SMC2633

tirzepatide solution for injection in pre-filled pen (Mounjaro®)

Eli Lilly and Company Limited

08 March 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

tirzepatide (Mounjaro®) is accepted for restricted use within NHSScotland.

Indication under review: for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:

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

SMC restriction: in addition to other oral anti-diabetic medicines as an option when glucagon-like peptide-1 (GLP-1) receptor agonists would be considered.

In three phase III studies, tirzepatide demonstrated statistically significant reductions from baseline in HbA1c compared with a GLP-1 receptor agonist and two basal insulins.

SMC cannot recommend the use of tirzepatide as monotherapy when metformin is considered inappropriate due to intolerance or contraindications as the company's submission related only to its use in addition to other medicinal products for the treatment of diabetes.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Tirzepatide is a long-acting dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, and first in its class. The starting dose of tirzepatide is 2.5 mg subcutaneously once weekly. After 4 weeks, the dose should be increased to 5 mg subcutaneously once weekly. If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose. The recommended maintenance doses are 5, 10 and 15 mg subcutaneously once weekly. The maximum dose is 15 mg subcutaneously once weekly.[1]

1.2. Disease background

Type 2 diabetes mellitus (T2DM) is a progressive metabolic condition, characterised by impaired glycaemic control that is associated with significant morbidity and mortality, affecting an increasing number of people in Scotland. If poorly managed, T2DM can increase the risk of a range of potentially chronic, life-changing, or even life-threatening complications. Obesity is an important risk factor for T2DM; higher body mass index (BMI) increases insulin resistance and is associated with poorer glycaemic control.[2, 3, 4]

1.3. Company proposed position

In addition to other oral anti-diabetic medicines as an option when glucagon-like peptide-1 (GLP-1) receptor agonists would be considered.

1.4. Treatment pathway and relevant comparators

Pharmacological treatments form part of the T2DM treatment pathway in Scotland, in conjunction with lifestyle management and consideration of psychosocial factors. The treatment pathway is complex and should be tailored for the individual. The most common first-line treatment option is metformin. Other first-line options include sulphonylureas such as gliclazide in people who are intolerant of, or have contraindications to metformin, and sodium-glucose co-transporter-2 (SGLT-2) inhibitors such as empagliflozin if both metformin and sulphonylureas are not appropriate. The most common dual therapy combination is metformin with an SGLT-2 inhibitor, although other combinations are possible (for example, metformin in combination with GLP-1 receptor agonist). The most common triple therapy combination is metformin, SGLT-2 inhibitor, and GLP-1 receptor agonist. Other treatment options include dipeptidyl peptidase-4 (DPP-4) inhibitors (such as linagliptin and sitagliptin) and the thiazolidinedione, pioglitazone. These broad treatment recommendations were confirmed by clinical experts consulted by SMC. The relevant comparators for this submission are GLP-1 receptor agonists: dulaglutide solution for injection, exenatide solution for injection *(discontinued March 2024)* and prolonged release suspension for injection, liraglutide solution for injection, semaglutide solution for injection and tablets.[5, 6]

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

The key evidence to support the efficacy and safety of tirzepatide for the treatment of T2DM comes from SURPASS-2, SURPASS-3, and SURPASS-4. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies[2, 7, 8, 9]

Criteria	SURPASS-2	SURPASS-3	SURPASS-4
Study design	Randomised, international, open-label, phase III studies.		
Eligible patients	• Age ≥ 18 years • T2DM inadequately controlled with metformin at a dose of at least 1,500 mg per day • Glycated haemoglobin level (HbA1c) 7.0 to 10.5 % • BMI ≥ 25 kg/m² • Stable weight (±5 %) in previous 3 months.	• Age ≥ 18 years • Insulin naive • T2DM inadequately controlled with metformin monotherapy or in combination with an SGLT-2 inhibitor • Glycated haemoglobin level (HbA1c) 7.0 to 10.5 % • BMI ≥ 25 kg/m² • Stable weight (±5 %) in previous 3 months.	• Age ≥ 18 years • T2DM inadequately controlled (glycated haemoglobin 7.5 to 10.5 %) with metformin, sulphonylurea or SGLT-2 inhibitor, alone or in any combination • BMI ≥ 25 kg/m² • Stable weight (±5 %) in the previous 3 months • Increased risk of cardiovascular events
Treatments	• Subcutaneous tirzepatide titrated to 5mg, 10mg or 15mg once weekly • Semaglutide titrated to 1mg once weekly	• Subcutaneous tirzepatide titrated to 5mg, 10mg or 15mg once weekly. Dose de-escalation permitted to 5mg or 10mg. • Insulin degludec titrated to a fasting blood glucose of less than 5.0 mmol/L (<90 mg/dL)).	• Subcutaneous tirzepatide titrated to 5mg, 10mg or 15mg once weekly. Dose de-escalation permitted to 5mg or 10mg. • Insulin glargine titrated weekly to a fasting blood glucose of less than 5.6 mmol/L (<100 mg/dL)).
Randomisation	Patients randomised 1:1:1:1 to receive tirzepatide 5 mg, 10 mg, 15 mg, or semaglutide 1 mg for 40 weeks. Randomisation stratified according to country and baseline haemoglobin level (≤8.5 % or >8.5 %).	Patients randomised 1:1:1:1 to receive tirzepatide 5 mg, 10 mg, 15 mg, or insulin degludec for 52 weeks. Randomisation stratified according to country, baseline HbA1c (≤8.5 % or >8.5 %), and current use of concomitant oral antihyperglycaemic medications.	Patients randomised 1:1:1:3 to receive tirzepatide 5 mg, 10 mg, 15 mg, or insulin glargine for 52 weeks. Randomisation stratified according to country, baseline HbA1c (≤8.5 % or >8.5 %) and baseline SGLT-2 inhibitor use.
Primary outcome	Change in HbA1c from baseline to week 40.	Change in HbA1c from baseline to week 52.	Change in HbA1c from baseline to week 52.
Secondary outcomes	Change in body weight from baseline to week 40 and attainment of glycated haemoglobin level targets < 7.0 % and < 5.7 %.	Change in HbA1c and body weight from baseline, and proportion of patients achieving an HbA1c target < 7.0 % (<53 mmol/mol) at week 52.	Change in body weight from baseline to week 52 and achievement of HbA1c target < 7.0 %.
Statistical analysis	A graphical statistical testing strategy was applied in the studies to control type 1 error rate with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Primary and key secondary outcomes were included in this approach. Other secondary outcomes were descriptive only and not inferential (no p-values reported).		

