MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

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TIRZEPATIDE FOR TREATMENT OF OBESITY

Keywords: body mass index (BMI) greater than 30, glucose-dependent insulinotropic polypeptide (GIP) agonist, glucagon-like peptide-1 (GLP-1) receptor agonist

SUMMARY OF TECHNOLOGY

Tirzepatide (marketed as Mounjaro™) is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist[1], developed by Eli Lilly (United States)[2] . It had been proven to be effective to improve glycaemic control in adults with Type 2 Diabetes Mellitus (T2DM) and had received its first approval in May 2022 by U.S Food and Drug Administration (FDA).[3] In the recent clinical trial among T2DM participant, therapy with tirzepatide 5–15 mg once weekly produces 8–12% body weight reduction, prompting ongoing investigation of tirzepatide for the treatment of obesity among non-diabetic population.[4]

Tirzepatide is prescribed as once-weekly subcutaneous medication with suggested starting dosage of 2.5 mg to 15 mg weekly.[5] This unimolecular dual-agonists targeting the receptors for GLP-1 and GIP had shown to decrease body weight and improve glucose handling in animal models of obesity and T2DM, non-human primates, and obese patients with T2DM.[6] Moreover, the dual-agonists exhibit greater efficacy relative to GLP-1R agonism alone in preclinical studies and clinical trials.[6] Glucose-dependent insulinotropic polypeptide is a hormone that may complement the effects of GLP-1 receptor agonism. Glucose-dependent insulinotropic polypeptide has been shown to decrease food intake while blunting the metabolic adaptive responses that usually occur with calorie restriction resulting in weight reductions, and when combined with GLP-1 receptor agonism, may result in greater effects on markers of metabolic dysregulation such as body weight, glucose and lipids.[1]

Tirzepatide receives U.S. FDA Fast Track designation on the 6th October 2022 for the treatment of adults with obesity, or overweight with weight-related comorbidities.[2] Currently, phase 3 clinical trial SURMOUNT-2 (NCT04657003) is still on-going and expect to be completed by the end of April 2023.[2] This medication is also investigated in phase III development for heart failure, obesity and cardiovascular disorders in T2DM, and in phase II development for non-alcoholic steatohepatitis.[2]

INNOVATIVENESS

Novel, completely new	
Incremental improvement of the existing technology	
New indication of an existing technology	/

DISEASE BURDEN

Obesity is a complex, multifactorial condition characterised by excess body fat. Obesity is associated with many other diseases, and it warrants recognition by healthcare providers. Generally, men with >25% body fat and women with >35% body fat are considered obese.[7] According to World Health Organization (WHO), a body mass index (BMI) over 25kg/m^2 is considered overweight, and over 30kg/m^2 is obese.[8]

Globally, obesity has nearly tripled since 1975. In 2016, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 650 million were obese.[8] According to an analysis of the Global Burden of Disease Study (1997 – 2016), in 2017, high BMI caused 2.4 million (95% UI 1.6 million, 3.4 million) deaths and 70.7 million (95% UI 49.1 million, 94.9 million) disability-adjusted life years (DALYs) in females, and 2.3 million (95% UI 1.4 million, 3.4 million) deaths and 77.0 million (95% UI 49.7 million, 108.2 million) DALYs in males.[9] Cardiovascular disease was the leading cause of high-BMI-related DALYs, followed by diabetes and kidney diseases, and neoplasms; they together accounted for 89.3% of all high-BMI-related DALYs.[9] In the United State, one in two adults are projected to have obesity by 2030, and about one in four to have severe obesity.[10]

According to Malaysian survey, it was found that 50.1% of adults in Malaysia were overweight or obese, with 30.4% being overweight and 19.7% obese.[11] A total of 52.6% of adults were found to have abdominal obesity.[11] The trends of overweight, obesity and abdominal obesity continue to rise compared to findings of 2011 and 2015.[11] Among children 5-17 years of age, a total of 15.0% were overweight, with 14.8% being obese. On the other hand, the number of children under 5 years of age being stunted, showed an increase compared to previous years, from 16.6% in 2011, 17.7% in 2015 to 21.8% in 2019.[12]

Obesity also imposes a large economic burden on the individual, and on families and nations. In 2014 the global economic impact of obesity was estimated to be USD 2.0 trillion or 2.8% of the global gross domestic product (GDP).[13]

CURRENT OPTIONS FOR PATIENTS

Multicomponent interventions are the treatment of choice with the initial goal of weight loss therapy to reduce body weight by approximately 10% from the baseline. Weight loss should be about 0.5 to 1 kg/week for a period of 6 months, with the subsequent strategy based on the amount of weight lost.[7] The weight management programmes include behaviour change strategies to increase physical activity levels or decrease inactivity, improve eating behaviour and the quality of the diet, and reduce energy intake.[11]

