CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

215866Orig1s002

Trade Name:	**Mounjaro**
Generic or Proper Name:	tirzepatide
Sponsor:	ELI LILLY AND CO
Approval Date:	July 28, 2023
Indication:	**Mounjaro (tirzepatide)** is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CENTER FOR DRUG EVALUATION AND RESEARCH

215866Orig1s002

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APPLICATION NUMBER:

215866Orig1s002

APPROVAL LETTER

NDA 215866/S-002
NDA 215866/S-006

SUPPLEMENT APPROVAL

Eli Lilly and Company
Attention: Sally Anliker, Associate Vice President,
Global Regulatory Affairs CMC
Linda S. Kelly, Director, Global Regulatory Affairs – North America
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Sally Anliker & Linda Kelly:

Please refer to your supplemental new drug applications (sNDAs) dated and received January 31 and April 18, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mounjaro (tirzepatide) injection.

The Prior Approval sNDA (S-002) provides for:

- The addition of a single-use glass vial presentation,
- The addition of (b) (4) a manufacturing site for the single-use glass vial presentation,
- The addition of (b) (4) quality control testing sites,
- The addition of (b) (4) a secondary packaging site for the vial presentation.

The "Changes Being Effected" sNDA (S-006) provides for updates to Section 4, Section 5.4, Section 6.2 and Section 17 of the Mounjaro Prescribing Information (PI) to reflect new safety information (anaphylaxis and angioedema).

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling with minor editorial revisions listed below and reflected in the enclosed labeling.

The prescribing information (PI), instructions for use (IFU) and medication guide (MG) were all revised to reflect the date of approval.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 215866/S-002, NDA 215866/S-006**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your sNDAs, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.[6]
If you have any questions, call Lindsey Kelly, Regulatory Project Manager, at 301-837-7654.

Sincerely,

{See appended electronic signature page}

Patrick Archdeacon, M.D.
Deputy Director
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use- vial
  - Instructions for Use- single-dose pen (previously approved May 13, 2022)
  - Quick Reference Guide (previously approved May 13, 2022)
- Carton and Container Labeling

[6] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PATRICK ARCHDEACON
07/28/2023 03:50:17 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215866Orig1s002

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MOUNJARO safely and effectively. See full prescribing information for MOUNJARO.

MOUNJARO® (tirzepatide) Injection, for subcutaneous use
Initial U.S. Approval: 2022

WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- **Tirzepatide causes thyroid C-cell tumors in rats. It is unknown whether MOUNJARO causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).**
- **MOUNJARO is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).**

---------- RECENT MAJOR CHANGES ----------

Contraindications (4)	04/2023
Warnings and Precautions	
Hypersensitivity Reactions (5.4)	04/2023

---------- INDICATIONS AND USAGE ----------

MOUNJARO® is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitations of Use:

- Has not been studied in patients with a history of pancreatitis (1, 5.2)
- Is not indicated for use in patients with type 1 diabetes mellitus (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended starting dosage is 2.5 mg injected subcutaneously once weekly (2.1)
- After 4 weeks, increase to 5 mg injected subcutaneously once weekly (2.1)
- If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose.
- The maximum dosage is 15 mg subcutaneously once weekly (2.1).
- Administer once weekly at any time of day, with or without meals. (2.2)
- Inject subcutaneously in the abdomen, thigh, or upper arm. (2.2)
- Rotate injection sites with each dose.

----------DOSAGE FORMS AND STRENGTHS----------

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 or single-dose vial (3)

---------- CONTRAINDICATIONS ----------

- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4, 5.1)
- Known serious hypersensitivity to tirzepatide or any of the excipients in MOUNJARO (4, 5.4)

----------WARNINGS AND PRECAUTIONS----------

- *Pancreatitis:* Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. (5.2)
- *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. (5.3)
- *Hypersensitivity Reactions:* Serious hypersensitivity reactions (e.g., anaphylaxis and angioedema) have been reported. Discontinue MOUNJARO if suspected and promptly seek medical advice. (5.4)
- *Acute Kidney Injury:* Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. (5.5)
- *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. (5.6)
- *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. (5.7)
- *Acute Gallbladder Disease:* Has occurred in clinical trials. If cholelithiasis is suspected, gallbladder studies and clinical follow-up are indicated. (5.8)

----------ADVERSE REACTIONS----------

The most common adverse reactions, reported in ≥5% of patients treated with MOUNJARO are: nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

MOUNJARO delays gastric emptying and has the potential to impact the absorption of concomitantly administered oral medications. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy:* Based on animal study, may cause fetal harm. (8.1)
- *Females of Reproductive Potential:* Advise females using oral 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. (7.2, 8.3, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 07/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescr bing information are not listed.

FULL PRESCRIBING INFORMATION

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, including medullary thyroid carcinoma (MTC), in humans as human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)]*.**
- **MOUNJARO is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) *[see Contraindications (4)]*. 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). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with MOUNJARO *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

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

Limitations of Use

- MOUNJARO has not been studied in patients with a history of pancreatitis *[see Warnings and Precautions (5.2)]*.
- MOUNJARO is not indicated for use in patients with type 1 diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

- The recommended starting dosage of MOUNJARO is 2.5 mg injected subcutaneously once weekly. The 2.5 mg dosage is for treatment initiation and is not intended for glycemic control.
- After 4 weeks, increase the dosage to 5 mg injected subcutaneously once weekly.
- If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose.
- The maximum dosage of MOUNJARO is 15 mg injected subcutaneously once weekly.
- If a dose is missed, instruct patients to administer MOUNJARO 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).

2.2 Important Administration Instructions

- Prior to initiation, train patients and caregivers on proper injection technique *[see Instructions for Use]*.
- Instruct patients using the single-dose vial to use a syringe appropriate for dose administration (e.g., a 1 mL syringe capable of measuring a 0.5 mL dose).
- Administer MOUNJARO once weekly, any time of day, with or without meals.
- Inject MOUNJARO subcutaneously in the abdomen, thigh, or upper arm.
- Rotate injection sites with each dose.
- Inspect MOUNJARO visually before use. It should appear clear and colorless to slightly yellow. Do not use MOUNJARO if particulate matter or discoloration is seen.
- When using MOUNJARO with insulin, administer as separate injections and never mix. It is acceptable to inject MOUNJARO and insulin in the same body region, but the injections should not be adjacent to each other.

3 DOSAGE FORMS AND STRENGTHS

Injection: Clear, colorless to slightly yellow solution in pre-filled single-dose pens or single-dose vials, each available in the following strengths:

- 2.5 mg/0.5 mL
- 5 mg/0.5 mL
- 7.5 mg/0.5 mL
- 10 mg/0.5 mL
- 12.5 mg/0.5 mL
- 15 mg/0.5 mL

4 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) *[see Warnings and Precautions (5.1)]*.
- Known serious hypersensitivity to tirzepatide or any of the excipients in MOUNJARO. Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with MOUNJARO *[see Warnings and Precautions (5.4)]*.

5 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 *[see Nonclinical Toxicology (13.1)]*. 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).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with MOUNJARO. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin values may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

5.2 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.

5.3 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 *[see Adverse Reactions (6.1), Drug Interactions (7.1)]*.

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.

5.4 Hypersensitivity Reactions

Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported in patients treated with MOUNJARO. 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 *[see Contraindications (4), Adverse Reactions (6.2)]*.

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.

5.5 Acute Kidney Injury

MOUNJARO has been associated with gastrointestinal adverse reactions, which include nausea, vomiting, and diarrhea *[see Adverse Reactions (6.1)]*. These events may lead to dehydration, which if severe could cause acute kidney injury.

In patients treated with GLP-1 receptor agonists, there have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Monitor renal function when initiating or escalating doses of MOUNJARO in patients with renal impairment reporting severe gastrointestinal adverse reactions.

5.6 Severe Gastrointestinal Disease

Use of MOUNJARO has been associated with gastrointestinal adverse reactions, sometimes severe *[see Adverse Reactions 6.1]*. MOUNJARO has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.

5.7 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.

5.8 Acute Gallbladder Disease

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

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.

6 ADVERSE REACTIONS

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

- Risk of Thyroid C-cell Tumors *[see Warnings and Precautions (5.1)]*
- Pancreatitis *[see Warnings and Precautions (5.2)]*
- Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin *[see Warnings and Precautions (5.3)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.4)]*
- Acute Kidney Injury *[see Warnings and Precautions (5.5)]*
- Severe Gastrointestinal Disease *[see Warnings and Precautions (5.6)]*
- Diabetic Retinopathy Complications *[see Warnings and Precautions (5.7)]*
- Acute Gallbladder Disease *[see Warnings and Precautions (5.8)]*

6.1 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.