Tirzepatide 5 mg, 10 mg and 15 mg demonstrated statistically significant reductions from baseline in HbA1c compared with semaglutide 1 mg and basal insulin (insulin degludec and insulin glargine) at week 40 and week 52, respectively. See Table 2.2 for details.

Table 2.2. Key efficacy results from SURPASS-2, -3, and -4[2, 7, 8, 9]

SURPASS-2				
	Tirzepatide 5 mg (n=470)	**Tirzepatide 10 mg (n=469)**	**Tirzepatide 15 mg (n=469)**	**Semaglutide 1 mg (n=468)**
Primary outcome: mean change from baseline in HbA1c (mmol/mol) at week 40				
Treatment-regimen estimand[a]				
Baseline → week 40	67.5 → 45.1	67.2 → 42.5	66.8 → 41.8	66.7 → 46.7
Change from baseline	-22.0	-24.5	-25.2	-20.3
Difference from semaglutide (95 % CI)	-1.6* (-3.0 to -0.3)	-4.2* (-5.6 to -2.8)	-4.9* (-6.3 to -3.5)	-
Efficacy estimand[b]				
Baseline → week 40	67.5 → 44.2	67.3 → 41.1	66.7 → 40.1	66.6 → 46.7
Change from baseline	-22.8	-25.9	-26.9	-20.3
Difference from semaglutide (95 % CI)	-2.5* (-3.9 to -1.1)	-5.6* (-7.0 to -4.1)	-6.6* (-8.0 to -5.1)	-
Percentage of patients with HbA1c <53 mmol/mol				
Treatment-regimen estimand[a]	82 %	86 %	86 %	79 %
Efficacy estimand[b]	86 %	89 %	92 %	81 %
Key secondary outcome: body weight (kg) at week 40				
Treatment-regimen estimand[a]				
Baseline → week 40	92.5 → 86.1	94.8 → 84.4	93.8 → 82.5	93.7 → 88.0
Change from baseline	-7.6	-9.3	-11.2	-5.7
Difference from semaglutide (95 % CI)	-1.9* (-2.8 to -1.0)	-3.6* (-4.5 to -2.7)	-5.5* (-6.4 to -4.6)	-
Efficacy estimand[b]				
Baseline → week 40	92.6 → 86.2	94.9 → 83.7	93.9 → 81.6	93.8 → 87.8
Change from baseline	-7.8	-10.3	-12.4	-6.2
Difference from semaglutide (95 % CI)	-1.7* (-2.6 to -0.7)	-4.1* (-5.0 to -3.2)	-6.2* (-7.1 to -5.3)	-
Percentage of patients with weight loss ≥10 %				
Treatment-regimen estimand[a]	34 %	47 %	57 %	24 %
Efficacy estimand[b]	36 %	53 %	65 %	25 %
Secondary outcome: lipid parameters at week 40				
Triglycerides (mg/dL)				
Baseline → week 40	165.9 → 134.1	167.4 → 125.5	163.6 → 124.4	165.2 → 146.4
Change from baseline	-31.4	-40.0	-41.1	-19.1
Total cholesterol (mg/dL)				
Baseline → week 40	171.5 → 161.1	171.3 → 160.3	168.6 → 159.8	170.9 → 162.3
Change from baseline	-9.4	-10.2	-10.7	-8.2

