Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2653

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

Eli Lilly and Company Limited

10 May 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic 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 weight management, including weight loss and weight maintenance, as an adjunct to a reduced-calorie diet and increased physical activity in adults with an initial Body Mass Index (BMI) of ≥30 kg/m^2 (obesity) or ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus).

SMC restriction: for use in adults with BMI ≥30 kg/m^2* and at least one weight-related comorbidity.
**a lower BMI cut-off may be more appropriate for members of minority ethnic groups known to be at equivalent risk of the consequences of obesity at a lower BMI than the white population.*

In phase III studies, tirzepatide, as an adjunct to diet and exercise, was associated with significant reduction in body weight compared with placebo in patients with BMI ≥30 kg/m^2 (obesity) or ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition.

Vice Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Tirzepatide is an agonist at glucose-dependent insulinotropic polypeptide (GIP) receptors, with activity similar to native GIP, and it is an agonist at glucagon-like peptide-1 (GLP-1) receptors, with activity lower than native GLP-1 hormone. Tirzepatide lowers body weight and body fat mass by decreasing food intake via regulation of appetite (increasing feelings of fullness and reducing food cravings) and modulation of fat utilisation. Tirzepatide is given by once weekly subcutaneous (SC) injection with dose titrated monthly from a starting dose of 2.5 mg, in 2.5 mg increments to a maintenance of 5 mg, 10mg or 15 mg.[1]

1.2. Disease background

In the 2022 Scottish Health Survey, 67% of adults were overweight with Body Mass Index (BMI) ≥25 kg/m², including 28% of men and 30% of women who were living with obesity (BMI ≥30 kg/m²). In Scotland, obesity is the second-biggest preventable cause of cancer (after smoking), and it is associated with over 2,000 cases of cancer a year. Being overweight is the most significant risk factor for developing type 2 diabetes, and it can increase risks of other conditions including cardiovascular disease (CVD) and hypertension; stroke; sleep apnoea; osteoarthritis and back pain; liver disease; and reproductive complications. It can impact mental health and has been associated with anxiety and depression.[2, 3]

1.3. Company proposed position

The submitting company has requested that tirzepatide is restricted for use in adults with BMI ≥30 kg/m^2 and at least one weight-related comorbidity.

1.4. Treatment pathway and relevant comparators

Management of weight can involve lifestyle and behavioural interventions; changes to physical activity and diet; pharmacological therapies and surgical interventions.[4] The GLP-1 agonists, liraglutide and semaglutide, are both licensed as an adjunct to reduced-calorie diet and increased physical activity for weight management in adults with initial BMI ≥30 kg/m² (obese) or ≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity.[5, 6] In May 2022, SMC published advice (SMC2455) that liraglutide (Saxenda®) is accepted for restricted use in those with BMI ≥35 kg/m² with non-diabetic hyperglycaemia (prediabetes) at high risk of type 2 diabetes and high risk of CVD. In October 2023, SMC published advice (SMC2497) that semaglutide (Wegovy®) is accepted for restricted use in those with BMI ≥30 kg/m^2 and at least one weight-related comorbidity. For both medicines, SMC advice specifies that patients should be treated in specialist weight management services.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Clinical evidence for weight loss with tirzepatide is from the SURMOUNT-1 and -3 studies in patients without type 2 diabetes and the SURMOUNT-2 study in patients with type 2 diabetes, as detailed in Table 2.1. A randomised withdrawal study, SURMOUNT-4, provided evidence on maintenance of effect.[7-10]

Table 2.1. Overview of relevant studies.[7-9]