Pool of Two Placebo-Controlled Clinical Trials

The data in Table 1 are derived from 2 placebo-controlled trials [1 monotherapy trial (SURPASS-1) and 1 trial in combination with basal insulin with or without metformin (SURPASS-5)] in adult patients with type 2 diabetes mellitus *[see Clinical Studies (14.2, 14.4)]*. These data reflect exposure of 718 patients to MOUNJARO and a mean duration of exposure to MOUNJARO of 36.6 weeks. The mean age of patients was 58 years, 4% were 75 years or older and 54% were male. The population was 57% White, 27% Asian, 13% American Indian or Alaska Native, and 3% Black or African American; 25% identified as Hispanic or Latino ethnicity. At baseline, patients had type 2 diabetes mellitus for an average of 9.1 years with a mean HbA1c of 8.1%. As assessed by baseline fundoscopic examination, 13% of the population had retinopathy. At baseline, eGFR was ≥90 mL/min/1.73 m^2 in 53%, 60 to 90 mL/min/1.73 m^2 in 39%, 45 to 60 mL/min/1.73 m^2 in 7%, and 30 to 45 mL/min/1.73 m^2 in 1% of patients.

Pool of Seven Controlled Clinical Trials

Adverse reactions were also evaluated in a larger pool of adult patients with type 2 diabetes mellitus participating in seven controlled clinical trials which included two placebo-controlled trials (SURPASS-1 and -5), three trials of MOUNJARO in combination with metformin, sulfonylureas, and/or SGLT2 Inhibitors (SURPASS-2, -3, -4) *[see Clinical Studies (14.3)]* and two additional trials conducted in Japan. In this pool, a total of 5119 adult patients with type 2 diabetes mellitus were treated with MOUNJARO for a mean duration of 48.1 weeks. The mean age of patients was 58 years, 4% were 75 years or older and 58% were male. The population was 65% White, 24% Asian, 7% American Indian or Alaska Native, and 3% Black or African American; 38% identified as Hispanic or Latino ethnicity. At baseline, patients had type 2 diabetes mellitus for an average of 9.1 years with a mean HbA1c of 8.3%. As assessed by baseline fundoscopic examination, 15% of the population had retinopathy. At baseline, eGFR was ≥90 mL/min/1.73 m^2 in 52%, 60 to 90 mL/min/1.73 m^2 in 40%, 45 to 60 mL/min/1.73 m^2 in 6%, and 30 to 45 mL/min/1.73 m^2 in 1% of patients.

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. These adverse reactions occurred more commonly on MOUNJARO than on placebo and occurred in at least 5% of patients treated with MOUNJARO.

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

Adverse Reaction	Placebo (N=235) %	MOUNJARO 5 mg (N=237) %	MOUNJARO 10 mg (N=240) %	MOUNJARO 15 mg (N=241) %
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

Note: Percentages reflect the number of patients who reported at least 1 occurrence of the adverse reaction.

In the pool of seven clinical trials, the types and frequency of common adverse reactions, not including hypoglycemia, were similar to those listed in Table 1.

Gastrointestinal Adverse Reactions

In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving MOUNJARO than placebo (placebo 20.4%, MOUNJARO 5 mg 37.1%, MOUNJARO 10 mg 39.6%, MOUNJARO 15 mg 43.6%). More patients receiving MOUNJARO 5 mg (3.0%), MOUNJARO 10 mg (5.4%), and MOUNJARO 15 mg (6.6%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.4%). The majority of reports of nausea, vomiting, and/or diarrhea occurred during dose escalation and decreased over time.

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%).

Other Adverse Reactions

Hypoglycemia

Table 2 summarizes the incidence of hypoglycemic events in the placebo-controlled trials.

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

	Placebo **%**	**MOUNJARO 5 mg** **%**	**MOUNJARO 10 mg** **%**	**MOUNJARO 15 mg** **%**
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

* Reflects the study treatment period. Data include events occurring during 4 weeks of treatment-free safety follow up. Events after introduction of a new glucose-lowering treatment are excluded.

** Episodes requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Hypoglycemia was more frequent when MOUNJARO was used in combination with a sulfonylurea *[see Clinical Studies (14)]*. 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.

Heart Rate Increase

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

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 seven clinical trials, hypersensitivity reactions occurred in 106/2,570 (4.1%) of MOUNJARO-treated patients with anti-tirzepatide antibodies and in 73/2,455 (3.0%) of MOUNJARO-treated patients who did not develop anti-tirzepatide antibodies *[see Clinical Pharmacology (12.6)].*

Injection Site Reactions

In the pool of placebo-controlled trials, injection site reactions were reported in 3.2% of MOUNJARO-treated patients compared to 0.4% of placebo-treated patients.

In the pool of seven clinical trials, injection site reactions occurred in 119/2,570 (4.6%) of MOUNJARO-treated patients with anti-tirzepatide antibodies and in 18/2,455 (0.7%) of MOUNJARO-treated patients who did not develop anti-tirzepatide antibodies *[see Clinical Pharmacology (12.6)].*

Acute Gallbladder Disease

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.

Laboratory Abnormalities

Amylase and Lipase Increase

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%. Placebo-treated patients had a mean increase from baseline in pancreatic amylase of 4% and no changes were observed in lipase. The clinical significance of elevations in lipase or amylase with MOUNJARO is unknown in the absence of other signs and symptoms of pancreatitis.

6.2 Postmarketing Experience

The following adverse reactions have been reported during post-approval use of MOUNJARO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity: anaphylaxis, angioedema

Gastrointestinal: ileus

7 DRUG INTERACTIONS

7.1 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When initiating MOUNJARO, consider reducing the dose of concomitantly administered insulin secretagogues (e.g., sulfonylureas) or insulin to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.3)].*

7.2 Oral Medications

MOUNJARO delays gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with MOUNJARO.

Monitor patients on oral medications dependent on threshold concentrations for efficacy and those with a narrow therapeutic index (e.g., warfarin) when concomitantly administered with MOUNJARO.

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. Hormonal contraceptives that are not administered orally should not be affected *[see Use in Specific Populations (8.3) and Clinical Pharmacology (12.2, 12.3)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data with MOUNJARO use in pregnant women are insufficient to 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 *(see Clinical Considerations)*. Based on animal reproduction studies, there may be risks to the fetus from exposure to tirzepatide during pregnancy. MOUNJARO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant rats administered tirzepatide during organogenesis, fetal growth reductions and fetal abnormalities occurred at clinical exposure in maternal rats based on AUC. In rabbits administered tirzepatide during organogenesis, fetal growth reductions were observed at clinically relevant exposures based on AUC. These adverse embryo/fetal effects in animals coincided with pharmacological effects on maternal weight and food consumption *(see Data)*.

The estimated background risk of major birth defects is 6–10% in women with pre-gestational diabetes with an HbA1c >7% and has been reported to be as high as 20–25% in women with an HbA1c >10%. 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.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia-related morbidity.

Data

Animal Data

In pregnant rats given twice weekly subcutaneous doses of 0.02, 0.1, and 0.5 mg/kg tirzepatide (0.03-, 0.07-, and 0.5-fold the MRHD of 15 mg once weekly based on AUC) during organogenesis, increased incidences of external, visceral, and skeletal malformations, increased incidences of visceral and skeletal developmental variations, and decreased fetal weights coincided with pharmacologically-mediated reductions in maternal body weights and food consumption at 0.5 mg/kg. In pregnant rabbits given once weekly subcutaneous doses of 0.01, 0.03, or 0.1 mg/kg tirzepatide (0.01-, 0.06-, and 0.2-fold the MRHD) during organogenesis, pharmacologically-mediated effects on the gastrointestinal system resulting in maternal mortality or abortion in a few rabbits occurred at all dose levels. Reduced fetal weights associated with decreased maternal food consumption and body weights were observed at 0.1 mg/kg. In a pre- and post-natal study in rats administered subcutaneous doses of 0.02, 0.10, or 0.25 mg/kg tirzepatide twice weekly from implantation through lactation, F_1 pups from F_0 maternal rats given 0.25 mg/kg tirzepatide had statistically significant lower mean body weight when compared to controls from post-natal day 7 through post-natal day 126 for males and post-natal day 56 for females.

8.2 Lactation

Risk Summary

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. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MOUNJARO and any potential adverse effects on the breastfed infant from MOUNJARO or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Use of MOUNJARO may reduce the efficacy of oral hormonal contraceptives due to delayed gastric emptying. This delay is largest after the first dose and diminishes over time. 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) and Clinical Pharmacology (12.2, 12.3)].*

8.4 Pediatric Use

Safety and effectiveness of MOUNJARO have not been established in pediatric patients (younger than 18 years of age).