Pharmacological treatment is only considered after dietary, exercise and behavioural approaches have been started and evaluated.[11] Some guidelines recommend that individuals who have attempted lifestyle improvements and continue to have a BMI of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with an obesity-related comorbidity are eligible for weight loss medication treatment.[14] According to Malaysian guideline, pharmacotherapy can be used as an adjunct to lifestyle changes to induce weight loss in some patients at comparatively lower BMI (BMI ≥ 27.5 kg/m^2 and in patients with a BMI ≥ 25 kg/m^2 with co-morbidities).[7]

There are nine FDA-approved anti-obesity medications (AOMs) remain on the market, with six approved for long-term weight loss as shown in Table 1.[14] Several other medications prescribed for conditions other than obesity have been found to be effective weight loss drugs in patients with obesity as listed in Table 2.[14]

Table 1 List Of FDA-Approved Anti-Obesity Medications.

Name (Trade Names)	Year Approved	Mechanism of Action / Clinical Effect	Average placebo-subtracted weight loss (%)	Achieved ≥5% Weight Loss, Intervention vs. placebo (%)
Approved for short-term use				
Phentermine (Adipex, Lomaira)	1959	Sympathomimetic / Suppresses appetite	4.4 at 28 wks	49 vs.16 at 28 wks
Diethylpropion	197 1979	Sympathomimetic / Suppresses appetite	6.6 at 6 months	67.6 vs. 25.0
Approved for long-term use				
Orlistat (Alli, Xenical)	1999	Intestinal lipase inhibitor / Reduces fat absorption by up to 30%	3.8	50.5 vs. 30.7
Phentermine-topiramate (Qsymia)	2012	Combination sympathomimetic and carbonic anhydrase inhibitor / Decreases appetite and binge eating behaviors	8.6	70 vs. 21
Bupropion-naltrexone (Contrave)	2014	Combination of a dopamine and norepinephrine re-uptake inhibitor and mu-opioid receptor antagonist / Decreases appetite and cravings	4.8	48 vs. 16
Liraglutide 3.0mg (Saxenda)	2014	GLP-1 receptor agonist / Decreases appetite, increases fullness, increases satiety	5.4	63.2 vs. 27.1
Gelesis100 (Plenity)	2019	Superabsorbent hydrogel particles of a cellulose-citric acid matrix / Increases fullness. Considered a	2.0 at 6 months	58.6 vs. 42.2

		medical device but functions as a medication.		
Setmelanotide (Imciveree)	2020	Melanocortin-4-receptor agonist / Decreases appetite	Not applicable 12.5-25.6	Not applicable 64-90
Semaglutide 2.4 mg (Wegovy)	2021	GLP-1 receptor agonist / Decreases appetite, increases fullness, increases satiety	12.4	86.4 vs. 31.5

Source: *Tchang BG, Aras M, Kumar RB, et al. Pharmacologic Treatment of Overweight and Obesity in Adults. (2021)*

Table 2 List of Non-FDA Approved (Off-Label) Medications That Cause Weight Loss.

Name (Trade Names)	Mechanism of Action / Clinical Effect
Bupropion (trade name Wellbutrin or Zyban)	used for depression and smoking cessation and can cause weight loss as a side effect.
Metformin (trade name Glucophage)	An antihyperglycaemic agent. Potential weight loss mechanisms include: • Activation of AMP-activated protein kinase (AMPK) to mimic an “energy deficient” state. • Increasing anorexigenic hormones GLP-1, growth/differentiation factor-15 (GDF-15), neuropeptide Y (NPY), and agouti-related protein (AgRP). • Increasing leptin sensitivity.
Pramlintide acetate (trade name Symlin)	FDA-approved for the treatment of type 1 and type 2 diabetes. Its effect on weight loss is thought to be mediated through central (brain) receptors that improve appetite control.
Sodium-Glucose Transporter-2 (SLGT2) Inhibitors	Eg: canagliflozin (Invokana), dapagliflozin (Farxiga), ertugliflozin (Steglatro), and empagliflozin (Jardiance).
Topiramate (trade name Topamax)	An antiepileptic agent that has been found to reduce body weight in patients with a variety of disorders including epilepsy, bipolar disorder, and binge eating disorder
Zonisamide (trade name Zonegran)	antiepileptic medication that has also been found to reduce body weight in patients.

Surgery is an option in selected patients with morbid obesity (BMI ≥ 40 kg/m2 or between 35 and 40, with major weight related comorbidities) when less invasive methods have failed and the patient is at high risk for obesity associated morbidity or mortality.[7]

POTENTIAL IMPACT OF TECHNOLOGY

a. Clinical Impact

Systematic search was conducted from scientific databases such as Medline, EBM Reviews, EMBASE via OVID, PubMed and from the general search engines [Google Scholar and US Food and Drug Administration (US FDA)] on effectiveness and safety of tirzepatide for the treatment of obesity.