SURPASS-3				
	Tirzepatide 5 mg (n=358)	**Tirzepatide 10 mg (n=360)**	**Tirzepatide 15 mg (n=358)**	**Insulin degludec (n=359)**
Mean change from baseline in HbA1c (mmol/mol) at week 52				
Efficacy estimand[b]				
Baseline → week 52	65.8 → 44.9	66.0 → 41.9	66.3 → 40.0	65.4 → 51.3
Change from baseline	-21.1	-24.0	-26.0	-14.6
Difference from insulin degludec (95 % CI)	-6.4* (-7.9 to -4.9)	-9.4* (-10.9 to -7.9)	-11.3* (-12.8 to -9.8)	-
Body weight (kg) at week 52				
Efficacy estimand[b]				
Baseline → week 52	94.5 → 87.3	94.3 → 84.2	94.9 → 81.9	94.2 → 97.1
Change from baseline	-7.5	-10.7	-12.9	2.3
Difference from insulin degludec (95 % CI)	-9.8* (-10.8 to -8.8)	-13.0* (-14.0 to -11.9)	-15.2* (-16.2 to -14.2)	-
SURPASS-4				
	Tirzepatide 5 mg (n=328)	**Tirzepatide 10 mg (n=326)**	**Tirzepatide 15 mg (n=337)**	**Insulin glargine (n=998)**
Primary outcome: mean change from baseline in HbA1c (mmol/mol) at week 52				
Efficacy estimand[b]				
Baseline → week 52	69.6 → 45.3	70.5 → 43.1	69.6 → 41.5	69.5 → 54.0
LS mean change from baseline	-24.5	-26.6	-28.2	-15.7
LS mean difference from insulin glargine (95 % CI)	-8.8* (-10.1 to -7.4)	-10.9* (-12.3 to -9.6)	-12.5* (-13.8 to -11.2)	-
Key secondary outcome: body weight (kg) at week 52				
Efficacy estimand[b]				
Baseline → week 52	90.3 → 83.4	90.7 → 81.1	90.0 → 78.9	90.3 → 92.4
Change from baseline	-7.1	-9.5	-11.7	1.9
Difference from insulin glargine (95 % CI)	-9.0* (-9.8 to -8.3)	-11.4* (-12.1 to -10.6)	-13.5* (-14.3 to -12.8)	-

Abbreviations: CI = confidence interval; HbA1c = glycosylated haemoglobin A1c; LS = least squares.
a = the treatment effect between tirzepatide and active comparator, including the effect of any additional antihyperglycemic medication for all patients who underwent randomisation, regardless of premature discontinuation of study treatment and use of rescue medication.
b = the treatment effect among all patients who underwent randomisation, had all the patients continued to receive study treatment without rescue medication.
* statistically significant p-value controlled for type 1 statistical error.

2.2. Health-related quality of life outcomes

In SURPASS-2, Health-Related Quality of Life (HRQoL) was assessed using six questionnaires: Impact of Weight on Quality of Life (IWQOL)-Lite-clinical trials (CT) version, Impact of Weight on Self Perception (IW-SP), Ability to Perform Physical Activities of Daily Living (APPADL), Diabetes Treatment Satisfaction Questionnaire status version (DTSQs), Diabetes Treatment Satisfaction Questionnaire change version (DTSQc) and EQ-5D-5L.[2]

For IWQOL-Lite-CT, there was a greater improvement in physical impact experienced by patients due to their weight, improvements in IWQOL-Lite-CT total scores for the 10 mg and 15 mg treatment groups only (this means an improvement in overall HRQoL and functioning associated with weight) and psychosocial scores for the 15 mg treatment group only (this means an improvement in the emotional and social impact experienced by patients due to their weight)

versus semaglutide. There was an improvement in IW-SP for the tirzepatide 15 mg group versus semaglutide, indicating better self perception. In addition, there was an improvement in APPADL score for the tirzepatide 15 mg group at 40 weeks, indicating better self reported ability to perform physical activities of daily living. There were no observed differences between tirzepatide and semaglutide for treatment satisfaction (DTSQs and DTSQc) or for EQ-5D-5L Health State Index scores (UK) or EQ VAS scores from baseline to week 40.[2]

In SURPASS-3 and SURPASS-4, HRQoL was assessed using five questionnaires: IW-SP, APPADL, DTSQs, DTSQc and EQ-5D-5L.[2]

In SURPASS-3, there were improvements in all three tirzepatide treatment groups (baseline to week 52) in IW-SP, APPADL, DTSQc total scores and EQ VAS scores versus insulin degludec. There were no observed differences between tirzepatide and insulin degludec in EQ-5D-5L scores.[2]

In SURPASS-4, there were improvements in all three tirzepatide treatment groups (baseline to week 52) in IW-SP, APPADL, DTSQc total scores, EQ VAS scores and EQ-5D-5L Index scores versus insulin glargine.[2]

2.3. Supportive studies

SURPASS-1 and SURPASS-5 were randomised, double-blind, placebo-controlled phase III studies in patients with T2DM. Patients received tirzepatide 5 mg, 10 mg, 15 mg, or placebo with either no background medications (SURPASS-1) or as an add-on to insulin glargine with or without metformin (SURPASS-5). Tirzepatide was superior to placebo in both studies in reducing HbA1c from baseline to week 40.[2]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing tirzepatide with all GLP-1 receptor agonists available in NHSScotland, the submitting company presented an indirect treatment comparison. This has been used to inform the economic case.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Bayesian NMA.
Population	Adult patients (≥18 years of age) with T2DM treated with one add-on oral antidiabetic drug (with >90 % on metformin) or one to two add-on oral antidiabetic drugs (with >50 % on metformin).
Comparators	Liraglutide, semaglutide (oral and subcutaneous), dulaglutide, exenatide, insulin degludec, insulin glargine, sitagliptin, glimepiride.
Studies included	45 studies included in the main analysis.
Outcomes	Efficacy outcomes included change from baseline in HbA1c, weight, LDL, HDL, BMI and eGFR. Safety outcomes included change from baseline in systolic blood pressure and proportion of patients experiencing nausea.
Results	Tirzepatide had superior efficacy to the comparators in terms of change from baseline in HbA1c, except for tirzepatide 5 mg versus semaglutide (1 mg), and dulaglutide (3 mg and 4.5 mg). For change from baseline in body weight, tirzepatide was superior to all comparators.
Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein; HDL = high-density lipoprotein; NMA = network meta-analysis.	

