

USPH3MAY2022
Mounjaro™ (tirzepatide) injection, for subcutaneous use

WARNING: RISK OF THYROID C-CELL TUMORS
In both male and female rats, tirzepatide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether MOUNJARO causes thyroid C-cell tumors...

INDICATIONS AND USAGE
MOUNJARO™ is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

DOSSAGE AND ADMINISTRATION
2.1 Dosage
The recommended starting dosage of MOUNJARO is 2.5 mg injected subcutaneously once weekly.

DOSSAGE FORMS AND STRENGTHS
Injection: Clear, colorless to slightly yellow solution available in pre-filled single-dose pens of the following strengths:

CONTRAINDICATIONS
MOUNJARO 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)

WARNINGS AND PRECAUTIONS
5.1 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.

ACUTE PANCREATITIS
Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists.

HYPERSENSITIVITY REACTIONS
Hypersensitivity reactions have been reported with MOUNJARO in clinical trials (e.g., urticaria and eczema).

ACUTE GALLBLADDER DISEASE
Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and postmarketing.

ADVERSE REACTIONS
The following serious adverse reactions are described below or elsewhere in the prescribing information:

Thyroid C-cell Tumors
Pancreatitis
Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin
Acute Kidney Injury
Severe Gastrointestinal Disease
Diabetic Retinopathy Complications
Acute Gallbladder Disease

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Common Adverse Reactions
Table 1 shows common adverse reactions, not including hypoglycemia, associated with the use of MOUNJARO in the pool of placebo-controlled trials.

Table 1: Adverse Reactions in Pool of Placebo-Controlled Trials Reported in ≥5% of MOUNJARO-treated Adult Patients with Type 2 Diabetes Mellitus

Table 2: Hypoglycemia Adverse Reactions in Placebo-Controlled Trials in Adult Patients with Type 2 Diabetes Mellitus

Other Adverse Reactions
Hypoglycemia
Table 2 summarizes the incidence of hypoglycemic events in the placebo-controlled trials.

3.4 Insulin Sensitivity
Tirzepatide increases insulin sensitivity, as demonstrated in a hyperinsulinemic euglycemic clamp study after 28 weeks of treatment.

3.5 Gastric Emptying
Tirzepatide delays gastric emptying. The delay is largest after the first dose and this effect diminishes over time.

3.6 Hepatic Impairment
The mean apparent steady-state volume of distribution of tirzepatide following subcutaneous administration in patients with type 2 diabetes mellitus is approximately 10.3 L.

3.7 Elimination
The apparent population mean clearance of tirzepatide is 0.061 L/h with an elimination half-life of approximately 5 days.

3.8 Metabolism
Tirzepatide is metabolized by proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid moiety and amide hydrolysis.

3.9 Excretion
The primary excretion routes of tirzepatide metabolites are via urine and feces. Intact tirzepatide is not observed in urine or feces.

3.10 Specific Populations
The intrinsic factors of age, gender, race, ethnicity, or body weight do not have a clinically relevant effect on the PK of tirzepatide.

3.11 Patients with Renal Impairment
Renal impairment does not impact the pharmacokinetics of tirzepatide. The pharmacokinetics of tirzepatide after a single 5 mg dose was evaluated in patients with different degrees of renal impairment.

3.12 Patients with Hepatic Impairment
Hepatic impairment does not impact the pharmacokinetics of tirzepatide. The pharmacokinetics of tirzepatide after a single 5 mg dose was evaluated in patients with different degrees of hepatic impairment.

3.13 Drug Interactions
Potential for Tirzepatide to Influence the Pharmacokinetics of Other Drugs
In vitro studies have shown low potential for tirzepatide to inhibit or induce CYP enzymes, and to inhibit drug transporters.

3.14 During Pregnancy, Lactation, and Fertility
MOUNJARO delays gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications.

3.15 Reproductive Toxicology
Fertility
A 2-year carcinogenicity study was conducted with tirzepatide in male and female rats at doses of 0.15, 0.50, and 1.5 mg/kg (0.1, 0.4, and 1-fold the MRHD of 15 mg once weekly based on AUC) administered by subcutaneous injection twice weekly.