Criteria	SURMOUNT-1	SURMOUNT-3	SURMOUNT-2
Study design	Double-blind, phase III	Double-blind phase III	Double-blind phase III
Eligible patients	≥18 years old; BMI ≥30 kg/m^2 or ≥27 kg/m^2 plus ≥1 co-morbidity (excluding diabetes). SURMOUNT-3: ≥5% weight loss after 12-week intensive lifestyle change		18 years old; BMI ≥27 kg/m^2 and type 2 diabetes. HbA_{1c} 7 to 10%
Treatments	Once weekly subcutaneous injection for 72 weeks		
	Tirzepatide 5 mg, 10 mg or 15 mg or placebo	Tirzepatide MTD (10 mg or 15 mg) or placebo	Tirzepatide 10 mg or 15 mg or placebo
Randomisation and stratification	Randomised equally across groups. Stratified by country, sex and additional criteria:		
	presence of prediabetes	weight loss after lifestyle change (<10% or ≥10%)	anti-hyperglycaemia drugs' weight effects
Co-primary outcomes	At week 72, (a) percent change in body weight; (b) body weight reduction ≥5%		
Secondary outcomes	Many secondary outcomes were included in complex hierarchies.		
Statistical analysis	Efficacy analysis set = data from mITT population (randomised and treated) during the treatment period, excluding data after discontinuation of study drug. Efficacy estimand = treatment effect had they remained on treatment to week 72, with missing values imputed using predicted values from MMRM.		

BMI = body mass index; HbA_{1c} = glycosylated haemoglobin (measured after ≥3 months on stable therapy); mITT = modified intention-to-treat; MMRM = mixed model repeated measures; MTD = maximum tolerated dose.

In the SURMOUNT-1, -2 and -3 studies, improvement in the co-primary outcomes were statistically significant for all doses of tirzepatide compared with placebo. There were benefits in blood pressure, lipids, waist circumference and glycosylated haemoglobin (HbA_{1c}), with selected results in Table 2.2.[7-9]

Table 2.2: Results of SURMOUNT-1, -2 and -3 studies at week 72.[1, 7-9]

SURMOUNT-1				SURMOUNT-3		SURMOUNT-2		
T 5mg	**T 10mg**	**T 15mg**	**PBO**	**T MTD**	**PBO**	**T 10mg**	**T 15mg**	**PBO**
n=630	n=636	n=630	n=643	n=287	n=292	n=312	n=311	n=315
Mean percent body weight change, % (co-primary outcome)								
-16*	-21*	-22*	-2.4	-21*	3.3	-13*	-16*	-3.3
Difference versus placebo in mean percent body weight change, %								
-14*	-19*	-20*		-24*		-10*	-12*	
Proportion of patients with body weight reduction ≥5% (co-primary outcome)								
89%*	96%*	96%*	28%	94%*	11%	82%*	86%*	31%
Mean change in systolic blood pressure (mmHg)								
-7.4	-8.8	-8.0	-1.3	-5.1	4.1	-6.1	-8.2	-1.0
Mean percent change in total cholesterol								
-5.0	-5.7	-7.5	-1.2	-3.0	5.2	-3.0	-2.2	2.1
Mean percent change in high density lipoprotein (HDL) cholesterol								
7.0	8.6	8.2	0.2	15	3.6	6.9	9.6	1.1
Mean change in waist circumference (cm)								
-14.6	-19.4*	-19.9*	-3.4	-16.8*	1.1	-11.2*	-13.8*	-3.4
Mean change in HbA1c (%)								
-0.4	-0.5	-0.5	-0.1	-0.5	0.0	-2.1*	-2.2*	-0.2

PBO = placebo; T MTD = maximum tolerated dose (10mg or 15mg) tirzepatide; T 5 mg, T 10 mg and T 15 mg = tirzepatide 5 mg, 10 mg and 15 mg, respectively. * p<0.01 versus placebo.

A double-blind, randomised-withdrawal, phase III study (SURMOUNT-4) had inclusion criteria that were similar to SURMOUNT-1 and -3. After 36-weeks' open-label titration to a maximum tolerated dose of tirzepatide 10 mg to 15 mg SC once weekly (93% had highest dose), 670 patients were equally randomised (stratified by country, sex, dose and weight loss at week 36 [<10% or ≥10%]) to continue tirzepatide (constant dose) or switch to placebo for 52 weeks. The primary outcome, mean percent change in body weight from randomisation (week 36) to week 88, was significantly greater with tirzepatide compared with placebo using the treatment-regimen estimand: -5.5% versus 14% (difference -19%, 95% confidence interval [CI]: -21% to -18%); and the efficacy-estimand: -6.7% versus 15% (difference -21%, 95% CI: -23% to -20%). More patients who continued tirzepatide, compared with placebo, maintained ≥80% of their open-label phase weight loss: 90% versus 17% using the treatment-regimen estimand.[10]

2.2. Evidence to support the positioning proposed by the submitting company

The company has requested that SMC considers tirzepatide when positioned for use in adults with BMI of ≥30 kg/m^2 and at least one weight-related comorbidity.