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

In the SURPASS-2 study, any adverse event (AE) was reported by 64 % (299/470) of patients in the tirzepatide 5 mg group, 69 % (322/469) in the tirzepatide 10 mg group, 69 % (324/470) in the tirzepatide 15 mg group and 64 % (301/469) in the semaglutide 1 mg group. In the tirzepatide 5 mg, 10 mg, 15 mg and semaglutide 1 mg groups respectively, patients reporting a serious AE were 7.0 %, 5.3 %, 5.7 % and 2.8 %; patients discontinuing therapy due to an AE was 6.0 %, 8.5 %, 8.5 % and 4.1 %.[7]

The most frequently reported AEs of any grade with an incidence ≥5 % in the tirzepatide 5 mg, 10 mg, 15 mg and semaglutide 1 mg groups were: nausea (17 %, 19 %, 22 % versus 18 %), diarrhoea (13 %, 16 %, 14 % versus 12 %), vomiting (5.7 %, 8.5 %, 9.8 % versus 8.3 %), dyspepsia (7.2 %, 6.2 %, 9.1 % versus 6.6 %), decreased appetite (7.4 %, 7.2 %, 8.9 % versus 5.3 %), constipation (6.8 %, 4.5 %, 4.5 % versus 5.8 %) and abdominal pain (3.0 %, 4.5 %, 5.1 % versus 5.1 %).[7]

Overall, the safety profile of tirzepatide is similar to GLP-1 receptor agonists. Hypoglycaemia events were low, and mainly in combination with other glucose-lowering treatments. Discontinuation due to gastrointestinal AEs was <5 %.[2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Three large, well-conducted, phase III studies versus active comparators, one of which compared tirzepatide with a relevant active comparator, semaglutide.
- Tirzepatide demonstrated statistically significant and clinically meaningful (excluding 5 mg tirzepatide) reductions from baseline in HbA1c compared with semaglutide 1 mg once weekly and basal insulin (insulin degludec and insulin glargine) at week 40 and week 52, respectively. Results were consistent between the treatment-regimen estimand and the efficacy estimand, and treatment effect maintenance of tirzepatide was demonstrated up to 104 weeks. Significantly greater proportions of patients achieved HbA1c targets of <53 mmol/mol (except tirzepatide 5 mg versus semaglutide in the treatment-regimen estimand), ≤48 mmol/mol (except tirzepatide 5 mg versus semaglutide in the treatment-regimen estimand), and <39 mmol/mol (normoglycaemia) compared with active comparators (some of these comparisons were not adjusted for type 1 error).[2]
- Tirzepatide demonstrated statistically significant and clinically meaningful reductions in body weight compared with semaglutide 1 mg and basal insulin. [2, 7]
- Lipid parameters and other cardiometabolic measures such as waist circumference and blood pressure also improved from baseline with tirzepatide.[2]
- Tirzepatide led to greater improvement in some HRQoL scores compared with semaglutide 1mg once weekly and basal insulin, indicating an increase in weight loss-related quality of life and overall quality of life. Although SURPASS-2, -3, and -4 were open-label which may have

biased results, HRQoL results from the double-blind, placebo-controlled studies (SURPASS-1 and -5) were supportive.[2]

4.2. Key uncertainties

- There are limited longer-term data, which is an important consideration for a chronic condition like T2DM. Although there was extended follow-up of a select group of patients from SURPASS-4 that suggested maintenance of improvements in glycaemic control and weight loss at week 104, there are no available data beyond week 104.[2]
- There are limited data for tirzepatide in combination with two other anti-diabetic medications. In SURPASS-2, patients taking two anti-diabetic medications prior to randomisation were excluded, meaning that there is no direct evidence for tirzepatide as part of a triple therapy regimen versus semaglutide (or any other GLP-1 receptor agonist) as part of a triple therapy regimen. In SURPASS-3, 32% (458/1,437) of the study population were receiving metformin plus SGLT2 inhibitor prior to randomisation (no other combinations of anti-diabetic medications were permitted). In SURPASS-4, 53% and 11% of the study population were receiving two or three anti-diabetic medications prior to randomisation, respectively. It is uncertain if the number of prior anti-diabetic medications impacts the relative treatment effect of tirzepatide.[2, 7, 8, 9]
- There are limited data to support use of tirzepatide in patients with BMI <25 kg/m^2. SURPASS-1 and SURPASS-5 recruited patients with BMI ≥ 23 kg/m^2, however the studies most relevant to this submission (SURPASS-2, -3, -4) only recruited patients with BMI ≥25 kg/m^2. This is of particular note given the weight loss effects of tirzepatide. The number of patients who had BMI ≤18.5 kg/m^2 at the end of SURPASS-1 and 5 was low, which is reassuring. However, some patients may experience weight loss as an undesired effect.[2]
- There is a lack of direct evidence of tirzepatide versus some of the relevant comparators. The indirect treatment comparison had the following limitations:
    - Substantial heterogeneity in baseline characteristics and in assessment timepoints (40 weeks for tirzepatide versus 22 to 30 weeks for comparators). A waning effect has been observed with GLP-1 receptor agonists, therefore this adds uncertainty.
    - Most studies included only had background treatment of metformin. Sparse evidence of relative efficacy of GLP-1 receptor agonists versus tirzepatide as part of triple therapy regimens.
    - Some inconsistencies between direct and indirect evidence suggesting uncertainty in the results.
    - Sparse network data informed some comparisons particularly for oral semaglutide (only two studies).
    - Highly selective safety outcome measures evaluated and HRQoL not evaluated.

