Tirzepatide (Mounjaro™)
Monograph

THE OHIO STATE UNIVERSITY HEALTH PLAN

Approval[1]: 2022
Generic (Trade name)[1]: Tirzepatide (Mounjaro™)
Manufacturer[1]: Eli Lilly and Company, LLC
Dosage Form[1]: 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, or 15 mg/0.5mL single-dose pens for subcutaneous injection

FDA-approved Indication[1]:
An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Disease State Background
Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by improper response to endogenous insulin leading to chronically elevated blood glucose levels (hyperglycemia). T2DM is also associated with altered metabolism of protein, lipids, and carbohydrates as well as increased risk of complications from vascular disease.[2,3] It is estimated that more than 37 million people have diabetes and T2DM accounts for 90-95% of all diabetes.[4] T2DM is associated with various modifiable risk factors, such as obesity, older age, certain races/ethnic groups, genetic predisposition, hypertension, dyslipidemia, and lack of physical activity.[2,3] T2DM is mostly diagnosed in patients over 40 years old and this age group accounts for more than 80% of the total patient population with T2DM.[4] The incidence and prevalence of T2DM are generally higher in minority groups.[4] The prevalence of T2DM in these demographic groups can be linked to possible factors such as stationary lifestyle, increased likelihood of comorbidities, lower socioeconomic status, and inherited genetic risk factors.[5]

Although the exact etiology of T2DM is unclear, the development of T2DM is often accompanied by malfunctioning insulin production of pancreatic β-cells and insulin resistance, which describes the decreased insulin sensitivity of tissue cells.[2] T2DM is diagnosed by elevation in one of the following tests: fasting blood glucose reading, 2-hour post-prandial reading, and A1c level.[2,3] Despite the relatively convenient diagnosing procedures, patients with T2DM can go undiagnosed for many years due to its subtle and nonspecific clinical presentations. Alarming symptoms are often associated with complications caused by chronically elevated blood glucose level. Long-term uncontrolled T2DM can cause chronic kidney disease (CKD), vision damage, peripheral vascular disease (i.e. diabetic foot syndrome), coronary artery disease (i.e. myocardial infarction), and cerebrovascular disease (i.e. stroke).[2] As the result, patients with T2DM have a 15% increased risk of all-cause mortality compared with people without diabetes.[5]

Table 1. Current FDA-approved drugs indicated for type 2 diabetes mellitus

Trade Name	Generic	Drug Class	Indication	Route of Administration	Approval
Glucophage	Metformin	Biguanide	T2DM,	Oral	1994
Farxiga	Dapagliflozin	SGLT2 inhibitor	T2DM, CKD, HFrEF	Oral	2014
Ozempic Rybelsus	Semaglutide	GLP-1 agonist	T2DM,	SubQ Oral	2017

Management of type 2 diabetes mellitus
The clinical guidelines developed by the American Diabetes Association are generally used by clinicians as primary source for diagnosis and treatment. The treatment goal is to maintain laboratory values within goal range: fasting glucose reading ≤130 mg/dL, post-prandial glucose reading ≤180 mg/dL, and glycated hemoglobin (A1c) < 7%.[2] The A1c goal can be more or less stringent depending on patient-specific factors,

such as disease duration, age, comorbidities, life expectancy, risk factors for hypoglycemia or drug adverse effects.[2,3] Non-pharmacological lifestyle modification is recommended as part of the first line treatment for patients with T2DM. This includes eating a healthy diet, engaging in regular physical activity, maintaining a healthy body weight, getting regular and sufficient sleep, and tobacco cessation.[6]

A first-line therapy option for T2DM is metformin which decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity.[7] The recommended maintenance dose for metformin is 2000 mg/day if patient tolerated. Second-line add-on therapies may be considered for patients whose A1c is not at goal with metformin and lifestyle modifications alone. The selection of these therapies is largely directed by comorbidities or co-existing risk factors. For patients with high ASCVD risk, heart failure or chronic kidney diseases, either Sodium-glucose Cotransporter-2 (SGLT-2) inhibitors or Glucagon-like Peptide-1 Receptor (GLP-1) agonists are the preferred options. SGLT-2 inhibitors are generally approved to be used in patients with eGFR between 25-45 mL/min/1.73 m^2 with depending on the specific agent.[3] All SGLT-2 inhibitors are contraindicated in patients receiving dialysis.[8] Majority of GLP-1 agonists do not require renal dosing adjustments with the exception of exendin-4 or incretin-mimetic analogs (daily exenatide, weekly exenatide, and lixisenatide).[3] In addition, a recent study found exendin-4 agents have not been able to demonstrate superiority in cardioprotective property compared to human GLP-1 receptor agonists (liraglutide, semaglutide, albiglutide, dulaglutide).[9] Another benefit of these two drug classes is that SGLT-2 inhibitors are weight neutral and GLP-1 agonists can lead to weight loss.[2]