3.16 Embryofetal Toxicology
The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

3.17 Lactation
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.

3.18 Fertility
Fertility
A 2-year carcinogenicity study was conducted with tirzepatide in male and female rats at doses of 0.15, 0.50, and 1.5 mg/kg (0.1, 0.4, and 1-fold the MRHD of 15 mg once weekly based on AUC) administered by subcutaneous injection twice weekly.

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Table 2: Hypoglycemia Adverse Reactions in Placebo-Controlled Trials in Adult Patients with Type 2 Diabetes Mellitus

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3.6 Hepatic Impairment
The mean apparent steady-state volume of distribution of tirzepatide following subcutaneous administration in patients with type 2 diabetes mellitus is approximately 10.3 L.

3.7 Elimination
The apparent population mean clearance of tirzepatide is 0.061 L/h with an elimination half-life of approximately 5 days.

3.8 Metabolism
Tirzepatide is metabolized by proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid moiety and amide hydrolysis.

3.9 Excretion
The primary excretion routes of tirzepatide metabolites are via urine and feces. Intact tirzepatide is not observed in urine or feces.

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Renal impairment does not impact the pharmacokinetics of tirzepatide. The pharmacokinetics of tirzepatide after a single 5 mg dose was evaluated in patients with different degrees of renal impairment.

3.12 Patients with Hepatic Impairment
Hepatic impairment does not impact the pharmacokinetics of tirzepatide. The pharmacokinetics of tirzepatide after a single 5 mg dose was evaluated in patients with different degrees of hepatic impairment.

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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.

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3.25 Reproductive Toxicology
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Fertility
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3.31 Reproductive Toxicology
Fertility
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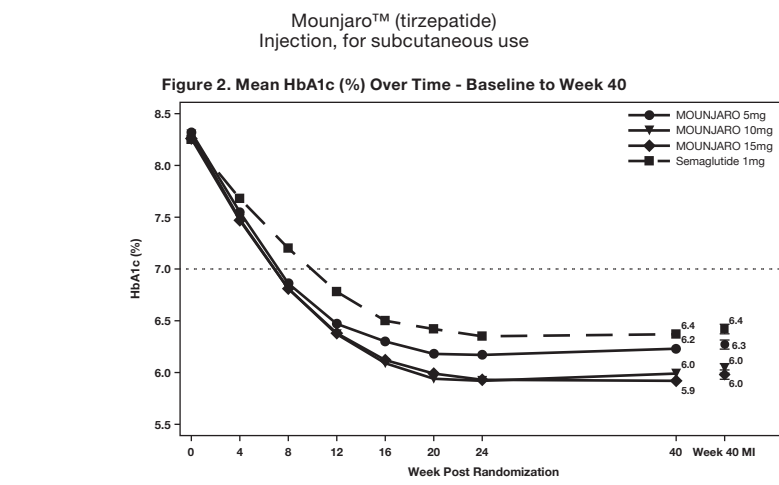
3.32 Reproductive Toxicology
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NUZ72AE000

00007628

PPD Information Box
Technical Information
Previous Item Code (to be destroyed) N/A
Logo



Number of patients

MOUNJARO 5mg	470	451	470
MOUNJARO 10mg	469	445	469
MOUNJARO 15mg	469	447	469
Semaglutide 1mg	468	443	468

Note: Displayed results are from modified intent-to-Treat Full Analysis Set. (1) Observed mean value from Week 0 to Week 40, and (2) least-squares mean ± standard error at Week 40 multiple imputation (MI).

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 5).

Table 5: 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 ^e	82 ^e	83 ^e
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 ^e (-10.0, -7.8)	-11.5 ^e (-12.6, -10.4)	-13.2 ^e (-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 SGLT2 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/m². 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 m² in 43%, 80 to 90 mL/min/1.73 m² in 40%, 45 to 90 mL/min/1.73 m² in 10%, and 30 to 45 mL/min/1.73 m² 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 6).

Table 6: 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 ^e	83 ^e	85 ^e
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 ^e (-8.9, -7.3)	-10.6 ^e (-11.4, -9.8)	-12.2 ^e (-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.