  Due to these limitations, the results of the NMA are uncertain. However, direct evidence versus semaglutide 1 mg is available.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that tirzepatide fills an unmet need in this therapeutic area and is a therapeutic advancement, due its effects on lowering HbA1c and reducing body weight. Most clinical experts would consider using tirzepatide in the third line of treatment, as an alternative to GLP-1 receptor agonists.

4.4. Service implications

Like most GLP-1 receptor agonists, tirzepatide is an injectable treatment. As a new class of medicine, primary care units may be more hesitant to initiate tirzepatide, and secondary care units may have to initiate tirzepatide, at least initially. Services will have to decide how best to manage the initiation and ongoing management of patients taking tirzepatide.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Diabetes Scotland, which is a Scottish charitable incorporated organisation.

- Diabetes Scotland has not received any pharmaceutical company funding in the past two years.

- Living with type 2 diabetes can lead to increased risk of chronic and acute complications and can impact emotional, psychological and mental health leading to people feeling depressed, stressed or anxious. The impact of a person living with diabetes can affect everyone around them. A diagnosis of diabetes will change the life of, not only the person diagnosed, but also their family and those who provide care.

- There are a wide range of treatments available for type 2 diabetes on the NHS. People should develop an individualised plan in conjunction with their healthcare professional to meet their needs and preferences. Tirzepatide provides a variation to existing treatment options as it is a dual GLP-1 and GIP receptor agonist. This will increase the options available to prescribers for treatment.

- The patient group supports the introduction of tirzepatide as a treatment option for type 2 diabetes. As an injectable treatment some patients may need assistance from a family member or carer to help administer the injection.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as presented in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost utility analysis.
Time horizon	50 years.
Population	The population used in the economic model considered tirzepatide as part of a dual or triple therapy in patients with T2DM with inadequate glycaemic control on one or more oral anti-diabetic drugs, as an option whenever GLP-1 receptor agonists would be considered.
Comparators	Dulaglutide solution for injection (1.5 mg, 3 mg, and 4.5 mg), semaglutide solution for injection (0.5 mg and 1.0 mg) or tablets (7 mg and 14 mg), and liraglutide solution for injection (1.2 mg and 1.8 mg).
Model description	A patient level simulation was used, the PRIME T2D Model.[13] Simulated patients were generated with defined demographics, baseline risk factors, and complication history. Initial treatments were tirzepatide or a comparator. There were several risk factors progressing over time in the model, including HbA1c, systolic blood pressure (SBP), LDL cholesterol, HDL cholesterol, andBMI. Treatment effects were applied to these risk factors (as a change from baseline) in the first year, with progression then generally following United Kingdom Prospective Diabetes Study Outcomes Model 2 (UKPDS OM2) risk factor progressions.[14]. An exception to this was SBP and BMI that remained constant while on treatment. Patients intensified treatment when HbA1c levels exceeded 58 mmol/mol, at which point patients received basal insulin and stopped their initial treatment. Upon intensification, risk factors returned to baseline (except for HbA1c which decreased) [23] and continued to follow UKPDS OM2 risk factor progressions long term. Macrovascular and microvascular complications were included in the simulation, defined by complication risk equations from UKPDS OM2 and the Building, Relating, Assessing, and Validating Outcomes (BRAVO) study.[15, 16] The complications were impacted by demographics, risk factors and complication history. For selected risk complications, where multiple models estimated risk simultaneously, model averaging was used, which weighted the included complication risk equations according to how close the simulated patient's characteristics were to the study population that derived the risk equation. In general, lower risk patients had a greater weighting to UKPDS OM2 equations and higher risk to BRAVO equations. Adverse events for hypoglycaemia (post-intensification) and nausea were included. Mortality was modelled using separate risk equations to evaluate mortality associated with diabetes-related complications (with or without prior history) and cause-subtracted life tables to evaluate the risk of death from other causes.
Clinical data	Baseline characteristics were mostly from The Health Improvement Network (THIN) second intensification cohort with some from SURPASS-2.[7, 10] Treatment effects were sourced from the NMA. These were applied as change from baseline in the following risk factors for each treatment in year 1: HbA1c, SBP, BMI, HDL, and LDL. Adverse events for nausea were from the NMA, with hypoglycaemia (post-intensification) from literature.[17]
Extrapolation	UKPDS OM2 risk factor progressions were used to estimate the long-term progression of risk factors.[14] UKPDS OM2 and BRAVO risk complication models were used to estimate risk complications.[15, 16] Following intensification to basal insulin therapy mean annual hypoglycaemic event rates were 0.32 and 3.84 events per patient year, for severe and non-severe hypoglycaemia, respectively.[17]
Quality of life	The base utility value (T2D with no complications) was derived using an age adjusted regression. [20] Complication and adverse event dis-utilities were applied to this base utility value using an additive method. There was a 0.0061 dis-utility applied to the impact of BMI for each BMI unit over 25.[17, 18] An administration utility benefit of 0.004 was included for oral semaglutide in the model.
Costs and resource use	The model included treatment acquisition (including background metformin), administration, monitoring, adverse events, complications and subsequent basal insulin costs.
PAS	There are no PAS discounts in place for tirzepatide or comparators.

