NEW DRUG APPROVAL

Brand Name	Mounjaro™
Generic Name	tirzepatide
Drug Manufacturer	Eli Lilly and Company

New Drug Approval

FDA approval date: May 13, 2022

Review designation: Priority

Type of review: Type 1 - New Molecular Entity; New Drug Application (NDA): 215866

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Type 2 Diabetes is defined as chronic hyperglycemia resulting from either decreased insulin secretion, impaired insulin action, or both in the absence of Type 1 diabetes (autoimmune destruction of the pancreatic beta cell), Type 3c diabetes (pancreaticogenic diabetes) or other specific type. Classically, type 2 diabetes occurs in the older, obese patients in the setting of strong family histories of diabetes and in association with other components of the metabolic syndrome. Diagnosis is made by (1) an A1c ≥6.5%, (2) a fasting glucose ≥126 mg/dL, (3) a 2h post 75 gm glucose load glucose of ≥200 mg/dL, or (4) a random glucose ≥200 mg/dL with symptoms, confirmed by a repeat or second test. An A1c of ≥6.5%, confirmed by second test, is diagnostic of diabetes. Alternatively, diabetes is diagnosed by two separate fasting glucose tests ≥126 mg/dL; with symptoms, a glucose ≥200 mg/dL confirmed on a separate day by a fasting glucose ≥126 mg/dL; or 2-hour post load glucose ≥200 mg/dL during an oral glucose tolerance test (OGTT). Essential components for diabetes treatment include diabetes self-management education and support, lifestyle interventions, and goal setting; glycemic management; and pharmacologic management of hypertension and hyperlipidemia.

About 10.5% of the U.S population has diabetes, with 85% of these people having type 2 diabetes. In addition, 34.5% of the adult US population has prediabetes. The prevalence of diabetes increases with age, with over 26.8% of those ≥65 years old having type 2 diabetes. Non-Caucasians have a prevalence of type 2 diabetes mellitus that is 2 to 6 times greater than that of Caucasians.

Efficacy

The effectiveness of Mounjaro™ as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus was established in five trials. In these trials, Mounjaro™ was studied as monotherapy (SURPASS-1); as an add-on to metformin, sulfonylureas, and/or sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors) (SURPASS-2, -3, and -4); and in combination with basal insulin with or without metformin (SURPASS-5). In these trials, Mounjaro™ (5 mg, 10 mg, and 15 mg given subcutaneously once weekly) was compared with placebo, semaglutide 1 mg, insulin degludec, and/or insulin glargine.

Monotherapy Use of Mounjaro™ in Adult Patients with Type 2 Diabetes Mellitus-

SURPASS-1 (NCT03954834) was a 40-week double-blind trial that randomized 478 adult patients with type 2 diabetes mellitus with inadequate glycemic control with diet and exercise to Mounjaro™ 5 mg, Mounjaro™ 10 mg, Mounjaro™ 15 mg, or placebo once weekly.

Patients had a mean age of 54 years, and 52% were men. The mean duration of type 2 diabetes mellitus was 4.7 years, and the mean BMI was 32 kg/m2. Overall, 36% were White, 35% were Asian, 25% were American Indians/Alaska Natives, and 5% were Black or African American; 43% identified as Hispanic or Latino ethnicity.

Monotherapy with Mounjaro™ 5 mg, 10 mg and 15 mg once weekly for 40 weeks resulted in a statistically significant reduction in HbA1c compared with placebo (see Table 1.)

Table 1: Results at Week 40 in a Trial of Mounjaro™ as Monotherapy in Adult Patients with Type 2 Diabetes Mellitus with Inadequate Glycemic Control with Diet and Exercise

	Placebo	Mounjaro™ 5 mg	Mounjaro™ 10 mg	Mounjaro™ 15 mg
Modified Intent-to-Treat (mITT) Population (N)[a]	113	121	121	120
HbA1c (%)				
Baseline (mean)	8.1	8.0	7.9	7.9
Change at Week 40[b]	-0.1	-1.8	-1.7	-1.7
Difference from placebo[b] (95% CI)	--	-1.7[c] (-2.0, -1.4)	-1.6[c] (-1.9, -1.3)	-1.6[c] (-1.9, -1.3)
Patients (%) achieving HbA1c <7%[d]	23	82[c]	85[c]	78[c]
Fasting Serum Glucose (mg/dL)				
Baseline (mean)	155	154	153	154
Change at Week 40[b]	4	-40	-40	-39
Difference from placebo[b] (95% CI)	--	-43[c] (-55, -32)	-43[c] (-55, -32)	-42[c] (-54, -30)
Body Weight (kg)				
Baseline (mean)	84.5	87.0	86.2	85.5
Change at Week 40[b]	-1.0	-6.3	-7.0	-7.8
Difference from placebo[b] (95% CI)	--	-5.3[c] (-6.8, -3.9)	-6.0[c] (-7.4, -4.6)	-6.8[c] (-8.3, -5.4)