8.5 Geriatric Use

In the pool of seven clinical trials, 1539 (30.1%) MOUNJARO-treated patients were 65 years of age or older, and 212 (4.1%) MOUNJARO-treated patients were 75 years of age or older at baseline.

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.

8.6 Renal Impairment

No dosage adjustment of MOUNJARO is recommended for patients with renal impairment. In subjects with renal impairment including end-stage renal disease (ESRD), no change in tirzepatide pharmacokinetics (PK) was observed *[see Clinical Pharmacology (12.3)]*. Monitor renal function when initiating or escalating doses of MOUNJARO in patients with renal impairment reporting severe adverse gastrointestinal reactions *[see Warnings and Precautions (5.5)].*

8.7 Hepatic Impairment

No dosage adjustment of MOUNJARO is recommended for patients with hepatic impairment. In a clinical pharmacology study in subjects with varying degrees of hepatic impairment, no change in tirzepatide PK was observed *[see Clinical Pharmacology (12.3)]*.

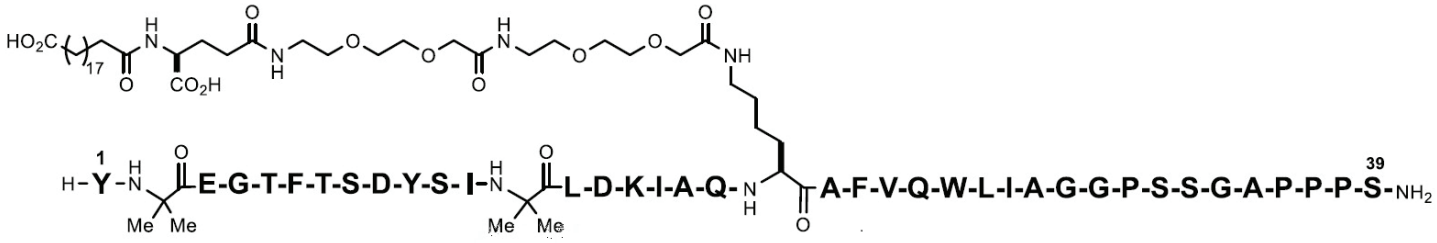
10 OVERDOSAGE

In the event of an overdosage, contact Poison Control for latest recommendations. Appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A period of observation and treatment for these symptoms may be necessary, taking into account the half-life of tirzepatide of approximately 5 days.

11 DESCRIPTION

MOUNJARO (tirzepatide) injection, for subcutaneous use, contains tirzepatide, a once weekly GIP receptor and GLP-1 receptor agonist. It is a 39-amino-acid modified peptide based on the GIP sequence. Tirzepatide contains 2 non-coded amino acids (aminoisobutyric acid, Aib) in positions 2 and 13, a C-terminal amide, and Lys residue at position 20 that is attached to 1,20-eicosanedioic acid via a linker. The molecular weight is 4813.53 Da and the empirical formula is $C_{225}H_{348}N_{48}O_{68}$.

Structural formula:



MOUNJARO is a clear, colorless to slightly yellow, sterile, preservative-free solution for subcutaneous use. Each single-dose pen or single-dose vial contains a 0.5 mL solution of 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg of tirzepatide and the following excipients: sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. MOUNJARO has a pH of 6.5 – 7.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism 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.

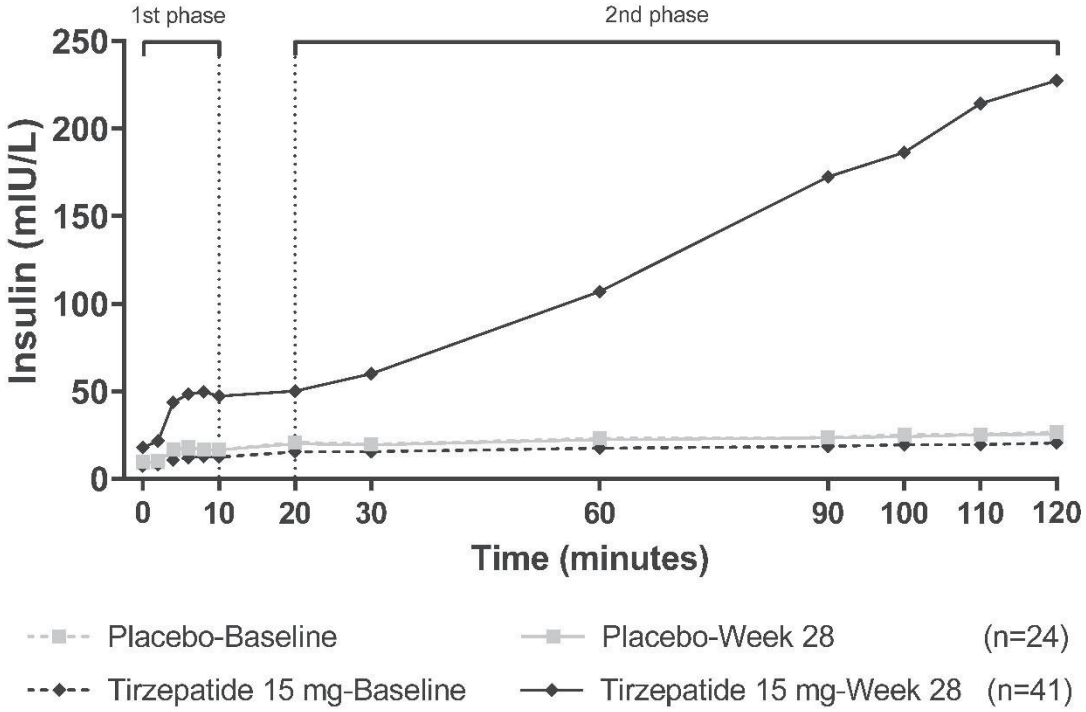
12.2 Pharmacodynamics

Tirzepatide lowers fasting and postprandial glucose concentration, decreases food intake, and reduces body weight in patients with type 2 diabetes mellitus.

First and Second-Phase Insulin Secretion

Tirzepatide enhances the first- and second-phase insulin secretion. (Figure 1)

Figure 1: Mean insulin concentration at 0-120 minutes during hyperglycemic clamp at baseline and Week 28



Insulin Sensitivity

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

Glucagon Secretion

Tirzepatide reduces fasting and postprandial glucagon concentrations. Tirzepatide 15 mg reduced fasting glucagon concentration by 28% and glucagon AUC after a mixed meal by 43%, compared with no change for placebo after 28 weeks of treatment.

Gastric Emptying

Tirzepatide delays gastric emptying. The delay is largest after the first dose and this effect diminishes over time. Tirzepatide slows post-meal glucose absorption, reducing postprandial glucose.

12.3 Pharmacokinetics

The pharmacokinetics of tirzepatide is similar between healthy subjects and patients with type 2 diabetes mellitus. Steady-state plasma tirzepatide concentrations were achieved following 4 weeks of once weekly administration. Tirzepatide exposure increases in a dose-proportional manner.

Absorption

Following subcutaneous administration, the time to maximum plasma concentration of tirzepatide ranges from 8 to 72 hours. The mean absolute bioavailability of tirzepatide following subcutaneous administration is 80%. Similar exposure was achieved with subcutaneous administration of tirzepatide in the abdomen, thigh, or upper arm.

Distribution

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. Tirzepatide is highly bound to plasma albumin (99%).

Elimination

The apparent population mean clearance of tirzepatide is 0.061 L/h with an elimination half-life of approximately 5 days, enabling once-weekly dosing.

Metabolism

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

Excretion

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

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.

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 (mild, moderate, severe, ESRD) compared with subjects with normal renal function. This was also shown for patients with both type 2 diabetes mellitus and renal impairment based on data from clinical studies *[see Use in Specific Populations (8.6)]*.

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 (mild, moderate, severe) compared with subjects with normal hepatic function *[see Use in Specific Populations (8.7)]*.

Drug Interactions Studies

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.

MOUNJARO delays gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications *[see Drug Interactions (7.2)]*.

The impact of tirzepatide on gastric emptying was greatest after a single dose of 5 mg and diminished after subsequent doses.

Following a first dose of tirzepatide 5 mg, acetaminophen maximum concentration (C_{max}) was reduced by 50%, and the median peak plasma concentration (t_{max}) occurred 1 hour later. After coadministration at week 4, there was no meaningful impact on acetaminophen C_{max} and t_{max}. Overall acetaminophen exposure (AUC_{0-24hr}) was not influenced.