For patients with a comorbidity excluding type 2 diabetes, a subgroup analysis of patients from the SURMOUNT-1 study who had BMI ≥30 kg/m^2 and at least one weight-related comorbidity provided an estimate of treatment effects. The outcomes appear to be similar to those in the whole study population.[11]

For patients with type 2 diabetes as a co-morbidity, subgroup analysis of the primary outcome in the SURMOUNT-2 study by BMI provide an estimate of treatment effect in patients with BMI ≥30 kg/m^2 and a comorbidity of type 2 diabetes (that is inadequately controlled, as HbA_{1c} ≥7% at baseline). The outcomes appear similar to the whole study population.[12]

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

2.3. Health-related quality of life outcomes

In SURMOUNT-1, the differences over placebo for change from baseline to Week 72 were less than 3.5 points on 100-point scales for all domains and summary scores in Short Form 36 Health Survey (SF-36). In the tirzepatide 5 mg, 10 mg and 15 mg groups, the difference over placebo for change from baseline to Week 72 in EQ-5D-5L visual analogue scale (VAS) was 4.4, 5.8 and 6.2 points (on 100-point scale); and in health state index was 0.03, 0.03 and 0.05, respectively. In the tirzepatide 5 mg, 10 mg and 15 mg groups, the difference over placebo for change from baseline to Week 72 in Impact of Weight on Quality of Life-Lite (IWQOL-Lite-CT) physical composite score was 7.2, 9.9 and 11.1, respectively, (on 100-point scale).[13]

In SURMOUNT-2, in the tirzepatide 10 mg and 15 mg groups, the differences over placebo for change from baseline to Week 72 in SF-36 physical function score were 1.8 and 2.3 on 100-point scales for all other domains and summary scores in SF-36. In the tirzepatide 10 mg and 15 mg groups, the difference over placebo for change from baseline to Week 72 in EQ-5D-5L VAS was similar. In the tirzepatide 10 mg and 15 mg groups, the difference over placebo for change from baseline to Week 72 in physical composite score was 6.9 and 7.8, respectively.[8, 12]

In SURMOUNT-3, there were also improvements over placebo for the change from baseline to Week 72 in EQ-5D-5L VAS and health state index in the tirzepatide maximum tolerated dose (MTD) group. [14]

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

2.4. Supportive studies

The SURPASS programme investigated tirzepatide for the treatment of type 2 diabetes in 40-week studies (except, SURPASS-3 and -4: 52 weeks). The SURPASS-2, -3 and -4 studies included patients with a BMI ≥25 kg/m^2 (overweight), with the majority of recruited patients having BMI ≥30 kg/m^2 (obese): 71%, 69% and 64%, respectively. The SURPASS-1 and -5 studies included patients with BMI ≥23 kg/m^2, with many of those recruited having BMI ≥30 kg/m^2: 53% and 68%, respectively. Weight change was measured as a secondary outcome in these studies. Tirzepatide 5 mg, 10 mg and 15 mg, compared with placebo, was associated with weight loss of 6.3 kg, 7.1 kg and 8.8 kg in SURPASS-1; and 7.8 kg, 9.9 kg and 12.6 kg (on background of titrated insulin glargine, with or without metformin) in SURPASS-5. SURPASS-2 compared tirzepatide 5 mg, 10 mg and 15 mg with semaglutide 1mg (which is lower than the dose licensed for weight management, 2.4 mg), both in combination with metformin, and found differences of 1.7 kg, 4.1 kg and 6.2 kg, respectively. In the SURPASS-3 and -4 studies the respective doses of tirzepatide were associated with favourable weight loss, compared with insulin degludec (9.8 kg, 13 kg and 15.2 kg) and with insulin glargine (9.0 kg, 11.4 kg and 13.5 kg), respectively.[1, 15, 16]