[a] The modified intent-to-treat population consists of all randomly assigned participants who were exposed to at least 1 dose of study drug. Patients who discontinued study treatment because they did not meet study enrollment criteria were excluded. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 25%, 2%, 3%, and 2% of patients randomized to placebo, Mounjaro™ 5 mg, 10 mg, and 15 mg, respectively. At Week 40 the HbA1c data were missing for 12%, 6%, 7%, and 14% of patients randomized to placebo, Mounjaro™ 5 mg, 10 mg, and 15 mg, respectively. Missing Week 40 data were imputed using placebo-based multiple imputation.

[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

[c] p< 0.001 (two-sided) for superiority vs. placebo, adjusted for multiplicity.

[d] Analyzed using logistic regression adjusted for baseline value and other stratification factors.

Mounjaro™ Use in Combination with Metformin, Sulfonylureas, and/or SGLT2 Inhibitors in Adult Patients with Type 2 Diabetes Mellitus

Add-on to metformin- SURPASS-2 (NCT03987919) was a 40-week open-label trial (double-blind with respect to Mounjaro™ dose assignment) that randomized 1879 adult patients with type 2 diabetes mellitus with inadequate

glycemic control on stable doses of metformin alone to the addition of Mounjaro™ 5 mg, Mounjaro™ 10 mg, or Mounjaro™ 15 mg once weekly or subcutaneous semaglutide 1 mg once weekly.

Patients had a mean age of 57 years and 47% were men. The mean duration of type 2 diabetes mellitus was 8.6 years, and the mean BMI was 34 kg/m2. Overall, 83% were White, 4% were Black or African American, and 1% were Asian; 70% identified as Hispanic or Latino ethnicity.

Treatment with Mounjaro™ 10 mg and 15 mg once weekly for 40 weeks resulted in a statistically significant reduction in HbA1c compared with semaglutide 1 mg once weekly (see Table 2.)

Table 2: Results at Week 40 in a Trial of Mounjaro™ versus Semaglutide 1 mg in Adult Patients with Type 2 Diabetes Mellitus Added to Metformin

	Semaglutide 1 mg	Mounjaro™ 5 mg	Mounjaro™ 10 mg	Mounjaro™ 15 mg
Modified Intent-to-Treat (mITT) Population (N)[a]	468	470	469	469
HbA1c (%)				
Baseline (mean)	8.3	8.3	8.3	8.3
Change at Week 40[b]	-1.9	-2.0	-2.2	-2.3
Difference from semaglutide[b] (95% CI)	--	-0.2[c] (-0.3, -0.0)	-0.4[d] (-0.5, -0.3)	-0.5[d] (-0.6, -0.3)
Patients (%) achieving HbA1c <7%[e]	79	82	86[f]	86[f]
Fasting Serum Glucose (mg/dL)				
Baseline (mean)	171	174	174	172
Change at Week 40[b]	-49	-55	-59	-60
Body Weight (kg)				
Baseline (mean)	93.7	92.5	94.8	93.8
Change at Week 40[b]	-5.7	-7.6	-9.3	-11.2
Difference from semaglutide[b] (95% CI)	--	-1.9[c] (-2.8, -1.0)	-3.6[d] (-4.5, -2.7)	-5.5[d] (-6.4, -4.6)

[a] The modified intent-to-treat population consists of all randomly assigned participants who were exposed to at least 1 dose of study drug. Patients who discontinued study treatment because they did not meet study enrollment criteria were excluded. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 3%, 2%, 1%, and 1% of patients randomized to semaglutide 1 mg, Mounjaro™ 5 mg, 10 mg, and 15 mg, respectively. At Week 40 the HbA1c endpoint was missing for 5%, 4%, 5%, and 5% of patients randomized to semaglutide 1 mg, Mounjaro™ 5 mg, 10 mg, and 15 mg, respectively. Missing Week 40 data were imputed using multiple imputation with retrieved dropout.