Following administration of a combined oral contraceptive (0.035 mg ethinyl estradiol and 0.25 mg norgestimate) in the presence of a single dose of tirzepatide 5 mg, mean C_{max} of ethinyl estradiol, norgestimate, and norelgestromin was reduced by 59%,66%, and 55%, while mean AUC was reduced by 20%, 21%, and 23%, respectively. A delay in t_{max} of 2.5 to 4.5 hours was observed.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the trials described below with the incidence of anti-drug antibodies in other trials.

During the 40- to 104-week treatment periods with ADA sampling conducted up to 44 to 108 weeks in seven clinical trials in adults with type 2 diabetes mellitus *[see Clinical Studies (14)],* 51% (2,570/5,025) of MOUNJARO-treated patients developed anti-tirzepatide antibodies. In these trials, anti-tirzepatide antibody formation in 34% and 14% of MOUNJARO-treated patients showed cross-reactivity to native GIP or native GLP-1, respectively.

Of the 2,570 MOUNJARO-treated patients who developed anti-tirzepatide antibodies during the treatment periods in these seven trials, 2% and 2% developed neutralizing antibodies against tirzepatide activity on the GIP or GLP-1 receptors, respectively, and 0.9% and 0.4% developed neutralizing antibodies against native GIP or GLP-1, respectively.

There was no identified clinically significant effect of anti-tirzepatide antibodies on pharmacokinetics or effectiveness of MOUNJARO. More MOUNJARO-treated patients who developed anti-tirzepatide antibodies experienced hypersensitivity reactions or injection site reactions than those who did not develop these antibodies *[see Adverse Reactions (6.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of 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. A 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 twice weekly subcutaneous doses of 0.5, 1.5, or 3 mg/kg (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). 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.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

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.

In adult patients with type 2 diabetes mellitus, treatment with MOUNJARO produced a statistically significant reduction from baseline in HbA1c compared to placebo. The effectiveness of MOUNJARO was not impacted by age, gender, race, ethnicity, region, or by baseline BMI, HbA1c, diabetes duration, or renal function.

14.2 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/m^2. 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 3).

Table 3: 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.

14.3 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/m^2. 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 4 and Figure 2).

Table 4: 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.

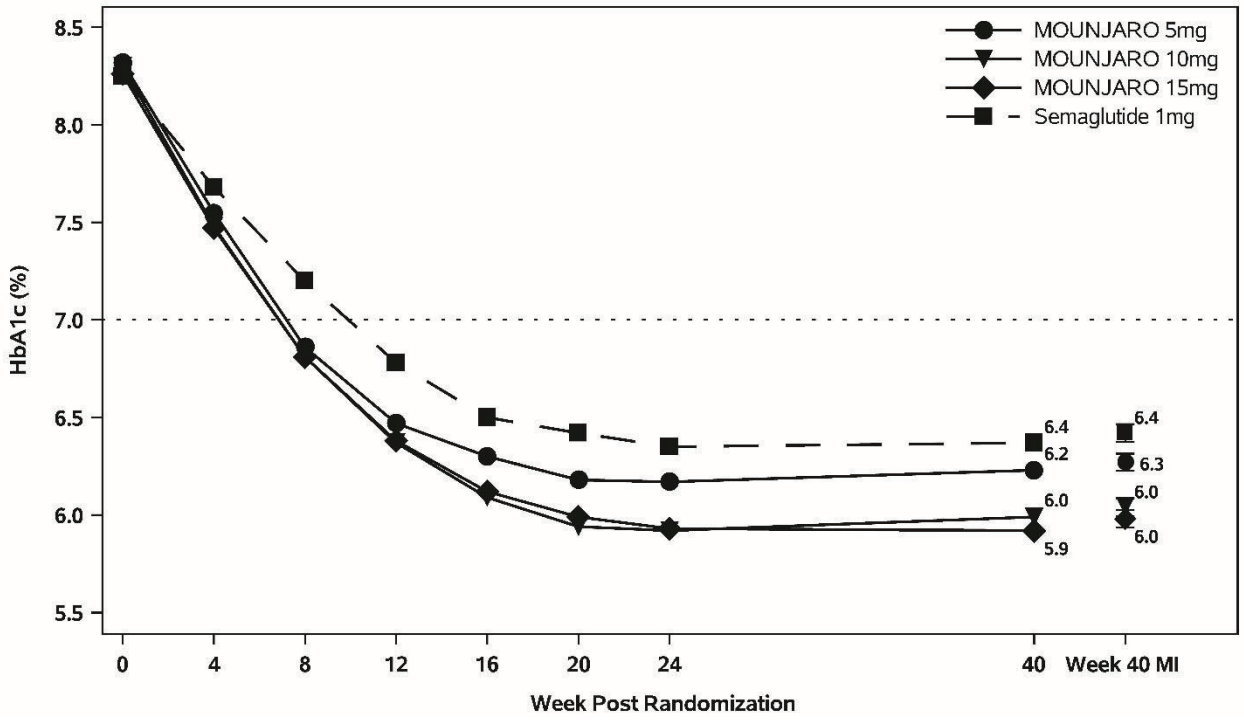
[c] p<0.05 (two-sided) for superiority vs. semaglutide, adjusted for multiplicity.

[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.

Figure 2. Mean HbA1c (%) Over Time - Baseline to Week 40



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/m^2. 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[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 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[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.

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/m^2. 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[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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

MOUNJARO is a clear, colorless to slightly yellow solution available in cartons containing 4 pre-filled single-dose pens or 1 single-dose vial as follows:

Total Strength per Total Volume	Pen NDC	Vial NDC
2.5 mg/0.5 mL	0002-1506-80	0002-1152-01
5 mg/0.5 mL	0002-1495-80	0002-1243-01

7.5 mg/0.5 mL	0002-1484-80	0002-2214-01
10 mg/0.5 mL	0002-1471-80	0002-2340-01
12.5 mg/0.5 mL	0002-1460-80	0002-2423-01
15 mg/0.5 mL	0002-1457-80	0002-3002-01

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 or single-dose vial can be stored unrefrigerated at temperatures not to exceed 30ºC (86ºF) 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 FDA-approved patient labeling *(Medication Guide 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)]*.

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 serious 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)].*

Administration

Instruct patients how to prepare and administer the correct dose of MOUNJARO and assess their ability to inject subcutaneously to ensure the proper administration of MOUNJARO. Instruct patients using the single-dose vial to use a syringe appropriate for dose administration (e.g., a 1 mL syringe capable of measuring a 0.5 mL dose) *[see Dosage and Administration (2.2)]*.

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)].*

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

MOU-0002-USPI-YYYYMMDD

Medication Guide
MOUNJARO® [mown-JAHR-OH]
(tirzepatide)
injection, for subcutaneous use

What is the most important information I should know about MOUNJARO?

MOUNJARO may cause serious side effects, including:

- **Possible thyroid tumors, including cancer.** Tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer. In studies with rats, MOUNJARO and medicines that work like MOUNJARO caused thyroid tumors, including thyroid cancer. It is not known if MOUNJARO will cause thyroid tumors, or a type of thyroid cancer called medullary thyroid carcinoma (MTC) in people.
- Do not use MOUNJARO if you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC), or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

What is MOUNJARO?

- MOUNJARO is an injectable prescription medicine that is used along with diet and exercise to improve blood sugar (glucose) in adults with type 2 diabetes mellitus.
- It is not known if MOUNJARO can be used in people who have had pancreatitis.
- MOUNJARO is not for use in people with type 1 diabetes.
- It is not known if MOUNJARO is safe and effective for use in children under 18 years of age.

Do not use MOUNJARO if:

- you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC) or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- you have had a serious allergic reaction to tirzepatide or any of the ingredients in MOUNJARO. See the end of this Medication Guide for a complete list of ingredients in MOUNJARO.

Before using MOUNJARO, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had problems with your pancreas or kidneys.
- have severe problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems with digesting food.
- have a history of diabetic retinopathy.
- are pregnant or plan to become pregnant. It is not known if MOUNJARO will harm your unborn baby. Tell your healthcare provider if you become pregnant while using MOUNJARO.
    - **Birth control pills by mouth may not work as well while using MOUNJARO**. If you take birth control pills by mouth, your healthcare provider may recommend another type of birth control for 4 weeks after you start MOUNJARO and for 4 weeks after each increase in your dose of MOUNJARO. Talk to your healthcare provider about birth control methods that may be right for you while using MOUNJARO.
- are breastfeeding or plan to breastfeed. It is not known if MOUNJARO passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while using MOUNJARO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. MOUNJARO may affect the way some medicines work, and some medicines may affect the way MOUNJARO works.