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

The company has provided a network meta-analysis (NMA) comparing tirzepatide versus semaglutide in adults with BMI ≥30 kg/m² with ≥1 weight-related comorbidity (that informs the base case economic analysis) and with semaglutide and liraglutide in adults with BMI ≥35 kg/m² with prediabetes and high cardiovascular disease (CVD) risk (that informs a scenario economic analysis). These two subgroups reflect the SMC restrictions for the GLP-1 agonists, semaglutide and liraglutide, respectively. The NMAs are detailed in Table 2.3.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Network meta-analysis
Population	**Base case**: adults with BMI ≥30 kg/m² with ≥1 weight-related comorbidity **Scenario**: adults with BMI ≥35 kg/m² with prediabetes and high cardiovascular disease
Comparators	**Base case**: semaglutide 2.4 mg **Scenario**: semaglutide 2.4 mg and liraglutide 3 mg
Studies included	**Base case**: SURMOUNT-1;[7] STEP-1[17] **Scenario**: SURMOUNT-1;[7] STEP-1;[17] SCALE Obesity and Prediabetes[18]
Outcomes	Change from baseline to week 56 to 72 in percent body weight loss, total cholesterol; high density lipoprotein (HDL) cholesterol; and systolic blood pressure (SBP).
Results	**Base case**: Tirzepatide 10 mg and 15 mg superior to semaglutide for percent weight loss. Tirzepatide superior for HDL, but no significant difference for total cholesterol or SBP. **Scenario**: Tirzepatide 10 mg and 15 mg superior to semaglutide for percent weight loss and superior to liraglutide, with tirzepatide 5 mg superior to liraglutide. There was generally no consistent difference between tirzepatide versus semaglutide and liraglutide for HDL or total cholesterol or SBP.

BMI = body mass index.

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

3. Summary of Safety Evidence

The safety profile of tirzepatide is similar to other GLP-1 agonists, including gastro-intestinal adverse events and, when used in combination with glucose-lowering medicines (such as insulin and sulphonylureas), hypoglycaemia events. However, unlike GLP-1 agonists, tirzepatide has been associated with increased calcitonin.[15]

Adverse event rates in SURMOUNT-1, -2 and -3 are detailed in Table 3.1. Across the studies, the most frequently reported adverse events were gastro-intestinal, with nausea occurring at rates of 20% to 40% within the tirzepatide groups across the studies, compared with rates of 6.3% to 14% in the placebo groups; vomiting (8.3% to 18% versus 1.4% to 3.2%), diarrhoea (19% to 31% versus 7.3% to 9.2%) and constipation (8.0% to 23% versus 4.1% to 6.8%). Also reported were injection site reactions (2.9% to 11% versus 0.3% to 1.0%).[7-9]

Table 3.1: Adverse events in SURMOUNT-1, -2 and -3 studies.[7-9]

SURMOUNT-1				SURMOUNT-3		SURMOUNT-2		
T 5mg	**T 10mg**	**T 15mg**	**PBO**	**T MTD**	**PBO**	**T 10mg**	**T 15mg**	**PBO**
n=630	n=636	n=630	n=643	n=287	n=292	n=312	n=311	n=315
Patients with any adverse event, %								
81	82	79	72	87	77	78	71	76
Patients with serious adverse event, %								
6.3	6.9	5.1	6.8	5.9	4.8	5.8	8.7	7.3
Adverse event leading to study treatment discontinuation, %								
4.3	7.1	6.2	2.6	10	2.1	3.8	7.4	3.8

PBO = placebo; T MTD = maximum tolerated dose (10mg or 15mg) tirzepatide; T 5 mg, T 10 mg and T 15 mg = tirzepatide 5 mg, 10 mg and 15 mg, respectively.