[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

[c] $p < 0.05$ (two-sided) for superiority vs. semaglutide, adjusted for multiplicity.

[d] $p < 0.001$ (two-sided) for superiority vs. semaglutide, adjusted for multiplicity.

[e] Analyzed using logistic regression adjusted for baseline value and other stratification factors.

[f] $p < 0.01$ (two-sided) for superiority vs. semaglutide, adjusted for multiplicity.

Add-on to metformin with or without SGLT2 inhibitor

SURPASS-3 (NCT03882970) was a 52-week open-label trial that randomized 1444 adult patients with type 2 diabetes mellitus with inadequate glycemic control on stable doses of metformin with or without SGLT2 inhibitor to the addition of Mounjaro™ 5 mg, Mounjaro™ 10 mg, Mounjaro™ 15 mg once weekly, or insulin degludec 100 units/mL once daily. In this trial, 32% of patients were on SGLT2 inhibitor. Insulin degludec was initiated at 10 units once daily

and adjusted weekly throughout the trial using a treat-to-target algorithm based on self-measured fasting blood glucose values. At Week 52, 26% of patients randomized to insulin degludec achieved the fasting serum glucose target of < 90 mg/dL, and the mean daily insulin degludec dose was 49 U (0.5 U per kilogram).
Patients had a mean age of 57 years, and 56% were men. The mean duration of type 2 diabetes mellitus was 8.4 years, and the mean baseline BMI was 34 kg/m2. Overall, 91% were White, 3% were Black or African American, and 5% were Asian; 29% identified as Hispanic or Latino ethnicity.

Treatment with Mounjaro™ 10 mg and 15 mg once weekly for 52 weeks resulted in a statistically significant reduction in HbA1c compared with daily insulin degludec (see Table 3).

Table 3: Results at Week 52 in a Trial of Mounjaro™ versus Insulin Degludec in Adult Patients with Type 2 Diabetes Mellitus Added to Metformin with or without SGLT2 Inhibitor

	Insulin Degludec	Mounjaro™ 5 mg	Mounjaro™ 10 mg	Mounjaro™ 15 mg
Modified Intent-to-Treat (mITT)[a] Population (N)	359	358	360	358
HbA1c (%)				
Baseline (mean)	8.1	8.2	8.2	8.2
Change at Week 52[b]	-1.3	-1.9	-2.0	-2.1
Difference from insulin degludec[b] (95% CI)	--	-0.6[c] (-0.7, -0.5)	-0.8[c] (-0.9, -0.6)	-0.9[c] (-1.0, -0.7)
Patients (%) achieving HbA1c <7%[d]	58	79[c]	82[c]	83[c]
Fasting Serum Glucose (mg/dL)				
Baseline (mean)	167	172	170	168
Change at Week 52[b]	-51	-47	-50	-54
Body Weight (kg)				
Baseline (mean)	94.0	94.4	93.8	94.9
Change at Week 52[b]	1.9	-7.0	-9.6	-11.3
Difference from insulin degludec[b] (95% CI)	--	-8.9[c] (-10.0, -7.8)	-11.5[c] (-12.6, -10.4)	-13.2[c] (-14.3, -12.1)

[a] The modified intent-to-treat population consists of all randomly assigned participants who were exposed to at least 1 dose of study drug. Patients who discontinued study treatment because they did not meet study enrollment criteria were excluded. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 1%,1%, 1%, and 2% of patients randomized to insulin degludec, Mounjaro™ 5 mg, 10 mg, and 15 mg, respectively. At Week 52 the HbA1c endpoint was missing for 9%, 6%, 10%, and 5% of patients randomized to insulin degludec, Mounjaro™ 5 mg, 10 mg, and 15 mg, respectively. Missing Week 52 data were imputed using multiple imputation with retrieved dropout.
[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.
[c] p< 0.001 (two-sided) for superiority vs. insulin degludec, adjusted for multiplicity.
[d] Analyzed using logistic regression adjusted for baseline value and other stratification factors.

