uncertainty regarding cost-effectiveness.

HRQoL parameters, in the model, included utilities (based on sex, age and BMI, adjusted for co-morbidities), disutilities associated with clinical, co-morbid events and adverse events. The data used to inform HRQoL parameters were sourced from multiple studies, and the risk for some double-counting of disutility due to BMI or clinical events could not be excluded. The model included drug acquisition costs for tirzepatide and liraglutide, and costs for the delivery of a "diet and exercise" intervention in a general practice setting. Healthcare resource use included costs associated with the management of GI-related AEs, annual ongoing management of co-morbidities, clinical events, monitoring, and bariatric surgery. The model assumes that patients discontinue tirzepatide if they experience primary treatment failure, defined as not achieving a ≥ 5% body weight reduction from baseline at six months after titrating to the highest tolerated dose. It is uncertain whether treatment discontinuation in clinical practice will be implemented as modelled by the Applicant.

The Review Group addressed some limitations in the Applicant's cost-effectiveness model by adjusting a number of parameters or assumptions. In the NCPE-adjusted base case, the baseline HbA1c for each BMI subpopulation was adjusted to align with values observed in the *SURMOUNT-1* study. The Review Group used the same risk equations for patients with and without T2DM (in preference to the Applicant's use of different risk equations for the populations). The Applicant's model generated unreliable predictions of OSA which was removed in the NCPE-adjusted base case. The Review Group used a different source of natural BMI progression, based on a study by Iyen *et al.,* (2021) in preference to an older, smaller study by Ara *et al.,* (2012) used by the Applicant.

Results

The cost-effectiveness results arising from the Applicant's and the NCPE-adjusted base-case analyses, in each (sub)population, are presented in Table 1 and Table 2, respectively.

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

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Population: Full licence(Ex-T2DM)					
"Diet and Exercise"	*42,090*	*15.34*			
Tirzepatide 5mg	105,475	16.10	63,385	0.77	82,655
Tirzepatide 10mg	114,340	16.36	72,250	1.03	70,366
Tirzepatide 15mg	115,136	16.42	73,046	1.08	67,593
BMI ≥ 30(+1 WRC)					
"Diet and Exercise"	*34,786*	*14.77*			
Tirzepatide 5mg	96,594	15.67	61,808	0.90	68,472
Tirzepatide 10mg	104,772	15.92	69,986	1.15	61,059
Tirzepatide 15mg	104,010	15.94	69,224	1.17	59,390
BMI ≥ 35(+1 WRC)					
"Diet and Exercise"	*36,957*	*14.63*			
Tirzepatide 5mg	97,632	15.54	60,675	0.91	66,770
Tirzepatide 10mg	105,935	15.80	68,978	1.17	58,767
Tirzepatide 15mg	105,755	15.90	68,798	1.27	54,227
BMI ≥ 35(liraglutide-MAP) b					
"Diet and Exercise"	*40,006*	*14.45*			
Tirzepatide 5mg	98,205	15.42	58,199	0.97	59,946
Tirzepatide 10mg	104,814	15.67	64,809	1.22	53,143
Tirzepatide 15mg	108,403	15.80	68,398	1.35	50,548
BMI ≥ 35(liraglutide-MAP) b					

Liraglutide 3mg	56,805	*14.81*			
Tirzepatide 5mg	95,882	15.28	39,077	0.47	83,824
Tirzepatide 10mg	101,553	15.48	44,748	0.66	67,449
Tirzepatide 15mg	103,522	15.60	46,717	0.79	59,392

[a] Corresponding probabilistic ICER using 1,000 iterations =€83,300/QALY for the Full licence (Ex-T2DM) population for tirzepatide 5mg. Figures in the table are rounded and obtained from a microsimulation model, and so calculations may not be directly replicable
[b] Note that in the BMI ≥ 35(liraglutide-MAP) population the estimates for total cost and total QALYs between the same doses of tirzepatide across treatment comparisons differ as efficacy estimate were derived using different methodology.
[c] All three doses of tirzepatide are provided once weekly, and the 3mg dose of liraglutide is provided once daily, via SC injection. All treatments are provided as an adjunct to "diet and exercise".
[d] Costs and benefits were discounted at an annual discount rate of 4% in line with national HTA guidelines.

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

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Population: Full licence(Ex-T2DM)					
"Diet and Exercise"	27,597	15.868			
Tirzepatide 5mg	93,247	16.480	65,649	0.612	107,350
Tirzepatide 10mg	102,591	16.727	74,994	0.859	87,332
Tirzepatide 15mg	103,414	16.765	75,817	0.897	84,525
BMI ≥ 30(+1 WRC)					
"Diet and Exercise"	20,003	15.266			
Tirzepatide 5mg	84,362	16.035	64,359	0.769	83,743
Tirzepatide 10mg	92,698	16.280	72,694	1.013	71,734
Tirzepatide 15mg	92,184	16.294	70,258	1.027	70,258
BMI ≥ 35(+1 WRC)					
"Diet and Exercise"	21,935	15.147			
Tirzepatide 5mg	86,178	15.892	64,243	0.744	86,291
Tirzepatide 10mg	94,689	16.136	72,754	0.988	73,618
Tirzepatide 15mg	94,601	16.214	72,666	1.067	68,122
BMI ≥ 35(liraglutide-MAP)					
"Diet and Exercise"	22,716	15.03			
Tirzepatide 5mg	86,058	15.79	63,342	0.77	82,711
Tirzepatide 10mg	92,941	16.02	70,225	0.99	70,608
Tirzepatide 15mg	97,008	16.13	74,292	1.10	67,248
BMI ≥ 35(liraglutide-MAP)					
Liraglutide 3mg	42,703	15.27			
Tirzepatide 5mg	83,309	15.66	40,606	0.39	104,544
Tirzepatide 10mg	89,492	15.84	46,789	0.57	82,371
Tirzepatide 15mg	91,966	15.94	49,263	0.67	73,816