Before using MOUNJARO, tell your healthcare provider if you are taking other medicines to treat diabetes including insulin or sulfonylureas which could increase your risk of low blood sugar. Talk to your healthcare provider about low blood sugar and how to manage it.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use MOUNJARO?

- Read the **Instructions for Use** that comes with MOUNJARO.
- Use MOUNJARO exactly as your healthcare provider tells you to. A healthcare provider should show you how to prepare and inject your dose of MOUNJARO before injecting for the first time.
- MOUNJARO is injected under the skin (subcutaneously) of your stomach (abdomen), thigh, or upper arm.
- **Use MOUNJARO 1 time each week, at any time of the day.**
- You may change the day of the week you use MOUNJARO as long as the time between the 2 doses is at least **3** days (72 hours).
- If you miss a dose of MOUNJARO, take the missed dose 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 take your next dose on the regularly scheduled day. **Do not** take **2** doses of MOUNJARO within **3** days of each other.
- MOUNJARO may be taken with or without food.
- **Do not** mix insulin and MOUNJARO together in the same injection.
- You may give an injection of MOUNJARO and insulin in the same body area (such as your stomach area), but not right next to each other.
- Change (rotate) your injection site with each weekly injection. **Do not** use the same site for each injection.
- If you take too much MOUNJARO, call your healthcare provider.

What are the possible side effects of MOUNJARO?

MOUNJARO may cause serious side effects, including:

- See **"What is the most important information I should know about MOUNJARO?"**
- **inflammation of your pancreas (pancreatitis).** Stop using MOUNJARO and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.
- **low blood sugar (hypoglycemia).** Your risk for getting low blood sugar may be higher if you use MOUNJARO with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin. **Signs and symptoms of low blood sugar may include:**
  - dizziness or light-headedness
  - sweating
  - confusion or drowsiness
  - headache
  - blurred vision
  - slurred speech
  - shakiness
  - fast heartbeat
  - anxiety, irritability, or mood changes
  - hunger
  - weakness
  - feeling jittery
- **serious allergic reactions.** Stop using MOUNJARO and get medical help right away if you have any symptoms of a serious allergic reaction including:
  - swelling of your face, lips, tongue or throat
  - problems breathing or swallowing
  - severe rash or itching
  - fainting or feeling dizzy
  - very rapid heartbeat
- **kidney problems (kidney failure).** In people who have kidney problems, diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems to get worse. It is important for you to drink fluids to help reduce your chance of dehydration.
- **severe stomach problems.** Stomach problems, sometimes severe, have been reported in people who use MOUNJARO. Tell your healthcare provider if you have stomach problems that are severe or will not go away.
- **changes in vision.** Tell your healthcare provider if you have changes in vision during treatment with MOUNJARO.
- **gallbladder problems.** Gallbladder problems have happened in some people who use MOUNJARO. Tell your healthcare provider right away if you get symptoms of gallbladder problems which may include:
  - pain in your upper stomach (abdomen)
  - fever
  - yellowing of skin or eyes (jaundice)
  - clay-colored stools

The most common side effects of MOUNJARO include:

- nausea
- diarrhea
- decreased appetite
- vomiting
- constipation
- indigestion
- stomach (abdominal) pain

Talk to your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of MOUNJARO. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store MOUNJARO?

- Store MOUNJARO in the refrigerator between 36ºF to 46ºF (2ºC to 8ºC). Store MOUNJARO in the original carton until use to protect it from light.
- If needed, each single-dose pen or single-dose vial can be stored at room temperature up to 86ºF (30ºC) for up to 21 days.
- Do not freeze MOUNJARO. Do not use MOUNJARO if frozen.

Keep MOUNJARO and all medicines out of the reach of children.

General information about the safe and effective use of MOUNJARO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use MOUNJARO for a condition for which it was not prescribed. Do not give MOUNJARO to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about MOUNJARO that is written for health professionals.

What are the ingredients in MOUNJARO?

Active ingredient: tirzepatide

Inactive ingredients: sodium chloride, sodium phosphate dibasic heptahydrate, and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH.

For more information, go to www.MOUNJARO.com or call 1-800-545-5979.

This Medication Guide has been approved by the U.S. Food and Drug Administration Approved: July 2023

MOU-0001-MG-YYYYMMDD

INSTRUCTIONS FOR USE

MOUNJARO® [mown-JAHR-OH]

(tirzepatide)

injection, for subcutaneous use

2.5 mg/0.5 mL single-dose vial

5 mg/0.5 mL single-dose vial

7.5 mg/0.5 mL single-dose vial

10 mg/0.5 mL single-dose vial

12.5 mg/0.5 mL single-dose vial

15 mg/0.5 mL single-dose vial

Important information you need to know before injecting MOUNJARO

Read this Instructions for Use before you start taking MOUNJARO and each time you get a new vial. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Do not share your needles or syringes with other people. You may give other people a serious infection or get a serious infection from them.

Talk to your healthcare provider about how to inject MOUNJARO the right way.

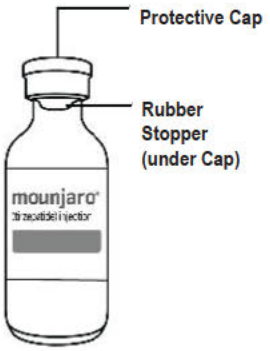
- MOUNJARO is a single-dose vial.
- MOUNJARO is used 1 time each week.
- Inject under the skin (subcutaneously) only.
- You or another person may inject into your stomach (abdomen) or thigh.
- Another person can inject into the back of your upper arm.

Gather supplies needed to give your injection

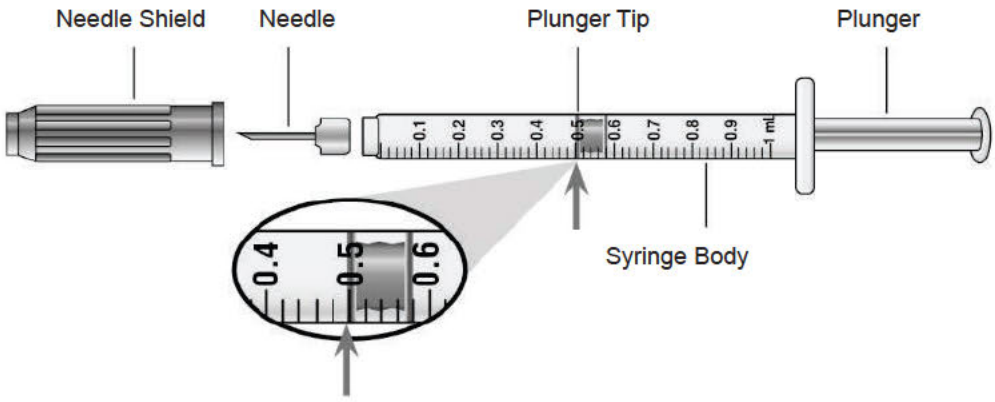
- 1 single-dose MOUNJARO vial
- 1 syringe and 1 needle, supplied separately (for example, use a 1 mL syringe and needle as recommended by your healthcare provider)
- 1 alcohol swab
- gauze
- 1 sharps container for throwing away used needles and syringes. **See** “Disposing of used needles and syringes” at the end of these instructions.

Guide to parts

Vial



Needle and Syringe (not included)



Note: The needle and syringe are not included. The needle and syringe recommended by your healthcare provider may look different than the needle and syringe in this Instructions for Use.

Preparing to inject MOUNJARO

Remove the vial from the refrigerator.

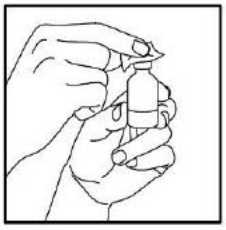
Check the vial label to make sure you have the right medicine and dose, and that it has not expired.