Add-on to 1-3 oral anti-hyperglycemic agents (metformin, sulfonylurea or SGLT-2 inhibitor)-

SURPASS-4 (NCT03730662) was a 104-week open-label trial (52-week primary endpoint) that randomized 2002 adult patients with type 2 diabetes mellitus with increased cardiovascular risk to Mounjaro™ 5 mg, Mounjaro™ 10 mg, Mounjaro™ 15 mg once weekly, or insulin glargine 100 units/mL once daily (1:1:1:3 ratio) on a background of metformin (95%) and/or sulfonylureas (54%) and/or SGLT2 inhibitors (25%).

Patients had a mean age of 64 years, and 63% were men. The mean duration of type 2 diabetes mellitus was 11.8 years, and the mean baseline BMI was 33 kg/m^2. Overall, 82% were White, 4% were Black or African American, and 4% were Asian; 48% identified as Hispanic or Latino ethnicity. Across all treatment groups, 87% had a history of cardiovascular disease. At baseline, eGFR was ≥90 mL/min/1.73 m^2 in 43%, 60 to 90 mL/min/1.73 m^2 in 40%, 45 to 60 mL/min/1.73 m^2 in 10%, and 30 to 45 mL/min/1.73 m^2 in 6% of patients.

Insulin glargine was initiated at 10 U once daily and adjusted weekly throughout the trial using a treat-to-target algorithm based on self-measured fasting blood glucose values. At Week 52, 30% of patients randomized to insulin glargine achieved the fasting serum glucose target of < 100 mg/dL, and the mean daily insulin glargine dose was 44 U (0.5 U per kilogram).

Treatment with Mounjaro™ 10 mg and 15 mg once weekly for 52 weeks resulted in a statistically significant reduction in HbA1c compared with insulin glargine once daily (see Table 4).

Table 4: Results at Week 52 in a Trial of Mounjaro™ versus Insulin Glargine in Adult Patients with Type 2 Diabetes Mellitus Added to Metformin and/or Sulfonylurea and/or SGLT2 Inhibitor

	Insulin Glargine	Mounjaro™ 5 mg	Mounjaro™ 10 mg	Mounjaro™ 15 mg
Modified Intent-to-Treat (mITT) Population (N)[a]	998	328	326	337
HbA1c (%)				
Baseline (mean)	8.5	8.5	8.6	8.5
Change at Week 52[b]	-1.4	-2.1	-2.3	-2.4
Difference from insulin glargine[b] (95% CI)	--	-0.7[c] (-0.9, -0.6)	-0.9[c] (-1.1, -0.8)	-1.0[c] (-1.2, -0.9)
Patients (%) achieving HbA1c <7%[d]	49	75[c]	83[c]	85[c]
Fasting Serum Glucose (mg/dL)				
Baseline (mean)	168	172	176	174
Change at Week 52[b]	-49	-44	-50	-55
Body Weight (kg)				
Baseline (mean)	90.2	90.3	90.6	90.0
Change at Week 52[b]	1.7	-6.4	-8.9	-10.6
Difference from insulin glargine[b] (95% CI)	--	-8.1[c] (-8.9, -7.3)	-10.6[c] (-11.4, -9.8)	-12.2[c] (-13.0, -11.5)

[a] The modified intent-to-treat population consists of all randomly assigned participants who were exposed to at least 1 dose of study drug. Patients who discontinued study treatment because they did not meet study enrollment criteria were excluded. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 1%, 0%, 0%, and 1% of patients randomized to insulin glargine, Mounjaro™ 5 mg, 10 mg, and 15 mg, respectively. At Week 52 the HbA1c endpoint was missing for 9%, 9%, 6%, and 4% of patients randomized to insulin glargine, Mounjaro™ 5 mg, 10 mg, and 15 mg, respectively. Missing Week 52 data were imputed using multiple imputation with retrieved dropout.

[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

[c] p< 0.001 (two-sided) for superiority vs. insulin glargine, adjusted for multiplicity.

[d] Analyzed using logistic regression adjusted for baseline value and other stratification factors.

Mounjaro™ Use in Combination with Basal Insulin with or without Metformin in Adult Patients with Type 2 Diabetes Mellitus

SURPASS-5 (NCT04039503) was a 40-week double-blind trial that randomized 475 patients with type 2 diabetes mellitus with inadequate glycemic control on insulin glargine 100 units/mL, with or without metformin, to Mounjaro™ 5 mg, Mounjaro™ 10 mg, Mounjaro™ 15 mg once weekly, or placebo. The dose of background insulin glargine was adjusted using a treat-to-target algorithm based on self-measured fasting blood glucose values, targeting < 100 mg/dL.