[a] Corresponding probabilistic ICER using 1,000 iterations =€104,682/QALY for the Full licence (Ex-T2DM) population for tirzepatide 5mg. Figures in the table are rounded and obtained from a microsimulation model, and so calculations may not be directly replicable
[b] Note that in the BMI ≥ 35(liraglutide-MAP) population the estimates for total cost and total QALYs between the same doses of tirzepatide across treatment comparisons differ as efficacy estimate were derived using different methodology.
[c] All three doses of tirzepatide are provided once weekly, and the 3mg dose of liraglutide is provided once daily, via SC injection. All treatments are provided as an adjunct to "diet and exercise".
[d] Costs and benefits were discounted at an annual discount rate of 4% in line with national HTA guidelines.

Sensitivity analysis

The Review Group conducted additional sensitivity and scenario analysis based on uncertain parameters and model assumptions The rate of natural BMI progression, baseline BMI, baseline HbA1c and mortality were identified as key model drivers. However, the model was highly insensitive to changes in parameters. Therefore, the Review Group has serious concerns regarding the ability of the model to fully explore the impact of potential scenarios. In particular, it was not possible to fully explore variation in the assumption that the relative treatment effect of tirzepatide increases over time, or variation in discontinuation due to treatment failure at different timepoints. A Price-ICER analysis was conducted to estimate the reductions in the price-to-wholesaler (PtW) of tirzepatide (expressed as a total rebate on the PtW) which would be required for tirzepatide 5mg to meet the €45,000/QALY and €20,000/QALY thresholds in the full licence$^{(Ex\text{-}T2DM)}$ population, versus "diet and exercise". Under the NCPE-adjusted base case assumptions, this analysis indicates that a reduction of about 67% and 90.5%, in the price-to-wholesaler of tirzepatide, would be required to meet the €45,000 per QALY and €20,000 per QALY thresholds respectively. The analysis is presented for the tirzepatide 5mg dose for indicative purposes, as the Applicant indicates that this is the most commonly used maintenance dose.

4. Budget impact of tirzepatide

The per-pack price to wholesaler of tirzepatide is listed as follows: 2.5mg dose: €324.37; 5mg dose: €337.22; 7.5mg/10mg/12.5mg/15mg doses: €365.31. The estimated total cost of tirzepatide, per patient per year to the HSE, ranges from €5,526 to €6,214 (including value-added tax [VAT]), depending on the dose. The Applicant included the full licensed population, including patients with and without T2DM. The Applicant submitted a budget-impact model (BIM), estimating the gross and net budget impact associated with tirzepatide reimbursement over the next five years. There is therefore considerable uncertainty associated with budget impact estimates. The Review Group addressed some limitations in the Applicant's BIM by adjusting the prevalence of overweight, obesity and WRC; and the market share of pharmacological therapy in the eligible population, all of which were considered to be underestimated in the Applicant's BIM. Discontinuation rates for tirzepatide and liraglutide were also adjusted to reflect data from the *SURMOUNT-1* trial, data from the HSE's MAP for liraglutide, and the *SCALE Obesity and Prediabetes Trial*.

The Applicant's five-year net drug-budget impact estimates ranged from €858.7 million (including VAT) in the full licence population to €87.9 million (including VAT) in the BMI ≥35$^{(+1\ WRC)}$ subpopulation. The NCPE-adjusted five-year net drug-budget impact estimates ranged from €5.23 billion (including VAT) to €1.44 billion (including VAT) in the full licence population and the BMI ≥ 35$^{(+1\ WRC)}$ subpopulation, respectively. An additional analysis by the NCPE in the BMI ≥40$^{(+1\ WRC)}$ subpopulation, estimated a five-year net drug-budget impact of €1.25 billion (including VAT). Some long-term cost-offsets associated with a reduction in healthcare costs are likely, but the magnitude of these offsets is uncertain.

5. Patient Organisation Submission

A patient organisation submission was received from The Irish Coalition for People Living with Obesity (ICPO).

6. Conclusion

The NCPE recommends that tirzepatide, as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial BMI of: ≥ 30kg/m^2, **or** ≥ 27kg/m^2 to < 30kg/m^2 in the presence of at least one WRC be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

Tirzepatide has demonstrated clinically meaningful benefits in terms of weight-loss and related outcomes. Three-year follow-up results are encouraging, and supportive of a maintenance in treatment effect, though continued efficacy in the long-term is still uncertain. The cost effectiveness of tirzepatide, compared with "diet and exercise" alone, is most pronounced in the subpopulation of patients with the highest BMI. The budget-impact associated with reimbursing tirzepatide for all eligible patients is extremely large, and unprecedented in terms of previously reimbursed pharmacological treatments in Ireland. 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.*