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Tirzepatide is the first medicine licensed for weight management that acts as an agonist at both GIP and GLP-1 receptors.
- In well conducted phase III studies, patients without diabetes, compared with placebo, tirzepatide fixed doses of 5 mg, 10 mg and 15 mg (as an adjunct to diet and lifestyle intervention) significantly improved mean percent weight loss by around 13% to 20%, with a larger difference of around 24% in patients who could be tolerate a maximum dose of tirzepatide of 10 mg to 15 mg after a period of intensive lifestyle intervention. In patients with type 2 diabetes (that was inadequately controlled; HbA_{1c} 7% to 10%), fixed doses of tirzepatide 10 mg and 15 mg (as an adjunct to diet and lifestyle intervention) improved mean percent weight loss by 10% to 12%, which appears smaller than the benefits in patients without diabetes.[7-9]
- Tirzepatide, compared with placebo, appeared to lower blood pressure and have benefits on lipid profile and waist circumference.[7-9]

4.2. Key uncertainties

- For patients without diabetes, the estimates of efficacy in the proposed positioning, patients with BMI ≥30 kg/m^2 and at least one weight-related co-morbidity are from post hoc subgroup analysis of SURMOUNT-1, which included patients with co-morbidities, excluding type 2 diabetes. The outcomes appear similar to the total study population.
- In the SURMOUNT-4 withdrawal study, there was significant weight regain of around 14% after one year in patients who stopped tirzepatide .[10] There is uncertainty around the duration of treatment with tirzepatide and the potential loss of benefits upon treatment discontinuation. Also, there is a lack of long-term data beyond 72 weeks on the use of tirzepatide for weight management.
- In the SURMOUNT-1 and -2 studies, patients had a consultation with a dietician to receive lifestyle management counselling at Weeks 0, 4, 8 and 12 during dose escalation and then at week 24 and every 12 weeks thereafter through 72 weeks. The benefits with tirzepatide over placebo, represent the additional weight loss achieved over these interventions. There is uncertainty around the magnitude of effect if tirzepatide in used without diet and exercise interventions.
- The indirect comparison of tirzepatide versus semaglutide and liraglutide is limited by use of post hoc subgroup analyses for tirzepatide and comparators in NMAs that inform the base case and scenario economic analysis. These analyses included data from only two and three studies, respectively, which had the same inclusion criteria and similar baseline demographics. This limits heterogeneity. However, there were differences in assessment timepoints of tirzepatide, semaglutide and liraglutide: 72, 68 and 57 weeks, respectively. Despite these limitations, the company's conclusions of benefits with tirzepatide 10 mg and 15 mg compared with semaglutide and liraglutide in relation to weight loss for the base case and scenario analysis are generally accepted. The NMA excluded studies in patients with type 2 diabetes as a comorbidity, therefore results are not generalisable to practice for patients with type 2 diabetes and obesity. It also did not assess safety or quality of life outcomes.
- The company's positioning is use in adults with BMI ≥30 kg/m^2 and at least one weight-related comorbidity, however a lower BMI cut-off may be more appropriate for members of minority ethnic groups known to be at equivalent risk of the consequences of obesity at a lower BMI than the white population.

4.3. Clinical expert input

Clinical experts consulted by SMC note that tirzepatide in the treatment of obesity is a therapeutic advance due to its efficacy. They consider that it would be used in place of other medicines that are used in weight management, particularly the GLP-1 agonists, semaglutide and liraglutide.

4.4. Service implications

Clinical experts consulted by SMC note that there are currently supply issues with some medicines for weight management, particularly GLP-1 agonists. Also, capacity issues can have an impact on access to these medicines, which are restricted to use within specialist weight management services.

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 All About Obesity, which is a charitable incorporated organization.
- All About Obesity has received 80% pharmaceutical company funding in the past two years, including from the submitting company.
- People living with obesity feel full of shame, many have spent the majority of their adult lives blaming themselves for living with the condition and have been made to feel that way by society. They are fighting against the stigma and discrimination of obesity on a daily basis. Caring for someone living with obesity is frustrating because there are not enough services, resources or support for people.
- Historically patients were frustrated by the limited access to weight management treatments. More recently with the addition of liraglutide and semaglutide, this has given patients hope, however being able to access these treatments is difficult.
- Tirzepatide provides hope to people living with obesity that they will be able to live healthier lives and maintain a healthier weight for longer periods of time by addressing the physiological aspects of obesity. The more therapeutics that are available for people living with obesity the better, because one size will not fit all.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The economic analysis is described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime – i.e. until the modelled patient dies
Population	Adults with a BMI of ≥30 kg/m^2 with at least one weight-related comorbidity
Comparators	Tirzepatide (combined with a reduced calorie diet and exercise) was compared with: • Semaglutide (combined with a reduced calorie diet and exercise) • A reduced calorie diet and exercise alone
Model description	An individual patient simulation model was used which tracked the health outcomes for distinct individuals across time. Patients were characterised based on their age, sex, height, BMI, SBP, total cholesterol, HDL, comorbidities, and treatment with corticosteroids and statins was included. Over the course of the model, patients could develop various weight-related comorbidities and complications. These were type 2 diabetes, angina, stroke, myocardial infarction, non-alcoholic fatty liver disease, obstructive sleep apnoea, knee replacement and bariatric surgery. At the start of the model patients were either classed as pre-diabetic or having normoglycemia. If pre-diabetic, patients could reverse that pre-diabetes in response to all treatments.