Patients had a mean age of 61 years, and 56% were men. The mean duration of type 2 diabetes mellitus was 13.3 years, and the mean baseline BMI was 33 kg/m2. Overall, 80% were White, 1% were Black or African American, and 18% were Asian; 5% identified as Hispanic or Latino ethnicity.

The mean dose of insulin glargine at baseline was 34, 32, 35, and 33 units/day for patients receiving Mounjaro™ 5 mg, 10 mg, 15 mg, and placebo, respectively. At randomization, the initial insulin glargine dose in patients with HbA1c ≤8.0% was reduced by 20%. At week 40, mean dose of insulin glargine was 38, 36, 29, and 59 units/day for patients receiving Mounjaro™ 5 mg, 10 mg, 15 mg, and placebo, respectively.

Treatment with Mounjaro™ 5 mg once weekly, 10 mg once weekly and 15 mg once weekly for 40 weeks resulted in a statistically significant reduction in HbA1c compared with placebo (see Table 5).

Table 5: Results at Week 40 in a Trial of Mounjaro™ Added to Basal Insulin with or without Metformin in Adult Patients with Type 2 Diabetes Mellitus

	Placebo	Mounjaro™ 5 mg	Mounjaro™ 10 mg	Mounjaro™ 15 mg
Modified Intent-to-Treat (mITT) Population (N)[a]	119	116	118	118
HbA1c (%)				
Baseline (mean)	8.4	8.3	8.4	8.2
Change at Week 40[b]	-0.9	-2.1	-2.4	-2.3
Difference from placebo[b] (95% CI)	--	-1.2[c] (-1.5, -1.0)	-1.5[c] (-1.8, -1.3)	-1.5[c] (-1.7, -1.2)
Patients (%) achieving HbA1c <7%[d]	35	87[c]	90[c]	85[c]
Fasting Serum Glucose (mg/dL)				
Baseline (mean)	164	163	163	160
Change at Week 40[b]	-39	-58	-64	-63
Difference from placebo[b] (95% CI)	--	-19[c] (-27, -11)	-25[c] (-32, -17)	-23[c] (-31, -16)
Body Weight (kg)				
Baseline (mean)	94.2	95.8	94.6	96.0
Change at Week 40[b]	1.6	-5.4	-7.5	-8.8
Difference from placebo[b] (95% CI)	--	-7.1[c] (-8.7, -5.4)	-9.1[c] (-10.7, -7.5)	-10.5[c] (-12.1, -8.8)

[a] The modified intent-to-treat population consists of all randomly assigned participants who were exposed to at least 1 dose of study drug. Patients who discontinued study treatment because they did not meet study enrollment criteria were excluded. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 4%, 1%, 0%, and 1% of patients randomized to placebo, Mounjaro™ 5 mg, 10 mg, and 15 mg, respectively. At Week 40 the HbA1c endpoint was missing for 2%, 6%, 3%, and 7% of patients randomized to placebo, Mounjaro™ 5 mg, 10 mg, and 15 mg, respectively. Missing Week 40 data were imputed using placebo-based multiple imputation.

[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

[c] $p < 0.001$ (two-sided) for superiority vs. placebo, adjusted for multiplicity.

[d] Analyzed using logistic regression adjusted for baseline value and other stratification factors.

Safety

ADVERSE EVENTS

The following gastrointestinal adverse reactions were reported more frequently in Mounjaro™-treated patients than placebo-treated patients (frequencies listed, respectively, as: placebo; 5 mg; 10 mg; 15 mg): eructation (0.4%, 3.0%, 2.5%, 3.3%), flatulence (0%, 1.3%, 2.5%, 2.9%), gastroesophageal reflux disease (0.4%, 1.7%, 2.5%, 1.7%), abdominal distension (0.4%, 0.4%, 2.9%, 0.8%).

Hypoglycemia was more frequent when Mounjaro™ was used in combination with a in a clinical trial up to 104 weeks of treatment, when administered with a sulfonylurea, hypoglycemia (glucose level <54 mg/dL) occurred in 13.8%, 9.9%, and 12.8%, and severe hypoglycemia occurred in 0.5%, 0%, and 0.6% of patients treated with Mounjaro™ 5 mg, 10 mg, and 15 mg, respectively.