6.2. Results

The base case results are presented below. In general, the incremental QALY gain for tirzepatide was driven by the modest reductions in cumulative incidence of diabetes-related complications. These were likely driven by the greater reductions in the HbA1c and BMI risk factors in the tirzepatide arm. A modest difference in life expectancy was also recorded. Most of the incremental cost for tirzepatide was from treatment acquisition, with costs offset by reductions in diabetes-related complication costs.

Table 6.2.1: Summary of base case results for tirzepatide 5 mg versus comparators.

	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£ per QALY gained)
Tirzepatide 5 mg	8.715	--	--	--
Dulaglutide 1.5 mg	8.615	705	0.100	7,073
Dulaglutide 3.0 mg	8.636	644	0.079	8,182
Dulaglutide 4.5 mg	8.657	628	0.058	10,891
Semaglutide 0.5 mg	8.634	682	0.081	8,401
Semaglutide 1.0 mg	8.673	708	0.042	16,817
Oral semaglutide 7 mg	8.595	742	0.120	6,202
Oral semaglutide 14 mg	8.642	719	0.073	9,873
Liraglutide 1.2 mg	8.581	672	0.134	5,021
Liraglutide 1.8 mg	8.600	-409	0.115	Dominant
Abbreviations: ICER = Incremental cost-effectiveness ratio; Inc = Incremental; QALY = quality-adjusted life year; mg = milligram. Dominant: The assessed medicine was estimated as having lower costs and greater health outcomes than the comparator.				

Table 6.2.2: Summary of base case results for tirzepatide 10 mg versus comparators.

	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£ per QALY gained)
Tirzepatide 10 mg	8.768	--	--	--
Dulaglutide 1.5 mg	8.615	1,389	0.153	9,091
Dulaglutide 3.0 mg	8.636	1,329	0.132	10,073
Dulaglutide 4.5 mg	8.657	1,312	0.111	11,843
Semaglutide 0.5 mg	8.634	1,367	0.134	10,171
Semaglutide 1.0 mg	8.673	1,393	0.095	14,616
Oral semaglutide 7 mg	8.595	1,427	0.173	8,254
Oral semaglutide 14 mg	8.642	1,403	0.126	11,140
Liraglutide 1.2 mg	8.581	1,356	0.187	7,254
Liraglutide 1.8 mg	8.600	276	0.168	1,642

Abbreviations: ICER = Incremental cost-effectiveness ratio; Inc = Incremental; QALY = quality-adjusted life year; mg = milligram

Table 6.2.3: Summary of base case results for tirzepatide 15 mg versus comparators.

	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£ per QALY gained)
Tirzepatide 15 mg	8.808	--	--	--
Dulaglutide 1.5 mg	8.615	2,047	0.192	10,642
Dulaglutide 3.0 mg	8.636	1,987	0.171	11,586
Dulaglutide 4.5 mg	8.657	1,970	0.150	13,104
Semaglutide 0.5 mg	8.634	2,025	0.174	11,641
Semaglutide 1.0 mg	8.673	2,051	0.135	15,209
Oral semaglutide 7 mg	8.595	2,085	0.212	9,815
Oral semaglutide 14 mg	8.642	2,061	0.166	12,453
Liraglutide 1.2 mg	8.581	2,014	0.227	8,893
Liraglutide 1.8 mg	8.600	934	0.208	4,498

Abbreviations: ICER = Incremental cost-effectiveness ratio; Inc = Incremental; QALY= quality-adjusted life year; mg = milligram

Table 6.2: Summary of base case results for tirzepatide 5mg, 10mg, and 15 mg versus comparators.

Comparator	Tirzepatide 5 mg versus comparator ICER (£ per QALY gained)	Tirzepatide 10 mg versus comparator ICER (£ per QALY gained)	Tirzepatide 15 mg versus comparator ICER (£ per QALY gained)
Dulaglutide 1.5 mg	7,073	9,091	10,642
Dulaglutide 3.0 mg	8,182	10,073	11,586
Dulaglutide 4.5 mg	10,891	11,843	13,104
Semaglutide 0.5 mg	8,401	10,171	11,641
Semaglutide 1.0 mg	16,817	14,616	15,209
Oral semaglutide 7 mg	6,202	8,254	9,815
Oral semaglutide 14 mg	9,873	11,140	12,453
Liraglutide 1.2 mg	5,021	7,254	8,893
Liraglutide 1.8 mg	Dominant	1,642	4,498

Abbreviations: ICER = Incremental cost-effectiveness ratio; Inc = Incremental; QALY= quality-adjusted life year; mg = milligram. Dominant: The assessed medicine was estimated as having lower costs and greater health outcomes than the comparator.

6.3. Sensitivity analyses

The submitting company provided scenario analysis in the comparison of tirzepatide with semaglutide, as the company noted semaglutide was the most cost-effective comparator in the base case. The submitting company noted the rationale for this approach was that key drivers of outcomes in the modelling analysis would be similar across all comparators but were most likely to affect the cost-effectiveness of tirzepatide in comparison with semaglutide. The most impactful scenarios were those that explored HbA1c and BMI clinical risk factors, intensification criteria, and weight/BMI utilities.

Table 6.3: Key scenario analyses. Tirzepatide 10 mg versus semaglutide 1.0 mg.