There was only one retrievable published scientific evidence on tirzepatide for the treatment of obesity. Another phase 3 clinical trial called SURMOUNT-2 (NCT04657003) is still on-going.

Efficacy

SURMOUNT-1 (NCT04184622) is a multi-center, randomised, double-blind, parallel, placebo-controlled trial comparing the efficacy and safety of tirzepatide 5 mg, 10 mg and 15 mg to placebo as an adjunct to a reduced-calorie diet and increased physical activity among adults without type 2 diabetes who have obesity, or overweight with at least one of the following comorbidities: hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease. The trial randomised 2,539 participants in a 1:1:1:1 ratio to receive either tirzepatide 5 mg, 10 mg or 15 mg or placebo. The co-primary objectives of the study were to demonstrate that tirzepatide 10 mg and/or 15 mg is superior in percentage of body weight reductions from baseline and percentage of participants achieving ≥5% body weight reduction at 72 weeks compared to placebo. Participants who had pre-diabetes at study commencement will remain enrolled in SURMOUNT-1 for an additional 104 weeks of treatment following the initial 72-week completion date to evaluate the impact on body weight and potential differences in progression to type 2 diabetes at three years of treatment with tirzepatide compared to placebo.[15] All participants in the tirzepatide treatment arms started the study at a dose of tirzepatide 2.5 mg once-weekly and then increased the dose in a step-wise approach at four-week intervals to their final randomised maintenance dose of 5 mg (via a 2.5 mg step), 10 mg (via steps at 2.5 mg, 5 mg and 7.5 mg) or 15 mg (via steps at 2.5 mg, 5 mg, 7.5 mg, 10 mg and 12.5 mg).[15] Baseline characteristics were comparable across all randomised groups, with the mean body weight of 104.8 kg and the mean BMI was 38.0. The trial achieved its primary target as shown in Figure 1. The mean percentage change in weight at week 72 was −15.0% (95% confidence interval [CI]; −15.9 to −14.2) with 5-mg weekly doses of tirzepatide, −19.5% (95% CI; −20.4 to −18.5) with 10-mg doses, and −20.9% (95% CI; −21.8 to −19.9) with 15-mg doses and −3.1% (95% CI; −4.3 to −1.9) with placebo.[15] There were more proportion of participants who achieved weight reduction of 5% or more among different dosage of tirzepatide group 85% (5 mg), 89% (10 mg), and 91% (15 mg) as compared to 35% in placebo group. It showed higher percentage of tirzepatide group who had 20% or more body weight reduction with 50% among 10-mg group and 57% among 15-mg groups as compared with 3% in the placebo group (P<0.001 for all comparisons with placebo).

Figure 1 Effect of Different dosage of Once-Weekly Tirzepatide, as Compared to Placebo, on Body Weight.[15]