In the pool of placebo-controlled trials, treatment with Mounjaro™ resulted in a mean increase in heart rate of 2 to 4 beats per minute compared to a mean increase of 1 beat per minute in placebo-treated patients. Episodes of sinus tachycardia, associated with a concomitant increase from baseline in heart rate of ≥15 beats per minute, also were reported in 4.3%, 4.6%, 5.9% and 10% of subjects treated with placebo, Mounjaro™ 5 mg, 10 mg, and 15 mg, respectively. For patients enrolled in Japan, these episodes were reported in 7% (3/43), 7.1% (3/42), 9.3% (4/43), and 23% (10/43) of patients treated with placebo, Mounjaro™ 5 mg, 10 mg, and 15 mg, respectively. The clinical relevance of heart rate increases is uncertain.

Hypersensitivity reactions have been reported with Mounjaro™ in the pool of placebo-controlled trials, sometimes severe (e.g., urticaria and eczema); hypersensitivity reactions were reported in 3.2% of Mounjaro™-treated patients compared to 1.7% of placebo-treated patients.

In the pool of placebo-controlled clinical trials, acute gallbladder disease (cholelithiasis, biliary colic and cholecystectomy) was reported by 0.6% of Mounjaro™-treated patients and 0% of placebo-treated patients.

In the pool of placebo-controlled clinical trials, treatment with Mounjaro™ resulted in mean increases from baseline in serum pancreatic amylase concentrations of 33% to 38% and serum lipase concentrations of 31% to 42%.

WARNINGS & PRECAUTIONS

Risk of Thyroid C-Cell Tumors

In both sexes of rats, tirzepatide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) in a 2-year study at clinically relevant plasma exposures. It is unknown whether Mounjaro™ causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined. Mounjaro™ is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of Mounjaro™ and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

Pancreatitis

Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists. In clinical studies, 14 events of acute pancreatitis were confirmed by adjudication in 13 Mounjaro™-treated patients (0.23 patients per 100 years of exposure) versus 3 events in 3 comparator-treated patients (0.11 patients per 100 years of exposure). Mounjaro™ has not been studied in patients with a prior history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for

development of pancreatitis on Mounjaro™. After initiation of Mounjaro™, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, discontinue Mounjaro™ and initiate appropriate management.

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin
Patients receiving Mounjaro™ in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogue) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

Hypersensitivity Reactions
Hypersensitivity reactions have been reported with Mounjaro™ in clinical trials (e.g., urticaria and eczema) and were sometimes severe. If hypersensitivity reactions occur, discontinue use of Mounjaro™; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous serious hypersensitivity reaction to tirzepatide or any of the excipients in Mounjaro™. Anaphylaxis and angioedema have been reported with GLP-1 receptor agonists. Use caution in patients with a history of angioedema or anaphylaxis with a GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to these reactions with Mounjaro™.

Acute Kidney Injury
Mounjaro™ has been associated with gastrointestinal adverse reactions, which include nausea, vomiting, and diarrhea. These events may lead to dehydration, which if severe could cause acute kidney injury.

Severe Gastrointestinal Disease
Use of Mounjaro™ has been associated with gastrointestinal adverse reactions, sometimes severe. Mounjaro™ has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.

Diabetic Retinopathy Complications in Patients with a History of Diabetic Retinopathy
Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Mounjaro™ has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

Acute Gallbladder Disease
Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and post marketing. In Mounjaro™ placebo-controlled clinical trials, acute gallbladder disease (cholelithiasis, biliary colic, and cholecystectomy) was reported by 0.6% of Mounjaro™-treated patients and 0% of placebo-treated patients. If cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated.

CONTRAINDICATIONS

- 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 Mounjaro™.

NEW DRUG APPROVAL

Clinical Pharmacology

MECHANISMS OF ACTION

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

Dose & Administration

ADULTS

- The recommended starting dosage is 2.5mg injected subcutaneously once weekly. The 2.5mg dosage is for treatment initiation and is not intended for glycemic control.
- After 4 weeks, increase the dosage to 5mg injected subcutaneously once weekly.
- If additional glycemic control is needed, increase the dosage in 2.5mg increments after at least 4 weeks on the current dose.
- The maximum dosage is 15mg injected subcutaneously once weekly.
- If a dose is missed, instruct patients to administer as soon as possible within 4 days (96 hours) after the missed dose. If more than 4 days have passed, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.
- The day of weekly administration can be changed, if necessary, as long as the time between the two doses is at least 3 days (72 hours).

PEDIATRICS

None

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL in single-dose pen.