For patients without the comorbidities described above, treatment options will be guided based on patient's preferences and management needs.[3] For patients who require greater glycemic control, GLP-1 agonists, insulin, or a treatment plan containing multiple agents are recommended.[3,7] In patients at higher risk for hypoglycemic, dipeptidyl peptidase-4 (DPP-4) inhibitor, and thiazolidinediones (TZDs) are recommended in addition to SGLT-2 inhibitors, GLP-1 agonists as they are less likely to cause hypoglycemia.[3,7] Lastly, if cost is a major concern, TZDs or sulfonylureas (SUs) are available as multi-brand generics at low prices.[7] Last-line options, include α-glucosidase inhibitors, meglitinides (glinides), bile acid sequestrants, dopamine-2 agonists, and amylin mimetics. These therapies are available as a last resort if patients cannot achieve target A1c goal with the preferred anti-diabetic agents or was unable to tolerate preferable anti-diabetic agents.[2]

Pharmacology[1]

Tirzepatide is a selective GIP receptor and GLP-1 receptor agonist and enhances first- and second-phase insulin secretion, and reduces glucagon levels, both in a glucose-dependent manner. It is a 39-amino-acid modified peptide with a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life.

Dosage and Administration[1]

The recommended starting dosage is 2.5 mg injected subcutaneously once weekly followed by an increase to 5 mg/week after 4 weeks. If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose (max dose: 15 mg/week).
Administer once weekly at any time of day, with or without meals. Inject subcutaneously in the abdomen, thigh, or upper arm. Rotate injection sites with each dose.

Pharmacokinetics[1]

Table 2. Pharmacokinetics of tirzepatide

Parameter	
Onset (minutes)	5 – 10 mins
Vd (L)	~ 10.3 L
T_{max} (hours)	8 – 72 hrs
Metabolism	proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid moiety and amide hydrolysis

Half-life (hours)	~ 120 hrs (5 days)
Vd: volume of distribution; C_{max}: maximum concentration at steady state; T_{max}: time to maximum concentration; AUC: area under the curve	

Adverse reactions[1]

Table 3. Adverse reactions of tirzepatide

Adverse Reactions Observed in ≥5% of Patients Treated with Tirzepatide				
Adverse Reaction	Placebo (N=235) n (%)	5 mg (N=237) n (%)	10 mg (N=240) n (%)	15 mg (N=241) n (%)
Nausea	4	12	15	18
Diarrhea	9	12	13	17
Decreased Appetite	1	5	10	11
Vomiting	2	5	5	9
Constipation	1	6	6	7
Dyspepsia	3	8	8	5
Abdominal Pain	4	6	5	5
Sinus Tachycardia*	4.3	4.6	5.9	10
N: number of patients; n: number of patients experiencing the event *Concomitant increase from baseline in HR of ≥15 beats/min				

Hypoglycemia Adverse Reactions				
	Placebo (N=235) n (%)	5 mg (N=237) n (%)	10 mg (N=240) n (%)	15 mg (N=241) n (%)
Monotherapy				
(40 weeks)	N=115	N=121	N=119	N=120
Blood glucose <54 mg/dL	1	0	0	0
Severe hypoglycemia*	0	0	0	0
Add-on to Basal Insulin with or without Metformin				
(40 weeks)	N=120	N=116	N=119	N=120
Blood glucose <54 mg/dL	13	16	19	14
Severe hypoglycemia*	0	0	2	1
N: number of patients; n: number of patients experiencing the event * Episodes requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.				

Other Adverse Reactions[1]		
	Placebo n (%)	Tirzepatide n (%)
Hypersensitivity Reaction*	1.7	3.2
Injection Site Reaction	0.4	3.2
Acute Gallbladder Disease**	0	0.6
* Urticaria and eczema ** Cholelithiasis, biliary colic and cholecystectomy		

Contraindications[1]

Tirzepatide is contraindicated in patients with:

- A personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- Known serious hypersensitivity to tirzepatide or any of the excipients in tirzepatide

Warnings and Precautions[1]

Pancreatitis

Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected.

Hypoglycemia with concomitant use of insulin secretagogues or insulin

Concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing dose of insulin secretagogue or insulin may be necessary.

Hypersensitivity Reactions

Hypersensitivity reactions have been reported. Discontinue tirzepatide if suspected.

Acute Kidney Injury

Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions.

Severe Gastrointestinal Disease

Use may be associated with gastrointestinal adverse reactions, sometimes severe. Has not been studied in patients with severe gastrointestinal disease and is not recommended in these patients.

Diabetic retinopathy complications in patients with a history of diabetic retinopathy

Has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Monitor patients with a history of diabetic retinopathy for progression.

Acute Gallbladder Disease

Has occurred in clinical trials. If cholelithiasis is suspected, gallbladder studies and clinical follow-up are indicated.

Drug Abuse and Dependence[1]

No clinically significant risks for abuse or dependence

Drug Interactions[1]

Tirzepatide delays gastric emptying and has the potential to impact the absorption of concomitantly administered oral medications. Use of tirzepatide in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may increase risk of hypoglycemia, including severe hypoglycemic events.