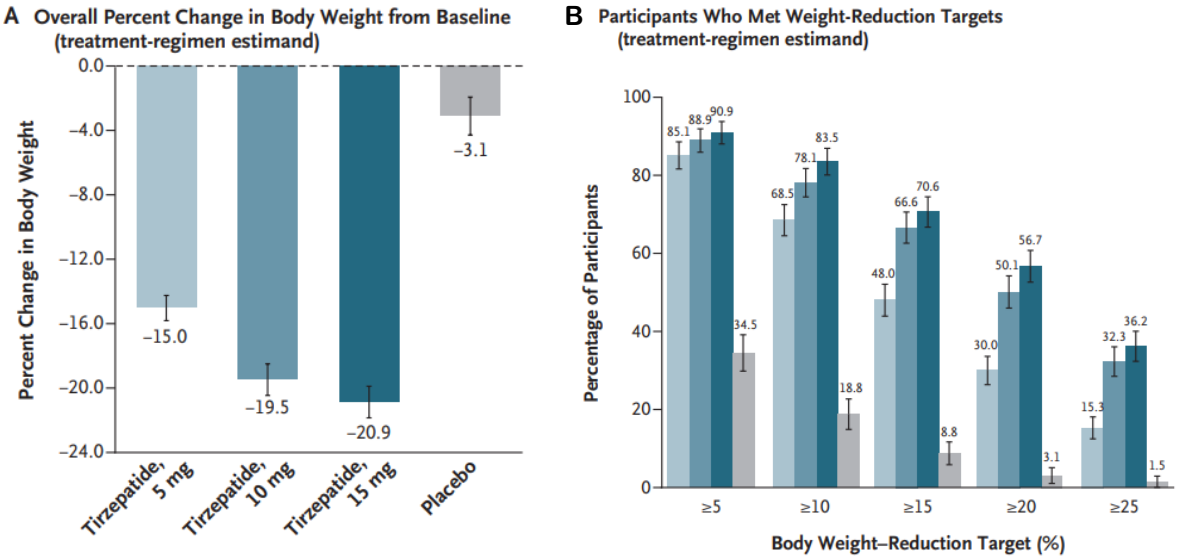

Figure 1 (A) the percent change in body weight from baseline to week 72, derived from an analysis of covariance model for the treatment-regimen estimand (TRE). 1 (B) show the percentages of participants who had weight reductions of at least 5%, 10%, 15%, 20%, and 25% from baseline to week 72. The percentage was calculated with the use of Rubin's rules by combining the percentages of participants who met the target in imputed data sets.

Subanalysis has shown significant change in waist circumference among tirzepatide group with different doses with −14.0 cm (95% CI, -14.9 to -13.1) among 5-mg group, −17.7cm (95% CI, -18.7 to -16.8) among 10-mg group and −18.5cm (95% CI, -19.3 to -17.6) among 15-mg group as compared to −4.0 cm (95% CI, -5.1 to -2.8) in placebo group ($p<0.001$). The mean reduction in total body fat mass was 33.9% with tirzepatide, as compared with 8.2% with placebo, for an estimated treatment difference relative to placebo of −25.7 percentage points (95% CI, −31.4 to −20.0).[15] Additional benefits with tirzepatide were also noted in reduction of systolic blood pressure with −7.2 (−7.8 to −6.7) among pooled tirzepatide group to −1.0 (−2.3 to −0.3) ($p<0.005$) in placebo group; reduction of fasting insulin level with −42.9 (−44.9 to −40.9) in pooled tirzepatide group versus −6.6 (−15.3 to 2.2) in placebo group; and reduction of triglyceride levels with −24.8 (−26.3 to −23.1) in pooled tirzepatide group versus −5.6 (−10.0 to −1.2) in placebo.[15]

b. Cost

There was no retrievable evidence on cost-effectiveness of tirzepatide for the treatment of obesity. However, this medication is already marketed for the treatment of Type 2 Diabetes Mellitus and the price ranges between USD 965 to 1020 (estimated around RM 4534 to 4792; 1USD=4.70RM) in the United States.[16] Institute for Clinical and Economic Review (ICER) has set a health-benefit price benchmark for tirzepatide should ranged between USD 5,500 and 5,700 per year (RM 25844.50 - 26784.30; 1USD=4.70RM).[17] The company has announced that tirzepatide will cost approximately $12,666 per year[18] (RM59517.53; 1 USD=4.70RM).

c. Societal/ethical

There was no retrievable evidence on societal or ethical issue on tirzepatide.

d. Safety

According to SURMOUNT-1 study, the most common adverse events with tirzepatide were gastrointestinal, and most were mild to moderate in severity, occurring primarily during dose escalation. Adverse events caused treatment discontinuation in 4.3%, 7.1%, 6.2%, and 2.6% of participants receiving 5-mg, 10-mg, and 15-mg tirzepatide doses and placebo. The most frequently reported adverse events were gastrointestinal (nausea, diarrhoea, and constipation). These adverse events occurred in more participants in the tirzepatide groups than in the placebo group, were transient and mild to moderate in severity, and occurred primarily during the dose-escalation period Serious adverse events were reported by 160 participants (6.3%) overall. Similar percentages of participants in the tirzepatide and placebo groups reported serious adverse events. No cases of medullary thyroid cancer were reported. Cholecystitis and acute cholecystitis were reported more frequently in the tirzepatide groups than in the placebo group although the incidences were low (≤0.6%).[15]

According to medication guidelines provided by the company, tirzepatide was cautioned to cause serious side effects, including possible thyroid tumors. 19 Thyroid C-cell tumors have been described after 2-years studies in rodents with both liraglutide (once daily) and exenatide (twice daily and once weekly), another different type of GLP-1 receptor agonists.[20] Nevertheless, the causative association between tirzepatide and thyroid tumors called medullary thyroid carcinoma (MTC) in human are still indeterminate.[19]

CONCLUSIONS

In conclusion, limited evidence has shown that tirzepatide has the potential to be used as an adjunct treatment of non-diabetic obesity along with lifestyle modification. Evidence has shown that tirzepatide has tolerable safety profile, however further evaluation is needed to determine the association of tirpezatide with thyroid cancer. Cost-effectiveness study is also recommended before it is widely used in our population.

EVIDENCE

Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide Once Weekly for the Treatment of Obesity. N Engl J Med. 2022;387(3):205-216.

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