NEW DRUGS

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Tirzepatide

Approved indication: insufficiently controlled type 2 diabetes in adults, as an adjunct to diet and exercise, either as monotherapy when metformin is not tolerated or contraindicated, or in combination with metformin or other antihyperglycaemic drugs

Mounjaro (Eli Lilly)
single-use vials containing solution for injection—2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, 15 mg/0.5 mL

Glucagon-like peptide-1 (GLP-1) receptor agonists have become well established in the management of type 2 diabetes, with the added benefit of assisting weight loss. Tirzepatide is a novel drug that acts as an agonist at receptors for both GLP-1 and gastric inhibitory polypeptide, another incretin that lowers blood glucose concentrations and reduces appetite. It is administered as a once-weekly subcutaneous injection.

The approved indication for tirzepatide is the treatment of adults with insufficiently controlled type 2 diabetes, as an adjunct to diet and exercise, either as monotherapy when metformin is not tolerated or contraindicated, or in combination with metformin or other antihyperglycaemic drugs.[1]

Tirzepatide's approval was based on 5 phase-3 trials (SURPASS-1 to 5), which studied tirzepatide in maintenance doses of 5 mg, 10 mg and 15 mg once weekly, either as monotherapy or add-on therapy, in people with type 2 diabetes and an elevated glycated haemoglobin (HbA1c). In all 5 studies, tirzepatide-treated patients achieved statistically greater reductions in HbA1c than patients in the comparator arm (Table 1).

Tirzepatide was also associated with weight loss in all 5 trials.[1] For example, in SURPASS-1, weight loss of 10% or more occurred in 30.6% and 47.4% of tirzepatide recipients at the lowest (5 mg) and highest (15 mg) doses respectively, compared with 0.9% of placebo recipients.[2] In SURPASS-2, weight loss of 10% or more occurred in 35.8% and 64.9% of tirzepatide recipients at the lowest and highest doses respectively, compared with 25.3% of semaglutide 1 mg recipients.[1,3]

Pre-specified cardiovascular safety meta-analyses of data from the SURPASS trials reported statistically nonsignificant reductions in cardiovascular events in patients who received tirzepatide compared to placebo and active comparators, over 12 months.[7] Longer-term studies evaluating cardiovascular outcomes are underway. Data on renal outcomes are limited, but a post-hoc analysis from SURPASS-4 reported statistically significant renal benefits from tirzepatide compared to insulin glargine.[8]

The most frequently reported adverse effects of tirzepatide were gastrointestinal, including nausea, diarrhoea, dyspepsia, constipation and vomiting. These were mostly mild or moderate.[2-6] They usually occurred during dose escalation and improved over time.[1,2]

Tirzepatide monotherapy was not associated with an increased risk of significant hypoglycaemia (blood glucose concentration less than 3.0 mmol/L).[2] However, there may be an increased risk in people taking tirzepatide with an insulin secretagogue (e.g. a sulfonylurea) or insulin.[1] Therefore, a reduction in the dose of these drugs, and close monitoring of blood glucose concentrations, may be required when initiating or up-titrating tirzepatide.

GLP-1 receptor agonists have been linked to pancreatic adverse effects, so tirzepatide should be used with caution in people with a history of pancreatitis.[1] Tirzepatide is Therapeutic Goods Administration pregnancy Category D.[1]

The recommended starting dose of tirzepatide is 2.5 mg once weekly. After 4 weeks, the dose is increased to 5 mg once weekly. If needed, further dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose. The recommended maintenance dose is 5 mg, 10 mg or 15 mg once weekly.[1] Tirzepatide is available in 6 strengths to enable dose titration (the 2.5 mg, 7.5 mg and 12.5 mg strengths are only for dose titration and not intended for maintenance treatment).

In Australia, tirzepatide is currently available in single-dose vials only, thus requiring a needle and syringe for administration. A pen device will be available in the future. Tirzepatide can be injected at any time of the day, with or without a meal.[1]

Tirzepatide is an alternative to GLP-1 receptor agonists for people with insufficiently controlled type 2 diabetes.

TT manufacturer provided additional useful information. The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

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Table 1 Selected HbA1c outcomes from the SURPASS-1 to 5 clinical trials[1-6]

Trial	Background antihyperglycaemic treatment (both groups)	Follow-up duration	Comparator treatment [NB1]	Difference from comparator in HbA1c (%) change at the approved tirzepatide maintenance doses [NB1] [NB2]		
				5 mg once weekly	10 mg once weekly	15 mg once weekly
SURPASS-1 (n = 478 patients)	nil	40 weeks	placebo once weekly	-1.91	-1.93	-2.11
SURPASS-2 (n = 1879 patients)	metformin monotherapy	40 weeks	semaglutide 1 mg once weekly	-0.23	-0.51	-0.60
SURPASS-3 (n = 1444 patients)	metformin, with or without a sulfonylurea and/or an SGLT2 inhibitor	52 weeks	insulin degludec once-daily titrated dose	-0.59	-0.86	-1.04
SURPASS-4 (n = 2002 patients)	metformin, a sulfonylurea, and/or an SGLT2 inhibitor	52 weeks	insulin glargine once-daily titrated dose	-0.80	-0.99	-1.14
SURPASS-5 (n = 475 patients)	insulin glargine, with or without metformin	52 weeks	placebo once weekly	-1.30	-1.66	-1.65

HbA1c = glycated haemoglobin; SGLT2 = sodium-glucose co-transporter 2

NB1: Tirzepatide and comparator treatments were administered by subcutaneous injection.

NB2: These data reflect the effects of tirzepatide when people adhered to treatment and did not require rescue therapy.

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