Table 4. Clinically Important Drug Interactions with tirzepatide

	Clinical Impact	Intervention
Oral hormonal contraceptives	Tirzepatide may decrease the serum concentration of Hormonal Contraceptives.	Patients should switch to a non-oral contraceptive method, or add a barrier method of contraception, for 4 weeks after initiation of tirzepatide and for 4 weeks after each dose escalation of tirzepatide.

Insulins	May enhance the hypoglycemic effect of Insulins.	Consider insulin dose reductions when used in combination with tirzepatide.
Sulfonylureas	May enhance the hypoglycemic effect of Sulfonylureas.	Consider sulfonylurea dose reductions when used in combination with tirzepatide.
Sincalide	May diminish the therapeutic effect of Sincalide due to effects on gallbladder function.	Consider discontinuing tirzepatide that may affect gallbladder motility prior to the use of sincalide to stimulate gallbladder contraction.

Hepatic Impairment[1]
No dosage adjustment of tirzepatide is recommended for patients with hepatic impairment.

Renal Impairment[1]
No dosage adjustment of tirzepatide is recommended for patients with renal impairment. Monitoring of renal function is advised when initiating or escalating doses of tirzepatide in patients with renal impairment due to increased risk of severe adverse gastrointestinal reactions.

Pregnancy and Lactation[1]
There are insufficient available data with tirzepatide use in pregnant women evaluate for a drug-related risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy. Based on animal reproduction studies, there may be risks to the fetus from exposure to tirzepatide during pregnancy. In both pregnant rats and rabbits, fetal growth reductions and fetal abnormalities were observed when tirzepatide was administered at clinically relevant exposures based on AUC during organogenesis. These adverse embryo/fetal effects in animals coincided with pharmacological effects on decreased maternal weight and food consumption.

There are no data on the presence of tirzepatide in animal or human milk, the effects on the breastfed infant, or the effects on milk production.

Pediatric Use[1]
Safety and effectiveness of tirzepatide have not been established in pediatric patients (younger than 18 years of age).

Geriatric Use[1]
No overall differences in safety or efficacy were detected between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
Number of geriatric patients included in clinical trials: 1539 (30.1%) tirzepatide-treated patients were 65 years of age or older, and 212 (4.1%) tirzepatide-treated patients were 75 years of age or older at baseline.

Carcinogenesis, Mutagenesis, Impairment of Fertility[1]
In a 2-year carcinogenicity animal study in male and female rats, doses of 0.15, 0.5, and 1.5 mg/kg (0.1-, 0.4-, and 1-fold the maximum human recommended dose (MRHD) of 15 mg once weekly based on AUC) were administered by subcutaneous injection twice weekly. Statistically significant increase in thyroid C-cell adenomas was observed in males (≥0.5 mg/kg) and females (≥0.15 mg/kg), and a statistically significant increase in thyroid C-cell adenomas and carcinomas combined was observed in males and females at all doses examined. In a 6-month carcinogenicity study in rasH2 transgenic mice, tirzepatide at doses of 1, 3, and 10 mg/kg administered by subcutaneous injection twice weekly was not tumorigenic.

Tirzepatide was not genotoxic in a rat bone marrow micronucleus assay.

In fertility and early embryonic development studies, male and female rats were administered 0.3-, 1-, and 2-fold and 0.3-, 0.9-, and 2-fold, respectively, the MRHD of 15 mg once weekly based on AUC. In male rats, no effects of tirzepatide were observed on sperm morphology, mating, fertility, and conception. In female rats, an increase in the number of females with prolonged diestrus and a decrease in the mean number of corpora lutea resulting in a decrease in the mean number of implantation sites and viable embryos was observed at all dose levels. These effects were considered secondary to the pharmacological effects of tirzepatide on food consumption and body weight.

Efficacy

Study 1 (SURPASS-1)

SURPASS-1 is a randomized, double-blind, placebo-controlled, phase 3 trial conducted to evaluate the efficacy of tirzepatide in improving glycemic control in adults with inadequately controlled T2DM. Patients were included if they were naïve to injectable diabetic therapy, had a level of HbA1c between 7.0% - 9.5% at screening, body mass index (BMI) ≥ 23 kg/m^2, stable weight (no change outside of 5%) during the previous 3 months and agreed not to attempt weight loss. Patients who were excluded if they met one of the following criteria: T1DM, history of pancreatitis, history of proliferative diabetic retinopathy, diabetic maculopathy, or non-proliferative diabetic retinopathy that requires acute treatment, eGFR<30 mL/min/1.73m^2, use of any oral antihyperglycemic medication for 3 months before screening. After the initial 3-week of screening and lead-in phase, 478 patients were randomly assigned via computer-generated random sequence into one of the 4 treatment groups: 5 mg, 10 mg, 15 mg, and placebo (n=121, 121, 120, and 113, respectively) in a double-blind fashion and received weekly injections. Participants in the 3 tirzepatide treatment groups followed a slow dose escalation regimen fixed at 2.5 mg-dose increments of tirzepatide every 4 weeks until the desired maintenance dose was reached. Therefore, the maintenance doses of 5, 10, and 15 mg were achieved at weeks 4, 12, and 20, respectively.