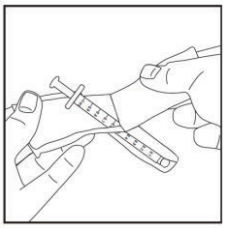
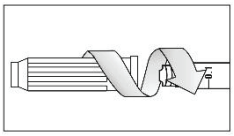
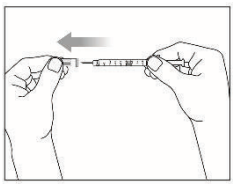
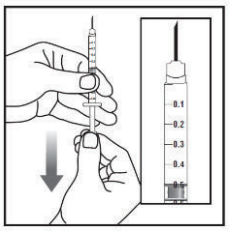
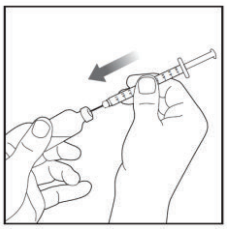
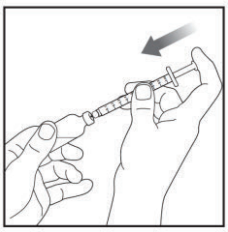
Make sure the medicine:

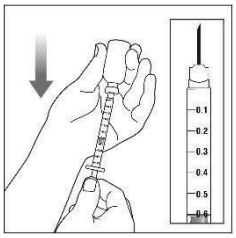
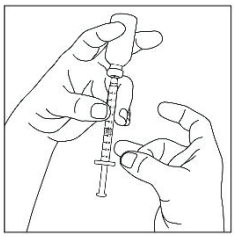
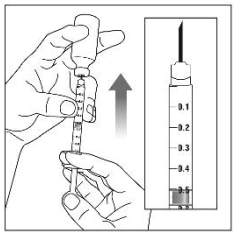
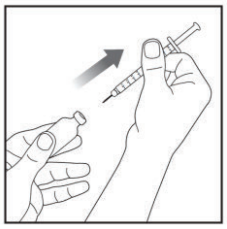
- is not frozen
- is colorless to slightly yellow
- is not cloudy
- does not have particles

Always use a new syringe and needle for each injection to prevent infections and blocked needles. Do not reuse or share your syringes or needles with other people. You may give other people a serious infection or get a serious infection from them.

Wash your hands with soap and water.

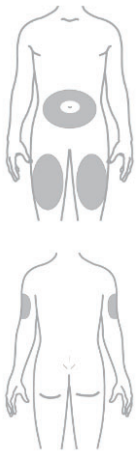
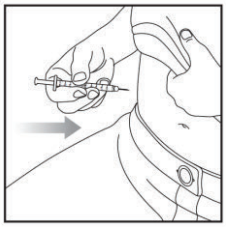
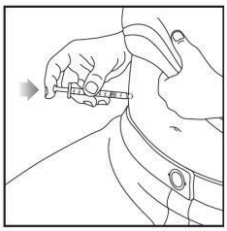
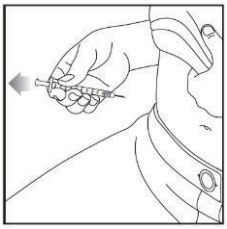
Step 1: Pull off the plastic protective cap. **Do not** remove the rubber stopper.	
Step 2: Wipe the rubber stopper with an alcohol swab.	

Step 3: Remove the outer wrapping from the syringe.	
Step 4: Remove the outer wrapping from the needle. The syringe that your healthcare provider recommended may have a pre-attached needle. If the needle is attached, skip to step 6.	
Step 5: Place the needle on top of the syringe and turn until it is tight and firmly attached.	
Step 6: Remove the needle shield by pulling straight off.	
Step 7: Hold the syringe in one hand with the needle pointing up. With the other hand pull down on the plunger until the plunger tip reaches the line on the syringe indicating that 0.5 mL of air has been drawn into the syringe.	
Step 8: Push the needle through the rubber stopper of the vial.	
Step 9: Push the plunger all the way in. This puts air into the vial and makes it easier to pull the solution from the vial.	

Step 10: Turn the vial and syringe upside down. Make sure that the tip of the needle is in the liquid and slowly pull the plunger down until the plunger tip is past the 0.5 mL line. If there are air bubbles, tap the syringe gently a few times to let any air bubbles rise to the top.	 
Step 11: Slowly push the plunger up until the plunger tip reaches the 0.5 mL line.	
Step 12: Pull the syringe out of the rubber stopper of the vial.	

Injecting MOUNJARO

- Inject exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you should pinch the skin before injecting.
- **Change (rotate) your injection site within the area you choose for each dose** to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites.
- **Do not** inject where the skin has pits, is thickened, or has lumps.
- **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.
- **Do not** mix MOUNJARO with any other medicine.
- **Do not** inject MOUNJARO in the same injection site used for other medicines.

Step 13: Choose your injection site. You can inject MOUNJARO under the skin (subcutaneously) of your stomach area (abdomen) or thighs. Someone else can inject in your stomach area, thighs, or the back of the upper arms.	
Step 14: Insert the needle into your skin.	
Step 15: Push down on the plunger to inject your dose. The needle should stay in your skin for at least 5 seconds to make sure you have injected all of your dose.	
Step 16: Pull the needle out of your skin. • If you see blood after you take the needle out of your skin, press the injection site with a piece of gauze or an alcohol swab. **Do not** rub the area. • **Do not** recap the needle. Recapping the needle can lead to a needle stick injury.	

Disposing of used needles and syringes

- Put your used needle and syringe in an FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) loose needles and syringes in your household trash.
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you

should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

Storing MOUNJARO

- Store all unopened vials in the refrigerator at 36°F to 46°F (2°C to 8°C).
- You may store the unopened vial at room temperature up to 86°F (30°C) for up to 21 days.
- **Do not** freeze. **Do not** use if MOUNJARO has been frozen.
- Store the vial in the original carton to protect from light.
- Throw away all opened vials after use, even if there is medicine left in the vial.

Keep MOUNJARO vials, syringes, needles, and all medicines out of the reach of children.

If you have any questions or problems with your MOUNJARO, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) or call your healthcare provider for help.

Manufactured by Eli Lilly and Company
Indianapolis, IN 46285, USA

MON-VL-0001-IFU-YYYYMMDD

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Approved: July/2023

INSTRUCTIONS FOR USE

MOUNJARO™ (mown-JAHR-OH)

(tirzepatide)

injection, for subcutaneous use

2.5 mg/0.5 mL single-dose pen

5 mg/0.5 mL single-dose pen

7.5 mg/0.5 mL single-dose pen

10 mg/0.5 mL single-dose pen

12.5 mg/0.5 mL single-dose pen

15 mg/0.5 mL single-dose pen

use 1 time each week

Important information you need to know before injecting MOUNJARO

Read this Instructions for Use and the Medication Guide before using your MOUNJARO Pen and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

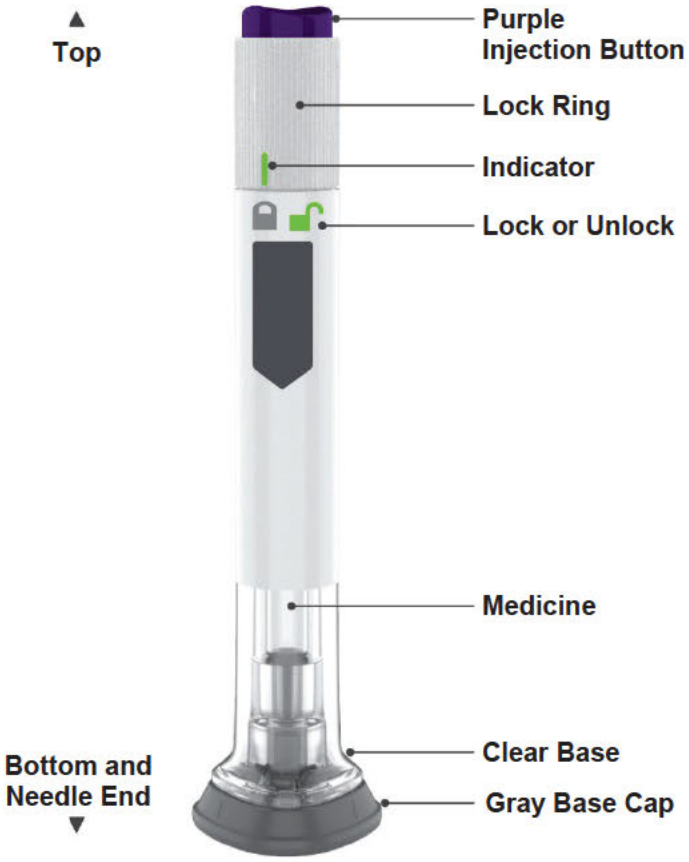
Talk to your healthcare provider about how to inject MOUNJARO the right way.

- MOUNJARO is a single-dose prefilled pen.
- MOUNJARO is used 1 time each week.
- Inject under the skin (subcutaneously) only.
- You or another person can inject into your stomach (abdomen) or thigh.
- Another person can inject into the back of your upper arm.

Storage and handling

- Store your Pen in the refrigerator between 36°F to 46°F (2°C to 8°C).
- You may store your Pen at room temperature up to 86°F (30°C) for up to 21 days.
- **Do not** freeze your Pen. If the Pen has been frozen, throw the Pen away and use a new Pen.
- Store your Pen in the original carton to protect your Pen from light.
- The Pen has glass parts. Handle it carefully. If you drop the Pen on a hard surface, **do not** use it. Use a new Pen for your injection.
- Keep your MOUNJARO Pen and all medicines out of the reach of children.