			Tirzepatide 10 mg versus semaglutide 1.0 mg		
	Scenario	**Base case**	**Inc. Costs (£)**	**Inc. QALYs**	**ICER (£ per QALY gained)**
		-	**1,393**	**0.095**	**14,616**
1	No HbA1c difference	HbA1c difference	1,078	0.035	30,908
2	No BMI difference	BMI difference	1,512	0.060	25,299
3	Only HbA1c difference between treatments	HbA1c, BMI, HDL, LDL, SBP differences.	1,493	0.052	28,659
4	Only BMI difference between treatments	HbA1c, BMI, HDL, LDL, SBP differences.	1,133	0.027	42,568
5	Only HbA1c and BMI differences between treatments	HbA1c, BMI, HDL, LDL, SBP differences.	1,409	0.076	18,540
6	Intensification to insulin after 3 years	Intensification at 58 mmol/mol HbA1c threshold	971	0.072	13,400
7	Intensification to insulin after 5 years	Intensification at 58 mmol/mol HbA1c threshold	1,716	0.091	18,779
8	Intensification at 80 mmol/mol HbA1c threshold	Intensification at 58 mmol/mol HbA1c threshold	5,244	0.201	26,133
9	Second intensification to basal-bolus therapy	One intensification step	1,302	0.103	12,616
10	No weight/BMI utilities	BMI utilities	1,393	0.058	22,449
11	Multiplicative approach to combining utilities	Additive approach to combining utilities	1,393	0.076	18,337
12	CORE Model	PRIME T2D Model	1,836	0.096	19,204

Abbreviations: BMI = body mass index; HbA1c = Glycated Haemoglobin; HDL = High Density Lipoprotein; ICER = Incremental cost-effectiveness ratio; Inc = Incremental; LDL = Low Density Lipoprotein; SBP = Systolic Blood Pressure

6.4. Key strengths

- The PRIME T2D Model is a published model with validation analyses demonstrating consistent long-term projections with a number of long-term studies, including cardiovascular outcomes trials.[13]
- The systematic literature review provided complication and adverse event utilities primarily derived using the EQ-5D instrument from UK-specific studies.

- A comprehensive selection of variables was considered in sensitivity analysis.

6.5. Key uncertainties

- There were several limitations identified in the direct evidence and NMA that increased uncertainty in the derived treatment effects and economic results. However, sensitivity analysis conducted in the NMA showed results consistent with the main analysis. The applied treatment effects were also explored in deterministic sensitivity analysis with limited ICER variation observed. Furthermore, although a set of conservative scenarios exploring no differences in the clinical risk factors generated larger variation in the ICER up to £42,568 (scenarios 1 to 5), these were unlikely to be appropriate given the supportive key efficacy results from SURPAS-2, -3 and, -4. In summary, although fully assessing the impact of the clinical limitations was challenging, only the most conservative scenarios increased the ICER substantially.
- In the model intensification to basal insulin occurs when HbA1c levels exceed 58 mmol/mol. This was noted by the submitting company as aligning to a previous SMC appraisal (Liraglutide SMC1044/15) and the economic modelling undertaken for NICE NG28.[17] There may be some variation in practice for intensifying to basal insulin therapy, with 86 mmol/mol highlighted in guidance from the Primary Care Diabetes Society (PCDS) and Association of British Clinical Diabetologists (ABCD).[19] A scenario considering a higher threshold of 80 mmol/mol for intensification demonstrated an increase in the ICER to £26,133 (scenario 8). However, the use of the 58mmol/mol threshold in the base case was likely reasonable and eased concern of this ICER variation.
- The scenario analysis was primarily conducted in one comparison, tirzepatide 10 mg versus semaglutide 1.0mg, as semaglutide was the most cost-effective of the comparators examined in the base case. The submitting company highlighted the rationale for this approach was that key drivers of outcomes in the modelling analysis would be similar across all comparators but were most likely to affect the cost-effectiveness of tirzepatide in comparison with semaglutide. Although this may be reasonable, without a full reporting of scenario analysis results versus all comparators this cannot be verified. Scenario analysis results for the least cost-effective comparison, tirzepatide 5 mg versus semaglutide 1.0 mg, were not available.
- Complications and adverse event dis-utilities were applied using an additive approach. There is not a consensus on whether to use an additive or multiplicative approach, but practical advice notes the multiplicative approach should be used.[22] Using this approach increased the ICER to £18,337 (Scenario 11).
- There were limitations in the justification for the use of the PRIME T2D model compared to the CORE model used in previous submissions to SMC for dulaglutide, semaglutide, and liraglutide (SMC 1110/15, SMC 2090, and SMC 1044/15). To alleviate concerns over model choice, the company provided ICER results using the CORE model, with these slightly higher than those generated from the PRIME T2D model (Scenario 12).
- The population in the economic case of the submitting company considered tirzepatide as a dual or triple therapy. However, the economic case was viewed as generalisable in the wider positioning of, in addition to other oral anti-diabetic medicines as an option when glucagon-like peptide-1 (GLP-1) receptor agonists would be considered.

7. Conclusion

After considering all the available evidence, the Committee accepted tirzepatide for use in NHSScotland.