The primary endpoint was the mean change from baseline in hemoglobin A1c (HbA1c) level at week 40, the end of trial. The secondary endpoints were mean change from baseline in fasting serum glucose (FSG), mean change from baseline in bodyweight and proportion of participants with HbA1c < 7.0%, ≤6.5% or <5.7%. All primary and secondary outcome markers exhibited statistically significant reduction in hyperglycemic readings compared to baseline readings in all tirzepatide groups. In addition, meaningful body weight reductions were also observed in all tirzepatide groups. These results indicated both statistically and clinically significant efficacy of tirzepatide in comparison to placebo for controlling T2DM in adult patients. The most frequent adverse events with tirzepatide were mild to moderate gastrointestinal adverse events. Injection-site reactions were reported by 2-3% of patients in tirzepatide groups compared to none in placebo group. And hypoglycemic events with BG <70 mg/dL were reported in 6-7% of patients in tirzepatide groups and only 1% of placebo group. Patients were followed for another 4 weeks for safety monitoring.

Study 2 (SURPASS-5)

In the same vein of SURPASS-1 trial, SURPASS-5 trial followed a similar study design protocol. Adult patients with uncontrolled T2DM were included if they had a baseline HbA1c of 7.0% – 10.5%, BMI ≥ 23 kg/m^2, were receiving stable doses of once-daily insulin glargine (>20 IU/day or >0.25 IU/kg/day) with or without metformin (≥1500 mg/day), and stable weight (no change outside of 5%) during the previous 3 months with agreement to not initiate attempts to lose weight other than those for diabetes treatment. Patients were excluded if they had T1DM, history of pancreatitis, non-proliferative diabetic retinopathy, diabetic maculopathy, hepatitis, hypoglycemia unawareness, gastroparesis, eGFR<30 mL/min/1.73m^2, or used of any

oral antihyperglycemic medication for 3 months before screening. After the initial 3-week of screening and lead-in phase, 475 patients who were on long-term insulin glargine with or without metformin were randomly assigned into one of the 4 treatment groups: 5 mg, 10 mg, 15 mg, and placebo (n=116, 119, 120, and 120, respectively) by a computer-generated random sequence using an interactive web response system. The study was conducted as a double-blind trial. All patients went through a stabilization period during the first 4 weeks after randomization with restricted insulin dose adjustments to ensure safety and minimize hypoglycemic risk. Following the initial stabilization period, patients entered the treatment period in which a titration schedule was followed until the desired maintenance dose was reached. The maintenance period was estimated to be weeks 24 to 40.

Primary outcome endpoint was the mean change from baseline in hemoglobin A1c (HbA1c) level at week 40, same as in SURPASS-1 trial. The secondary endpoints were also similar, including mean change from baseline in fasting serum glucose (FSG), mean change from baseline in bodyweight and proportion of participants with HbA1c < 7.0%, ≤6.5% or <5.7%. The results echoed the conclusion of SURPASS-1 trial and all primary and secondary outcomes markers showed both statistically and clinically significant results in glycemic control. Significant body weight reductions were also observed across all tirzepatide treatment groups. These results further supported the efficacy of tirzepatide in patients with more advanced T2DM. Adverse events were reported at a similar rate by all groups with the most frequent adverse event being gastrointestinal events in tirzepatide groups. Injection-site reactions were reported by 2.5-6.7% of patients in tirzepatide groups compared with 0.8% in placebo group. And incidence of severe hypoglycemia with BG<54 mg/dL were reported by 14.2-19.3% in the tirzepatide groups compared with 12.5% in the placebo group. Incidence rates of moderate hypoglycemia with BG<70 mg/dL were similar across all groups. And participants were followed for another 4 weeks to ensure their safety.

Tirzepatide (Mounjaro™)
Monograph

THE OHIO STATE UNIVERSITY HEALTH PLAN

<table>
<tr><th>Trial</th><th>Arms</th><th>N</th><th>Duration</th><th>Eligibility</th><th>Design and Demographics</th><th>Endpoints</th><th>Results</th></tr>
<tr>
<td>Rosenstock J, et al. [10]

Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): A double-blind, randomized, phase 3 trial</td>
<td>• Placebo (n=113)
• Tirzepatide 5 mg (n=121)
• Tirzepatide 10 mg (n=121)
• Tirzepatide 15 mg (n=120)

Modified intend-to-treat population</td>
<td>478</td>
<td>40-week study period

4-week safety follow-up period</td>
<td>Inclusion:
• ≥18 yrs
• Inadequate T2DM control with diet and exercise alone
• Naïve to injectable diabetic therapy
• HbA1c of 7.0% - 9.5% at screening
• Body mass index (BMI) ≥ 23 kg/m^2
• Stable weight (no change outside of 5%) during the previous 3 months and agreed not to attempt weight loss
Exclusion:
• T1DM
• History of pancreatitis
• History of proliferative diabetic retinopathy, diabetic maculopathy, or non-proliferative diabetic retinopathy that requires acute treatment
• eGFR<30 mL/min/1.73m^2
• Use of any oral antihyperglycemic medication for 3 months before screening</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, parallel group phase 3 trial