	The model initially used a 4-week cycle length for the first 2 years, before switching to a yearly cycle length when less movement between treatment status and outcomes is expected. A half cycle correction was applied where appropriate.
Clinical data	The main clinical source on the efficacy of tirzepatide was the SURMOUNT-1 study.[7] This helped inform some, but not all, of the starting characteristics of patients. The SURMOUNT-1 study did not include semaglutide as a comparator, and so the company conducted an NMA to compare treatment arms. This estimated the treatment effect across 4 surrogate endpoints - body weight, SBP, HDL and total cholesterol. The changes in these surrogate endpoints were assumed to happen linearly over the observed treatment period in the included studies, which was 72 weeks for tirzepatide and 68 weeks for semaglutide and diet and exercise alone. Patients receiving tirzepatide would discontinue treatment if they failed to achieve a 5% reduction in their body weight 6 months after titrating to their maintenance dose, so called primary treatment failure. That time point for tirzepatide was week 30, 38 or 46 for the 5 mg, 10 mg and 15 mg dose maintenance dose respectively. For semaglutide, a similar rule was applied 26 weeks after starting treatment. The proportion of patients experiencing primary treatment failure was based on observed data from the SURMOUNT-1 study for tirzepatide and clinical opinion for semaglutide. Primary treatment failure was not applicable to diet and exercise alone.
Extrapolation	The treatment effect of tirzepatide is assumed to remain constant as long as a patient was on treatment. In addition to primary treatment failure patients could discontinue if experiencing adverse events based on the rate observed in the SURMOUNT-1 study. Semaglutide could also be discontinued as a result of adverse events, with the rate drawn from the STEP-1 study.[18] Semaglutide was used for up to 2 years, in line with the assumptions in the SMC appraisal of semaglutide (SMC2497). Upon discontinuation of tirzepatide and semaglutide, patients were assumed to continue the diet and exercise portion of their treatment. When stopping treatment, for any reason, the treatment effect of tirzepatide and semaglutide on surrogate endpoints was lost over a course of 3 years and patients aligned with the surrogate endpoints of those who had received diet and exercise alone. In the diet and exercise arm, the values of surrogate end points were assumed stable after the 68 week point, apart from weight, which rose slowly over time in line with Ara et al (2012).[20]Each cycle, the model used the patient characteristics at that time as inputs for risk equations. These risk equations defined the per cycle probability that the patient would develop type 2 diabetes, stroke, myocardial infarction, angina, knee replacement, obstructive sleep apnoea and non-alcoholic fatty liver disease. The proportion of patients achieving pre-diabetes reversal was defined based on the observed outcomes in the SURMOUNT-1 and STEP-1 studies. This was applied in the first period, which the company states was conservative in regards to diet and exercise alone. The risk of bariatric surgery was constant for those eligible for surgery. Mortality was modelled separately between cardiovascular death and all other causes. A fixed proportion of cardiovascular events were assumed to result in fatalities. Non-cardiovascular death was modelled using general population mortality filtered for non-cardiovascular cause of death. This was adjusted to account for the higher rate of mortality at higher BMI values, if the patient had experienced previous cardiovascular events, had type 2 diabetes or had non-alcoholic fatty liver disease.
Quality of life	The SURMOUNT-1 study collected data on quality of life using the EQ-5D instrument. However, for the modelling, the company used an external source, Søltoft et al. (2009).[21] The main reasoning behind this was the higher sample size in Søltoft et al., meaning that baseline utilities could be much more tailored to the patients age, sex and BMI. Additional disutilities from the literature were applied for the various complications and outcomes the patient could undergo. A disutility was included for adverse events, although the only adverse event included in the model was for severe or serious gastrointestinal events.
Costs and resource use	Medicine costs included acquisition costs and adverse event costs for tirzepatide and semaglutide. Both treatments were administered at home, at no cost, after 2 demonstrations