8. Guidelines and Protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published "Management of diabetes: a national clinical guideline (SIGN 116)" in March 2010 and "Pharmacological management of glycaemic control in people with type 2 diabetes: a national clinical guideline (SIGN 154)" in November 2017. The SIGN website notes that some recommendations may be out of date.[5, 6]

The National Institute for Health and Care Excellence (NICE) guideline number 28: "Type 2 diabetes in adults: management" was published in December 2015 and updated in June 2022.[10]

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published a consensus statement on the management of hyperglycaemia in type 2 diabetes in adults in 2006, which was updated in 2019 and 2022.[11]

9. Additional Information

9.1. Product availability date

12 February 2024.

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
tirzepatide	**Initially 2.5 mg once weekly for 4 weeks, then increased to 5 mg once weekly for at least 4 weeks, then increased if necessary up to 15 mg once weekly, dose to be increased in steps of 2.5 mg at intervals of at least 4 weeks.**	**5 mg once weekly (maintenance) = £1,196** **10 mg once weekly (maintenance) = £1,391** **15 mg once weekly (maintenance) = £1,586**

Costs from MIMS online on 21 February 2024.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget impact.

*Other data were also assessed but remain confidential.**

References

1. Eli Lilly and Company Limited. Tirzepatide solution for injection in pre-filled pen. Summary of product characteristics. Electronic Medicines Compendium. www.medicines.org.uk Last updated 29 September 2023.

2. European Medicines Agency (EMA). European Public Assessment Report. Tirzepatide (Mounjaro). EMA/791310/2022. 21 July 2022. www.ema.europa.eu

3. DeFronzo RA, Ferrannini E, Groop L, Henry RR, Herman WH, Holst JJ, et al. Type 2 diabetes mellitus. Nat Rev Dis Primers. 2015 Jul 23;1:15019. doi: 10.1038/nrdp.2015.19. PMID: 27189025.

4. Diabetes UK. Number of people with type 2 diabetes in Scotland increases by 40% in a decade. 2020. Available at: https://www.diabetes.org.uk/in_your_area/scotland/news/increase-diabetes

5. Scottish Intercollegiate Guidelines Network (SIGN). SIGN 116. Management of diabetes. A national clinical guideline. March 2010 (updated November 2017). Available at: www.sign.ac.uk (Accessed 08 January 2024).

6. Scottish Intercollegiate Guidelines Network (SIGN). SIGN 154. Pharmacological management of glycaemic control in people with type 2 diabetes. November 2017. Available at: www.sign.ac.uk (Accessed 08 January 2024).

7. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. New England Journal of Medicine. 2021 Aug 5;385(6):503-15.

8. Ludvik B, Giorgino F, Jódar E, Frias JP, Landó LF, Brown K, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. The Lancet. 2021 Aug 14;398(10300):583-98.

9. Del Prato S, Kahn SE, Pavo I, Weerakkody GJ, Yang Z, Doupis J, et al. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. The Lancet. 2021 Nov 13;398(10313):1811-24.

10. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: management NICE guideline [NG28]. Published: 02 December 2015 Last updated: 29 June 2022. Available at: https://www.nice.org.uk/guidance/ng28 (Accessed 08 January 2024).

11. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2022 Nov 1;45(11):2753-2786. doi: 10.2337/dci22-0034. PMID: 36148880; PMCID: PMC10008140.

12. Novo Nordisk Limited. Semaglutide solution for injection in pre-filled pen. Summary of product characteristics. Electronic Medicines Compendium. www.medicines.org.uk Last updated 15 August 2023.

13. Pollock RF, Norrbacka K, Boye KS, et al. The PRIME Type 2 Diabetes Model: a novel, patient-level model for estimating long-term clinical and cost outcomes in patients with type 2 diabetes mellitus. J Med Econ 2022;25:393-402

14. Leal J, Alva M, Gregory V, et al. Estimating risk factor progression equations for the UKPDS Outcomes Model 2 (UKPDS 90). Diabet Med 2021;38:e14656

15. Hayes AJ, Leal J, Gray AM, et al. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia 2013;56:1925-33.

16. Shao H, Fonseca V, Stoecker C, et al. Novel Risk Engine for Diabetes Progression and Mortality in USA: Building, Relating, Assessing, and Validating Outcomes (BRAVO). Pharmacoeconomics 2018;36:1125-113.

17. National Institute of Health and Care Excellence (NICE). NG28. Type 2 diabetes in adults: management. Health Economic Model Report. Available at NG28 Health economic model report (nice.org.uk) Accessed 20 December 2023).

18. Bagust A, Beale S. Modelling EuroQol health-related utility values for diabetic complications from CODE-2 data. Health Econ 2005;14:217–30.

19. Beba K., Cahill K. , Dhatariya K., Diggle J., Hambling C., Milne N., et al. Glucagon-Like-Peptide 1 Receptor Agonist National Shortage Guidance from the Primary Care Diabetes Society (PCDS) and Association of British Clinical Diabetologists (ABCD). 2023. Available at: https://diabetesonthenet.com/wp-content/uploads/PCDS_ABCD-GLP-1-RA-shortage_20230628.pdf (Accessed 10 January 2024).

20. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value in Health 2010;13:509-518.

21. Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). Med Decis Making 2002;22:340–9.

22. Ara, R., Wailoo, A.J. NICE DSU Technical Support Document 12: The use of health state utility values in decision models. 2011. Available from http://www.nicedsu.org.uk.

23. Willis M, Asseburg C, Nilsson A, et al. Multivariate Prediction Equations for HbA(1c) Lowering, Weight Change, and Hypoglycemic Events Associated with Insulin Rescue Medication in Type 2 Diabetes Mellitus: Informing Economic Modeling. Value Health 2017;20:357-371.

This assessment is based on data submitted by the applicant company up to and including 16 February 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are

therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.