Baseline demographics
• Mean age: 54.1 years old
• Mean duration of T2DM: 4.7 years
• Women: 48% (40% in 10 mg group)
• Caucasian: 36%
• Asian: 35%
• American Indian/ Alaska Native: 25%
• Black: 5%
• Hispanic/Latino: 43%</td>
<td>Primary endpoint:
• Mean change from baseline in HbA1c at 40 weeks

Key secondary endpoints:
• Mean change from baseline in fasting serum glucose (FSG)
• Mean change from baseline in bodyweight
• Proportion of participants with HbA1c < 7.0% or <5.7%</td>
<td>
<table>
<tr><th colspan="5">Primary Outcome*</th></tr>
<tr><td></td><td>5 mg (n=121)</td><td>10 mg (n=121)</td><td>15 mg (n=120)</td><td>Placebo (n=113)</td></tr>
<tr><td>HbA1c (%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Baseline (mean)</td><td>8.0</td><td>7.9</td><td>7.9</td><td>8.1</td></tr>
<tr><td>Change at week 40</td><td>-1.87</td><td>-1.89</td><td>-2.07</td><td>0.04 (p=0.72)</td></tr>
<tr><th colspan="5">Key Secondary Outcomes*</th></tr>
<tr><td>FSG (mg/dL)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Baseline (mean)</td><td>154</td><td>153</td><td>154</td><td>155</td></tr>
<tr><td>Change at week 40</td><td>-43.6</td><td>-45.9</td><td>-49.3</td><td>12.9 (p=0.0014)</td></tr>
<tr><td>Body weight (kg)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Baseline (mean)</td><td>87.0</td><td>86.2</td><td>85.5</td><td>84.5</td></tr>
<tr><td>Change at week 40</td><td>-7.0</td><td>-7.8</td><td>-9.5</td><td>-0.7 (p=0.22)</td></tr>
<tr><td>Number of participants reaching HbA1c<7.0%</td><td>105 (n=87%)</td><td>108 (n=92%)</td><td>102 (n=88%)</td><td>22 (n=19%)</td></tr>
<tr><td>Number of participants reaching HbA1c≤6.5%</td><td>99 (n=82%)</td><td>96 (n=81%)</td><td>100 (n=86%)</td><td>11 (n=10%)</td></tr>
<tr><td>Number of participants reaching HbA1c<5.7%</td><td>41 (n=34%)</td><td>36 (n=31%)</td><td>60 (n=52%)</td><td>1 (n=1%)</td></tr>
<tr><td colspan="5">*p value <0.001 unless specifically noted</td></tr>
</table>

Conclusion:
In conclusion, tirzepatide once a week administration at all doses showed robust reductions compared with placebo in glycemic markers and meaningful body weight reductions in patients with T2DM with diet and exercise alone. Tirzepatide resulted in robust reductions in HbA1c, fasting serum glucose levels, as well as patient-recorded self-monitoring of blood glucose levels.
</td>
</tr>
<tr>
<td>Limitations</td>
<td colspan="7">• Relatively shorty duration of trial (40 weeks) to see full weight loss effects
• Self-reported gastrointestinal adverse events: can lead to over- or under-estimation of true treatment-related adverse events
• Black or African American patient population was significantly underrepresented considering the prevalence of T2DM in this population
• Relatively small study population (N=478)</td>
</tr>
</table>

Last reviewed: [06/28/2022]

Tirzepatide (Mounjaro™)
Monograph

THE OHIO STATE UNIVERSITY HEALTH PLAN

Trial	Arms	N	Duration	Eligibility	Design and Demographics	Endpoints	Results
Dahl D, et al.[11] Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients with Type 2 Diabetes The SURPASS-5 Randomized Clinical Trial	• Placebo (n=120) • Tirzepatide 5 mg (n=116) • Tirzepatide 10 mg (n=119) • Tirzepatide 15 mg (n=120) Modified intend-to-treat population	475	4-week insulin stabilization period 36-week insulin titration period 4-week safety follow-up	Inclusion: • ≥18 yrs with T2DM • Baseline HbA1c of 7.0% – 10.5% • BMI ≥ 23 kg/m^2 • Receiving stable doses of once-daily insulin glargine (>20 IU/day or >0.25 IU/kg/day) with or without metformin (≥1500 mg/day) • Stable weight (no change outside of 5%) during the previous 3 months with agreement to not initiate attempts to lose weight other than those for diabetes treatment Exclusion: • T1DM • History of pancreatitis • Non-proliferative diabetic retinopathy • Diabetic maculopathy • Hepatitis • Hypoglycemia unawareness • Gastroparesis • eGFR<30 mL/min/1.73m^2 • Use of any oral antihyperglycemic medication for 3 months before screening	Multicenter, randomized, double-blind, placebo-controlled phase 3 trial Baseline demographics: • Mean age: 61 years old • Mean BMI: 33.4 kg/m^2 • Mean duration of T2DM: 13.3 years • Mean HbA1c: 8.31% • Median insulin glargine dose: 30.0 IU/day • Metformin use: 82.9% • Women: 44% (39% in 10 mg group) • Caucasian: 80% • Asian: 18% • American Indian/ Alaska Native: 0.4% • Black: 1% • Hispanic/ Latino: 5%	Primary endpoint: • Mean change from baseline in HbA1c at week 40 Secondary endpoints: • Proportion of patients with HbA1c <7.0%, ≤6.5%, or <5.7% • Mean change from baseline in fasting serum glucose (FSB) • Mean change from baseline in body weight • Mean change from baseline in daily insulin glargine dose	**Primary Outcome*** **Key Secondary Outcomes***