	by a nurse. No costs were directly attributed to diet and exercise, despite all patients in the SURMOUNT-1 study receiving regular diet and lifestyle advice. Wider NHS costs included in the model were for monitoring (GP and nurse visits and blood tests) and for the treatment of complications of obesity.
Patient access scheme (PAS)	No PAS is in place on tirzepatide A PAS discount is in place for semaglutide and this was included in the results used for decision-making by using estimates of the comparator PAS price.

6.2. Results

The main base case results, excluding the PAS on semaglutide, are presented in Table 6.2.1, 6.2.2 and 6.2.3 below. Each table presents results for a separate dose of tirzepatide.

Disaggregated results show that the main difference in costs is the acquisition cost of tirzepatide, with some subsequent savings on the costs of complications. Similarly, QALY gains for patients receiving tirzepatide are as a result of fewer complications of obesity.

Table 6.2.1: Base-case results for tirzepatide 5 mg (List prices)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Tirzepatide	£31,644	18.694	16.255	-	-	-	-
Semaglutide	*	18.389	*	*	0.305	*	£9,569
Diet and Exercise	£23,697	18.358	15.551	£7,947	0.336	0.704	£11,289

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality adjusted life year.

* = Results commercial in confidence

Table 6.2.2: Base-case results for tirzepatide 10 mg (List prices)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Tirzepatide	£31,641	18.771	16.274	-	-	-	-
Semaglutide	*	18.389	*	*	0.322	*	£9,261
Diet and Exercise	£23,697	18.358	15.551	£7,944	0.353	0.723	£10,992

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality adjusted life year.

* = Results commercial in confidence

Table 6.2.3: Base-case results for tirzepatide 15 mg (List prices)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Tirzepatide	£33,712	18.750	16.365	-	-	-	-
Semaglutide	*	18.389	*	*	0.360	*	£11,053
Diet and Exercise	£23,697	18.358	15.551	£10,015	0.392	0.814	£12,296

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality adjusted

life year.
* = Results commercial in confidence

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

6.3. Sensitivity analyses

The company explored areas of uncertainty using probabilistic and deterministic sensitivity analysis as well as scenario analysis. A selection of scenarios are presented below. For simplicity, only scenarios for the 10 mg dose of tirzepatide are shown, and these are exclusive of the PAS discount on semaglutide.

Table 6.3: Scenario analyses for tirzepatide 10 mg (List prices)

				ICER (£/QALY)	
	Parameter	**Base case**	**Scenario**	**Semaglutide**	**Diet & exercise**
	Base case			£9,261	£10,992
1	Time of Return to Prediabetes for Diet and Exercise	2 years	3 years	£9,261	£11,343
2			5 years	£9,261	£12,122
3	Model Type for Efficacy Endpoints:	Efficacy endpoint estimands	Treatment Regimen Estimands	£10,171	£12,135
4	Efficacy Waning Period Post-Discontinuation	3 years	1 year	£9,362	£12,579
5			2 years	£8,821	£11,679
6	Risk Equation for Development of T2DM	QDiabetes[22]	Framingham Offspring Study[23]	£15,458	£19,455
7	Source for Natural Weight Regain Post Discontinuation	Ara *et al.* 2012	Iyen et al. 2021[26]	£9,910	£11,675
8	Tirzepatide treatment duration	Indefinite	2 years	Dominant	£6,498
9			5 years	£143	£9,080
10			10 years	£5,913	£9,653
11	Treatment population	BMI of ≥30 kg/m^2 with at least one weight-related comorbidity	BMI of ≥35 kg/m^2 with at least one weight-related comorbidity	£7,971	£9,569
12	Starting comorbidities	Patients could not have T2DM, previous cardiovascular events, NAFLD or OSA at baseline	Proportions of previous cardiovascular events, NAFLD and OSA at baseline matched to SURMOUNT-1. No T2DM maintained	£9,368	£10,602