14.4 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 7).

Table 7: 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 ^e	90 ^e	85 ^e
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 ^e (-27, -11)	-25 ^e (-32, -17)	-23 ^e (-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 ^e (-8.7, -5.4)	-9.1 ^e (-10.7, -7.5)	-10.5 ^e (-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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

MOUNJARO is a clear, colorless to slightly yellow solution available in pre-filled single-dose pens as follows:

Total Strength per Total Volume	Carton Contents
2.5 mg/0.5 mL	4 single-dose pens
5 mg/0.5 mL	4 single-dose pens
7.5 mg/0.5 mL	4 single-dose pens
10 mg/0.5 mL	4 single-dose pens
12.5 mg/0.5 mL	4 single-dose pens
15 mg/0.5 mL	4 single-dose pens

Not all strengths, pack sizes or presentations may be marketed.

16.2 Storage and Handling

- Store MOUNJARO in a refrigerator at 2°C to 8°C (36°F to 46°F).
- If needed, each single-dose pen can be stored unrefrigerated at temperatures not to exceed 30°C (86°F) for up to 21 days.
- Do not freeze MOUNJARO. Do not use MOUNJARO if frozen.
- Store MOUNJARO in the original carton to protect from light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the approved *Package insert and Instructions for Use*.

Risk of Thyroid C-Cell Tumors

Inform patients that MOUNJARO causes thyroid C-cell tumors in rats and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, persistent hoarseness, dysphagia, or dyspnea) to their healthcare provider [see *Boxed Warning and Warnings and Precautions (5.1)*].



Mounjaro™ (tirzepatide) Injection, for subcutaneous use

Pancreatitis

Inform patients of the potential risk for pancreatitis. Instruct patients to discontinue MOUNJARO promptly and contact their healthcare provider if pancreatitis is suspected (severe abdominal pain that may radiate to the back, and which may or may not be accompanied by vomiting) [see *Warnings and Precautions (5.2)*].

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

Inform patients that the risk of hypoglycemia is increased when MOUNJARO is used with an insulin secretagogue (such as a sulfonylurea) or insulin. Educate patients on the signs and symptoms of hypoglycemia [see *Warnings and Precautions (5.3)*].

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions have been reported with use of MOUNJARO. Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking MOUNJARO and seek medical advice promptly if such symptoms occur [see *Warnings and Precautions (5.4)*].

Acute Kidney Injury

Advise patients treated with MOUNJARO of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs [see *Warnings and Precautions (5.5)*].

Severe Gastrointestinal Adverse Reactions

Inform patients of the potential risk of severe gastrointestinal adverse reactions. Instruct patients to contact their healthcare provider if they have severe or persistent gastrointestinal symptoms [see *Warnings and Precautions (5.6)*].

Diabetic Retinopathy Complications

Inform patients to contact their healthcare provider if changes in vision are experienced during treatment with MOUNJARO [see *Warnings and Precautions (5.7)*].

Acute Gallbladder Disease

Inform patients of the risk of acute gallbladder disease. Instruct patients to contact their healthcare provider for appropriate clinical follow-up if gallbladder disease is suspected [see *Warnings and Precautions (5.8)*].

Pregnancy

Advise a pregnant woman of the potential risk to a fetus. Advise women to inform their healthcare provider if they are pregnant or intend to become pregnant [see *Use in Specific Populations (8.1)*].

Contraception

Use of MOUNJARO may reduce the efficacy of oral hormonal contraceptives. Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with MOUNJARO [see *Drug Interactions (7.2)*, *Use in Specific Populations (8.3)*, and *Clinical Pharmacology (12.3)*].

Missed Doses

Inform patients if a dose is missed, it should be administered as soon as possible within 4 days after the missed dose. If more than 4 days have passed, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, inform patients to resume their regular once weekly dosing schedule [see *Dosage and Administration (2.1)*].

Manufactured and packaged by:

Eli Lilly and Company
Indianapolis, IN 46285, USA

Prescription only.

PPD Information Box

Technical Information:

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Previous Item Code (to be destroyed)

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