	5 mg (n=116)	10 mg (n=119)	15 mg (n=120)	Placebo (n=120)
HbA1c (%)				
Baseline (mean)	8.30	8.36	8.22	8.38
Change at week 40	-2.11	-2.40	-2.34	-0.86
FSG (mg/dL)				
Baseline (mean)	162.9	162.6	160.4	164.4
Change at week 40	-58.2	-64.0	-62.6	-39.2
Body weight (kg)				
Baseline (mean)	95.8	94.6	96.0	94.2
Change at week 40	-5.4	-7.5	-8.8	1.6
Number of participants reaching HbA1c<7.0%	101 (n=87%)	106 (n=90%)	100 (n=85%)	41 (n=35%)
Number of participants reaching HbA1c ≤6.5%	86 (n=74%)	101 (n=86%)	94 (n=80%)	21 (n=17%)
Number of participants reaching HbA1c<5.7%	28 (n=24%)	49 (n=42%)	59 (n=50%)	3 (n=2.7%)

*p value <0.001

Conclusion:
Compared to placebo, the addition of subcutaneous tirzepatide to titrated insulin glargine resulted in statistically significant improvements in glycemic control in patient with inadequately controlled T2DM. Tirzepatide resulted in robust reductions in HbA1c, fasting serum glucose levels, and body weight.

Limitations
- Relatively small patient population (N=475) with only 1% of black/African American patients
- Participants were treated with insulin glargine with or without metformin which cause the results may not be directly extrapolated to other regimens using different oral antihyperglycemic drugs
- Lack of adjustment of insulin dose for the first 4 weeks of treatment may have initially favored patients receiving tirzepatide
- Self-reported gastrointestinal adverse events

Table 5. Glossary of terms used in efficacy tables

Abbreviation	Term
BMI	Body mass index (kg/m^2)
HbA1c	Hemoglobin A1c, also known as glycated hemoglobin
T1DM	Type I diabetes mellitus
T2DM	Type II diabetes mellitus

Pricing and Utilization[12,13,14,15]

Table 6. Pricing for tirzepatide and competitors

	Tirzepatide	Semaglutide (Ozempic/Rybelsus)	Dulaglutide (Trulicity)
Administration	SubQ injection	SubQ injection / Oral	SubQ injection
Dosing (lowest effective dose)	5 mg/week	0.5 mg injection/week or 7 mg tablet/day	0.75 mg/week
Cost per week (AWP)	$263.58	Ozempic: $178.41 Rybelsus: $249.76	$265.97

Efficacy Comparison

SURPASS-2 trial[16] was a phase 3, open-label, non-inferiority trial published in 2021 comparing efficacy of tirzepatide and semaglutide in 1,879 adult patients with T2DM. Patients were randomly assigned to 4 groups: tirzepatide 5 mg, 10 mg, 15 mg, and semaglutide 1 mg. Results were obtained at week 40 with the primary efficacy endpoint being the mean change from baseline in HbA1c. HbA1c was reduced -2.01%, -2.24%, -2.30%, in tirzepatide groups and -1.86% in semaglutide group. As for secondary outcomes, a total of 82%-86% of patients in the tirzepatide groups and 79% of patients in semaglutide group had a HbA1c level <7.0% at the end of trial. The percentage of patients reaching HbA1c goal of ≤6.5% were 69%, 77%, 80% in tirzepatide groups, and 64% in semaglutide group. Whereas patients who were able to reach a level of HbA1c <5.7% were 27%, 40%, 46% in tirzepatide groups, and 19% in semaglutide group. The mean change from baseline in fasting serum glucose (FSB) were reported to be -56.0 mg/dL, -61.6 mg/dL, -63.4 mg/dL in tirzepatide groups, and -48.6 mg/dL in semaglutide group. At week 40, mean body weight reductions are -7.6 kg, -9.3 kg, -11.2 kg in tirzepatide groups, and -1.9 kg in semaglutide group. Based on results obtained at week 40, all three groups of patients on tirzepatide showed slightly greater reduction in HbA1c levels, FSB, and body weight from baseline than semaglutide. Overall, the resulting data was statistically significant and supported therapeutic non-inferiority but did not show significant superiority.