13	Treatment waning	No weight gain while on pharmacological treatment	Weight gain in line with diet and exercise after 5 years on treatment	£11,995	£10,347
14		Full treatment effect of tirzepatide maintained as long as on treatment	Full treatment effect of tirzepatide over diet and exercise is lost over 5 years between year 5 and year 10	£18,793	£18,753
15			Full treatment effect of tirzepatide over diet and exercise is lost over 5 years between year 10 and year 15	£13,183	£14,506

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; T2DM = type 2 diabetes mellitus; CVD = cardiovascular disease

6.4. Key strengths

The key strengths of the economic case were assessed as being:

- The model design and time horizons appear appropriate for the decision problem.
- The model utilises many of the same assumptions and data sources as the SMC submission for semaglutide (SMC2497)
- Data comparing tirzepatide against placebo came from a phase III randomised study, SURMOUNT-1. This showed that tirzepatide is more effective at promoting weight loss than diet and exercise alone.

6.5. Key uncertainties

The key uncertainties of the economic case were assessed as being:

- There were concerns that the patients included in the model were not representative of those who may be expected to be treated in Scotland. Patients entering the model were described as having one weight related condition, but were prevented from having type 2 diabetes, previous cardiovascular events, non-alcoholic fatty liver disease or obstructive sleep apnoea. This may mean that tirzepatide was modelled at preventing conditions that are already present in the Scottish treatment population, overestimating its treatment effect. However, the company has also stated that the model may underestimate the overall efficacy in a type 2 diabetic population, as it does not track the glycaemic benefits from tirzepatide. They have also highlighted that the proportion of people in the SURMOUNT-1 study with previous cardiovascular disease and obstructive sleep apnoea is small. Overall, the effects of these omissions are small, but it remained a source of

uncertainty.

- To define patients, the company used data from external sources. These sources were typically not from Scotland, and not from obese populations. Therefore, the inputted values may not be generalisable to the Scottish population of eligible patients. However, one source of discrepancy, the ethnicity of patients, was explored by the SMC Assessment Team. Aligning the ethnicity to the 2011 census data, the latest available, was found to have little impact upon the economic results. Therefore, the overall impact of adjusting for other patient characteristics is uncertain.
- Within the SURMOUNT-1 study, patients in both arms of the model were supported by dietary advice and lifestyle counselling. This was also the case in the STEP-1 study which explored the efficacy of semaglutide. Should treatments be delivered in the absence of dietary and exercise advice, the scale of the treatment effect is uncertain. Further, the costs of diet and exercise advice do not appear to have been included in the modelling, meaning total costs in each arm are likely underestimated. As these elements were provided equally across all arms, this likely has minimal effect upon the economic results, as diet and exercise advice costs would largely cancel out.
- There is no direct evidence comparing tirzepatide with semaglutide. The company has had to rely on a NMA. While this appears to use a reasonable approach, it still introduces a higher degree of uncertainty into the economic modelling.

7. Conclusion

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

8. Guidelines and Protocols

The National Institute for Health and Care Excellence (NICE) clinical guideline 189 (CG189): Obesity: identification, assessment and management was published on 27 November 2014 and last updated in 26 July 2023.

9. Additional Information

9.1. Product availability date

8 November 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost year (£)
Tirzepatide	**5 mg to 15 mg subcutaneously once weekly**	**1,196 to 1,586**

Costs from BNF as of 7th May 2024. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 1,013,311 patients eligible for treatment within each year. The estimated uptake rate was 0.5% in year 1 and 3.0% in year 5. This resulted in 5,067 patients estimated to receive treatment in year 1 rising to 30,399 patients in year 5. Given the company's proposed positioning (which includes use in both primary and secondary care), this is likely to be a significant underestimate.

Based on the company's projections, the gross medicines budget impact was estimated to be £6.4m in year 1 rising to £38.3m in year 5. As other medicines were assumed to be displaced the net medicines budget impact was estimated to be £4.6m in year 1 rising to £33.6m in year 5.

These estimates do not take account of any patient access schemes applied to displaced medicines.

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

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive

access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.