A trial conducted in Japan, the SURPASS J-mono trial was a randomized, double-blind trial comparing the efficacy and safety of tirzepatide and dulaglutide in 636 adult patients with T2DM. Although it has not been officially published yet, the study results are publicly available as of April, 2022.[17]. Patients were randomly assigned to 4 groups: tirzepatide 5 mg, 10 mg, 15 mg, and dulaglutide 0.75 mg. The primary endpoint was the mean change in HbA1c from baseline at week 52. HbA1c was reduced by -2.37%, -2.55%, -2.82% in tirzepatide groups, and -1.29% in dulaglutide group. Secondary outcomes assessed for proportion of patients with HbA1c <7.0% and reported the results to be 93.67%, 96.79%, 99.37% in tirzepatide groups, and 67.30% in dulaglutide groups. Mean change from baseline in fasting serum glucose (FSB) was reported to be -57.9 mg/dL, -64.6 mg/dL, -67.6 mg/dL in tirzepatide groups, and -31.9 mg/dL in dulaglutide group. For reduction in body weight from baseline, -5.8 kg, -8.5 kg, -10.7 kg in tirzepatide groups, and -0.5 kg in dulaglutide group were reported. The data indicates a favorable outcome for all tirzepatide groups in reducing HbA1c, FBS, and body weight from baseline values compared to dulaglutide 0.75 mg. Preliminary conclusion shows superiority of tirzepatide to dulaglutide 0.75 mg. However, no conclusion can be drawn for higher doses of dulaglutide due to lack of data and the study population only included Japanese patients.

Adverse Event Comparison
As SURPASS-2 trial[16] concluded, adverse event profiles were similar across all four groups, tirzepatide 5 mg, 10 mg, 15 mg, and semaglutide 1 mg, with gastrointestinal adverse more prominent than others. These GI adverse events were reported at a similar rate across all treatment groups, including nausea (17.4-22.1%), diarrhea (13.2-16.4%), vomiting (5.7-9.8%) and constipation (4.5-6.8%). Serious adverse events that were observed more in tirzepatide groups included acute cholecystitis, acute myocardial infraction, chest pain, upper abdominal pain, atrial fibrillation, urinary tract infection, severe hypoglycemia, and syncope. These serious adverse events were reported more frequently with 5.3-7.0% of patients in tirzepatide groups compared to 2.8% of patients in semaglutide group. Clinically significant hypoglycemia, which is defined by a blood glucose level <54 mg/dL, was observed in 0.6%, 0.2%, and 1.7% of patients in respective tirzepatide groups compared with 0.4% in semaglutide group. Injection-site reactions were more frequently observed in tirzepatide groups and occurred in 1.9 to 4.5% of the patients, whereas only 0.2% in semaglutide group reported such reactions.

Based on the data from the recently completed SURPASS J-mono trial[17], incidence rates of serious adverse events were similar among all groups with no death in any group. Gastrointestinal adverse events were the predominant adverse events observed in all groups. However, more patients in the tirzepatide groups experienced GI adverse events than dulaglutide group. Nausea was reported in 12.0-20.0% of patients in tirzepatide groups compared with 7.6% in dulaglutide group. Diarrhea was reported in 8.9-17.0% of patients in tirzepatide groups compared with 6.9% in dulaglutide group. Vomiting was reported in 5.1-11.9% of patients in tirzepatide groups compared with 1.3% in dulaglutide group. And lastly, constipation was reported in 13.8-17.7% of patients in tirzepatide groups compared with 10.7% in dulaglutide group. But the injection-site reactions rates were lower in tirzepatide groups (1.3-5.6%) compared with the dulaglutide group (7.6%). Future studies including higher doses of dulaglutide are needed to better compare the safety data of these two drugs.

Summary
Tirzepatide is a novel anti-diabetic agent with two mechanisms of action. It acts as agonist for both GIP and GLP-1 receptors to lower glycemic markers in patients with T2DM. The two clinical trials comparing tirzepatide to placebo demonstrated the effectiveness and safety of tirzepatide in reducing HbA1c, fasting serum glucose, and body weight. SURPASS-1 trial studied tirzepatide as mono therapy against placebo and SURPASS-5 trial studied tirzepatide with the concomitant use of long-acting insulin glargine with or without metformin. Both studies concluded the superiority of tirzepatide in reducing HbA1c, fasting serum glucose, and body weight with no significant safety concerns.

Two additional trials were conducted to compare tirzepatide with two other GLP-1 agonist medications, semaglutide and dulaglutide. Tirzepatide was found to be non-inferior to semaglutide and superior to dulaglutide. However, the trial comparing tirzepatide with semaglutide was unblinded which may increase the risk of the placebo effect. And the trial comparing tirzepatide with dulaglutide was conducted in Japan and only included Japanese/Asian patients. Although the efficacy data of tirzepatide was significant, extrapolation of it to patients of other racial groups may be questionable.

Possible utilization may be seen in patients with T2DM that are nonresponsive to current GLP-1 agonist treatments. And we may likely see tirzepatide used off-label for weight loss. The cost of tirzepatide is similar to dulaglutide and is about $350 more expensive than semaglutide per month.

Recommendation: Non-preferred brand

Rationale: Although tirzepatide is the first dual-MOA agent, current efficacy and safety data only supports its non-inferiority in comparison with semaglutide in managing T2DM in adult patients. Yet tirzepatide was shown to be more effective than dulaglutide. One of the major concerns is the lack of long-term data to support the use of tirzepatide as chronic treatment. Another concern is the potential off-label use for weight loss purposes. Therefore, the placement of a prior authorization is warranted but should include less restrictive criteria to allow optimal access.

RECOMMENDED PRIOR AUTHORIZATION CRITERIA

1. Initial Therapy: Approve for 3 months if the patient meets the following criterion:
    a. Diagnosis of Type 2 diabetes confirmed by patient chart and HbA1c ≥ 6.5%

2. Subsequent Therapy Requests:
    a. Meaningful clinical response endorsed by provider, AND
    b. Provider statement testifying for absence in symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness)

CONDITIONS NOT RECOMMENDED FOR APPROVAL

There is lack of evidence in efficacy or potential safety concerns in using these agents in the following conditions:

1. Treatment of Type 1 diabetes
2. Appetite suppression or treatment of obesity
3. Personal or family history of medullary thyroid carcinoma or personal history of multiple endocrine neoplasia syndrome type 2
4. Pregnancy
5. History of pancreatitis

Prepared by: Haley Sun

Reviewed by: Courtney Reilly, PharmD

References

1. Mounjaro (tirzepatide) [prescribing information]. Lilly USA, LLC.; 2022.
2. Introduction: Standards of Medical Care in Diabetes – 2019. American Diabetes Association. Diabetes Care 2019;42(Suppl. 1): S1–S193. https://doi.org/10.2337/dc19-S001. Accessed June 7, 2022.
3. Standards of Medical Care in Diabetes—2022 Abridged for Primary Care Providers. American Diabetes Association. Clin Diabetes 2022;40(1):10–38. https://doi.org/10.2337/cd22-as01. Accessed June 7, 2022.
4. Division of Diabetes Translation. Centers for Disease Control and Prevention. https://www.cdc.gov/diabetes/index.html. Published June 1, 2022. Accessed June 7, 2022.
5. Galicia-Garcia U, Benito-Vicente A, Jebari S, et al. Pathophysiology of Type 2 Diabetes Mellitus. Int J Mol Sci. 2020;21(17):6275. Published 2020 Aug 30. doi:10.3390/ijms21176275
6. Raveendran AV, Chacko EC, Pappachan JM. Non-pharmacological Treatment Options in the Management of Diabetes Mellitus. Eur Endocrinol. 2018;14(2):31-39. doi:10.17925/EE.2018.14.2.31
7. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes 2020. American Diabetes Association. Diabetes Care 2020;43(Suppl.1):S98–S110. Accessed June 7, 2022.
8. Zanoli L, Granata A, Lentini P, et al. Sodium-glucose linked transporter-2 inhibitors in chronic kidney disease. *ScientificWorldJournal*. 2015; 2015:317507. doi:10.1155/2015/317507
9. Górriz JL, Soler MJ, Navarro-González JF, et al. GLP-1 Receptor Agonists and Diabetic Kidney Disease: A Call of Attention to Nephrologists. *J Clin Med*. 2020;9(4):947. Published 2020 Mar 30. doi:10.3390/jcm9040947
10. Rosenstock J, Wysham C, Frías JP, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (surpass-1): A double-blind, randomised, phase 3 trial. *The Lancet*. 2021;398(10295):143-155. doi:10.1016/s0140-6736(21)01324-6
11. Dahl D, Onishi Y, Norwood P, et al. Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients With Type 2 Diabetes: The SURPASS-5 Randomized Clinical Trial. JAMA. 2022;327(6):534–545. doi:10.1001/jama.2022.0078
12. Tirzepatide. Lexi-Drug. Hudson, OH: Lexicomp. http://online.lexi.com/. Updated date June 3, 2022. Accessed date June 17, 2022.
13. Semaglutide. Lexi-Drug. Hudson, OH: Lexicomp. http://online.lexi.com/. Updated date June 2, 2022. Accessed date June 17, 2022.
14. Dulaglutide. Lexi-Drug. Hudson, OH: Lexicomp. http://online.lexi.com/. Updated date June 2, 2022. Accessed date June 17, 2022.
15. Block J. Eli Lilly's new diabetes drug mounjaro priced below Novo Nordisk's Wegovy (NYSE:LLY). SeekingAlpha. https://seekingalpha.com/news/3841486-eli-lilly-new-diabetes-drug-mounjaro-tirzepatidepriced-below-novo-nordisk-wegovy-semaglutide. Published May 20, 2022. Accessed June 17, 2022.
16. Tirzepatide versus semaglutide once weekly in type 2 diabetes. *New England Journal of Medicine*. 2022;386(7). doi:10.1056/nejmc2114590
17. A Study of Tirzepatide (LY3298176) Compared to Dulaglutide in Participants With Type 2 Diabetes (SURPASS J-mono). ClinicalTrials.gov. Identifier: NCT03861052. Updated April 14, 2022. Accessed June 17, 2022. https://www.clinicaltrials.gov/ct2/show/results/NCT03861052