Guide to parts



Preparing to inject MOUNJARO

Remove the Pen from the refrigerator.

Leave the gray base cap on until you are ready to inject.

Check the Pen label to make sure you have the right medicine and dose, and that it has not expired.

Inspect the Pen to make sure that it is not damaged.

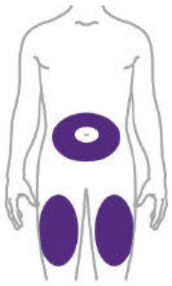
Make sure the medicine:

- is not frozen
- is colorless to slightly yellow
- is not cloudy
- does not have particles

Wash your hands.

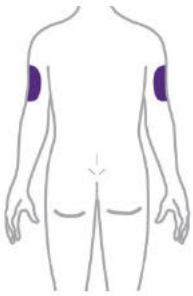
Step
1

Choose your injection site



Your healthcare provider can help you choose the injection site that is best for you.

You or another person can inject the medicine in your stomach (abdomen) or thigh.



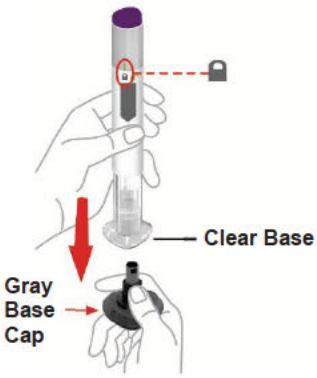
Another person should give you the injection in the back of your upper arm.

Change (rotate) your injection site each week.

You may use the same area of your body but be sure to choose a different injection site in that area.

Step
2

Pull off the gray base cap



Make sure the Pen is **locked**.

Do not unlock the Pen until you place the clear base on your skin and are ready to inject.

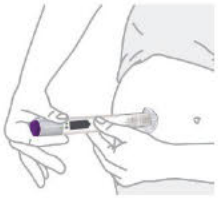
Pull the gray base cap straight off and throw it away in your household trash.

Do not put the gray base cap back on – this could damage the needle.

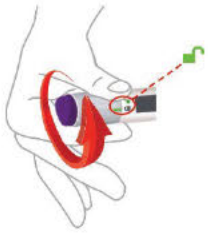
Do not touch the needle.

Step
3

Place clear base on skin, then unlock

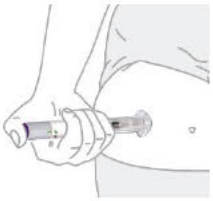


Place the clear base flat against your skin at the injection site.



Unlock by turning the lock ring.

Step 4 **Press and hold up to 10 seconds**



Press and hold the purple injection button for up to 10 seconds.

Listen for:

- First click = injection started
- Second click = injection completed

You will know your injection is complete when the gray plunger is visible.

After your injection, place the used Pen in a sharps container.

See **Disposing of your used Pen.**

Disposing of your used Pen

- Put your used Pen in an FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) Pens in your household trash.
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- **Do not** recycle your used sharps disposal container.

Commonly asked questions

What if I see air bubbles in my Pen?

Air bubbles are normal.

What if my Pen is not at room temperature?

It is not necessary to warm the Pen to room temperature.

What if I unlock the Pen and press the purple injection button before pulling off the gray base cap?

Do not remove the gray base cap. Throw away the Pen and get a new Pen.

What if there is a drop of liquid on the tip of the needle when I remove the gray base cap?

A drop of liquid on the tip of the needle is normal. **Do not** touch the needle.

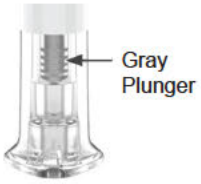
Do I need to hold the injection button down until the injection is complete?

This is not necessary, but it may help you keep the Pen steady against your skin.

I heard more than 2 clicks during my injection—2 loud clicks and 1 soft one. Did I get my complete injection?

Some people may hear a soft click right before the second loud click. That is the normal operation of the Pen. **Do not** remove the Pen from your skin until you hear the second loud click.

I am not sure if my Pen worked the right way.



Check to see if you have received your dose. Your dose was delivered the right way if the gray plunger is visible. Also, see **Step 4** of the instructions.

If you do not see the gray plunger, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) for further instructions. Until then, store your Pen safely to avoid an accidental needle stick.

What if there is a drop of liquid or blood on my skin after my injection?

This is normal. Press a cotton ball or gauze over the injection site. **Do not** rub the injection site.

Other information

- If you have vision problems, **do not** use your Pen without help from a person trained to use the MOUNJARO Pen.

Where to learn more

- If you have questions or problems with your MOUNJARO Pen, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) or call your healthcare provider.
- For more information about the MOUNJARO Pen, visit our website at www.mounjaro.com.

QR CODE

Scan this code to launch
www.mounjaro.com

Marketed by:
Lilly USA, LLC
Indianapolis, IN 46285, USA

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Approved: May 2022

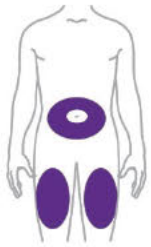
MOU-0001-IFU-YYYYMMDD

Quick Reference Guide

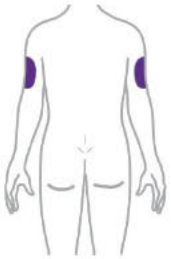
These are not complete instructions. Read the full INSTRUCTIONS FOR USE.

Step
1 Choose your injection site

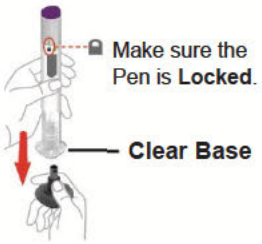
You or another person can inject the medicine in your stomach (abdomen) or thigh.



Another person should give you the injection in the back of your upper arm.



Step
2 Pull off the gray base cap

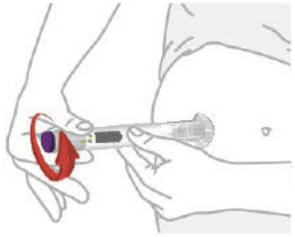


Pull the gray base cap straight off and throw it away in your household trash.

Do not put the gray base cap back on.

Do not touch the needle.

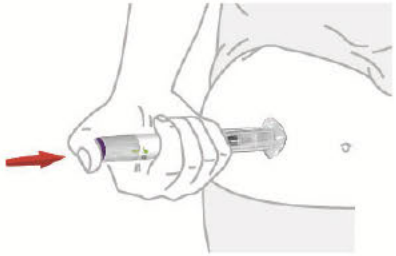
Step
3 Place clear base on skin, then unlock



Place the clear base flat against your skin at the injection site.

Unlock by turning the lock ring.

Step
4 Press and hold up to 10 seconds



Press and hold the purple injection button for up to 10 seconds.

Listen for:

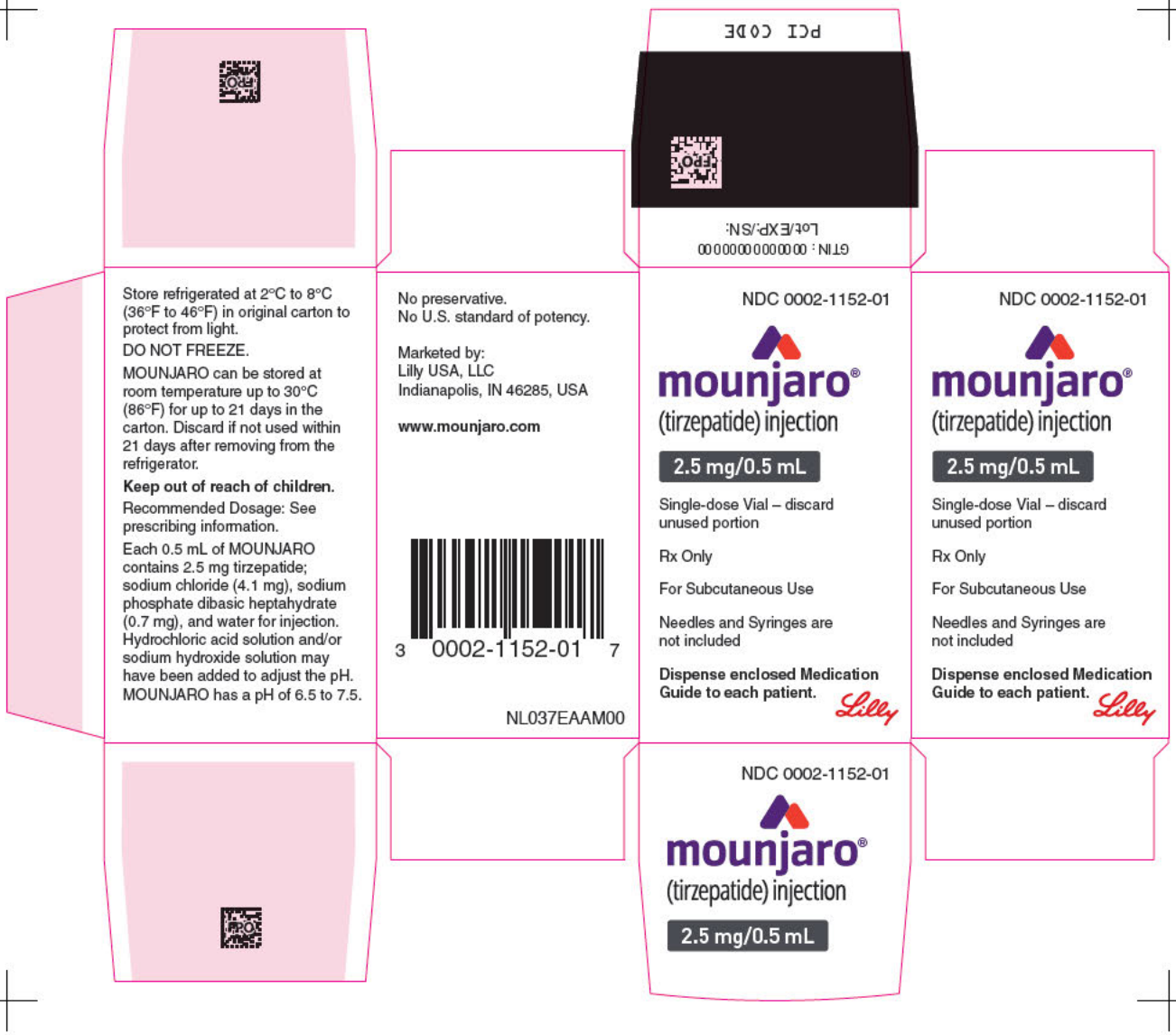
- First click = injection started
- Second click = injection completed

Injection is complete when you see the gray plunger.

After your injection

Place the used Pen in a sharps container.

See **Disposing of your used Pen** in the full **INSTRUCTIONS FOR USE**.


PCI CODE
GTIN: 00000000000000
Lot/EXP./SN:
Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.
DO NOT FREEZE.
MOUNJARO can be stored at room temperature up to 30°C (86°F) for up to 21 days in the carton. Discard if not used within 21 days after removing from the refrigerator.
Keep out of reach of children.
Recommended Dosage: See prescribing information.
Each 0.5 mL of MOUNJARO contains 2.5 mg tirzepatide; sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. MOUNJARO has a pH of 6.5 to 7.5.
No preservative.
No U.S. standard of potency.
Marketed by:
Lilly USA, LLC
Indianapolis, IN 46285, USA
www.mounjaro.com
3 0002-1152-01 7
NL037EAAM00
NDC 0002-1152-01
mounjaro®
(tirzepatide) injection
2.5 mg/0.5 mL
Single-dose Vial – discard unused portion
Rx Only
For Subcutaneous Use
Needles and Syringes are not included
Dispense enclosed Medication Guide to each patient.
Lilly
NDC 0002-1152-01
mounjaro®
(tirzepatide) injection
2.5 mg/0.5 mL
Single-dose Vial – discard unused portion
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(b) (4)


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Keep out of reach of children.
Recommended Dosage: See prescribing information.
Each 0.5 mL of MOUNJARO contains 5 mg tirzepatide; sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. MOUNJARO has a pH of 6.5 to 7.5.
No preservative.
No U.S. standard of potency.
Marketed by:
Lilly USA, LLC
Indianapolis, IN 46285, USA
www.mounjaro.com
3 0002-1243-01 2
NL038EAAM00
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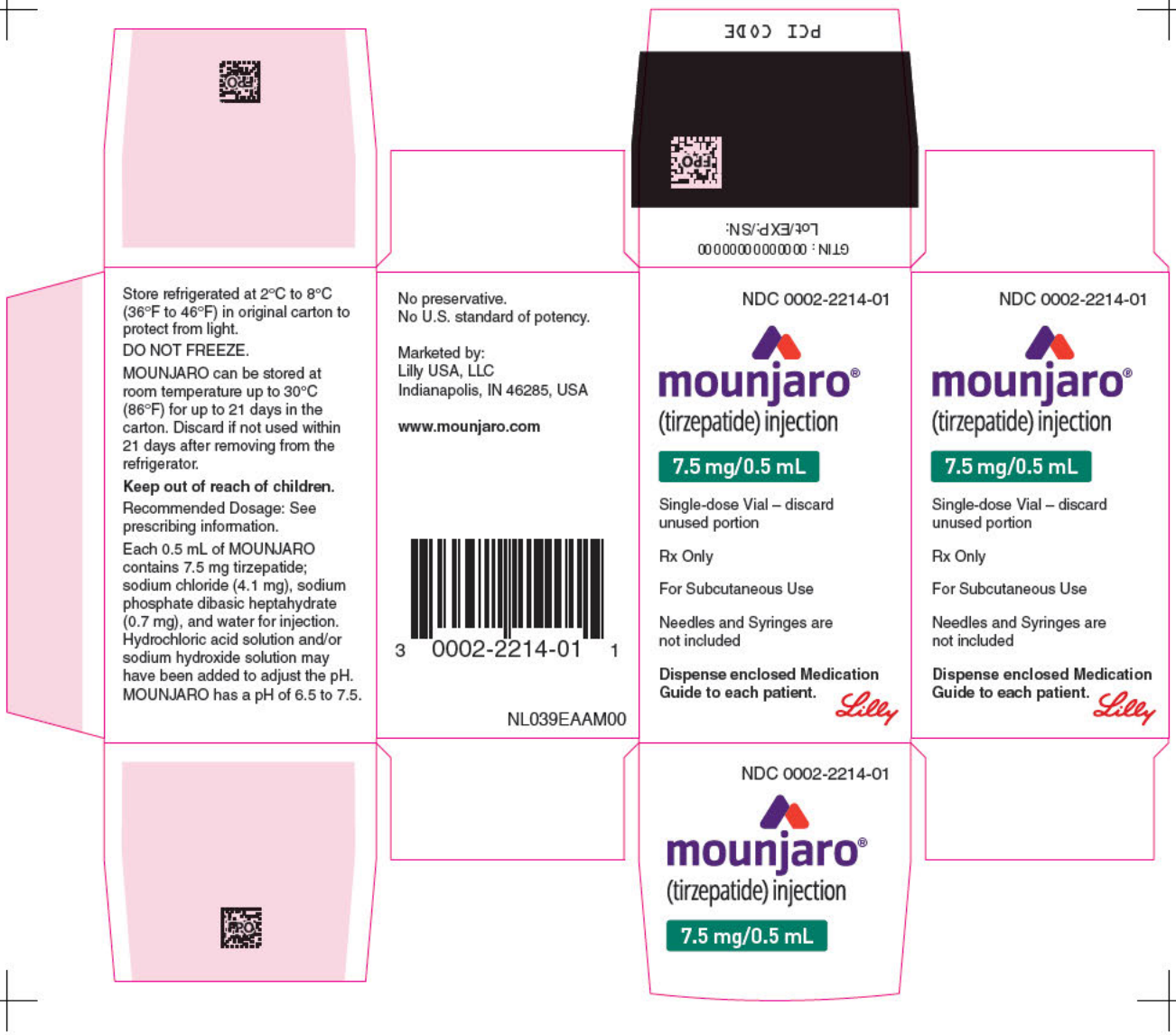
(tirzepatide) injection
5 mg/0.5 mL

(b) (4)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Keep out of reach of children.
Recommended Dosage: See prescribing information.
Each 0.5 mL of MOUNJARO contains 7.5 mg tirzepatide; sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. MOUNJARO has a pH of 6.5 to 7.5.
No preservative.
No U.S. standard of potency.
Marketed by:
Lilly USA, LLC
Indianapolis, IN 46285, USA
www.mounjaro.com
3 0002-2214-01 1
NL039EAAM00
NDC 0002-2214-01
mounjaro®
(tirzepatide) injection
7.5 mg/0.5 mL
Single-dose Vial – discard unused portion
Rx Only
For Subcutaneous Use
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(tirzepatide) injection
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Single-dose Vial – discard unused portion
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7.5 mg/0.5 mL

(b) (4)


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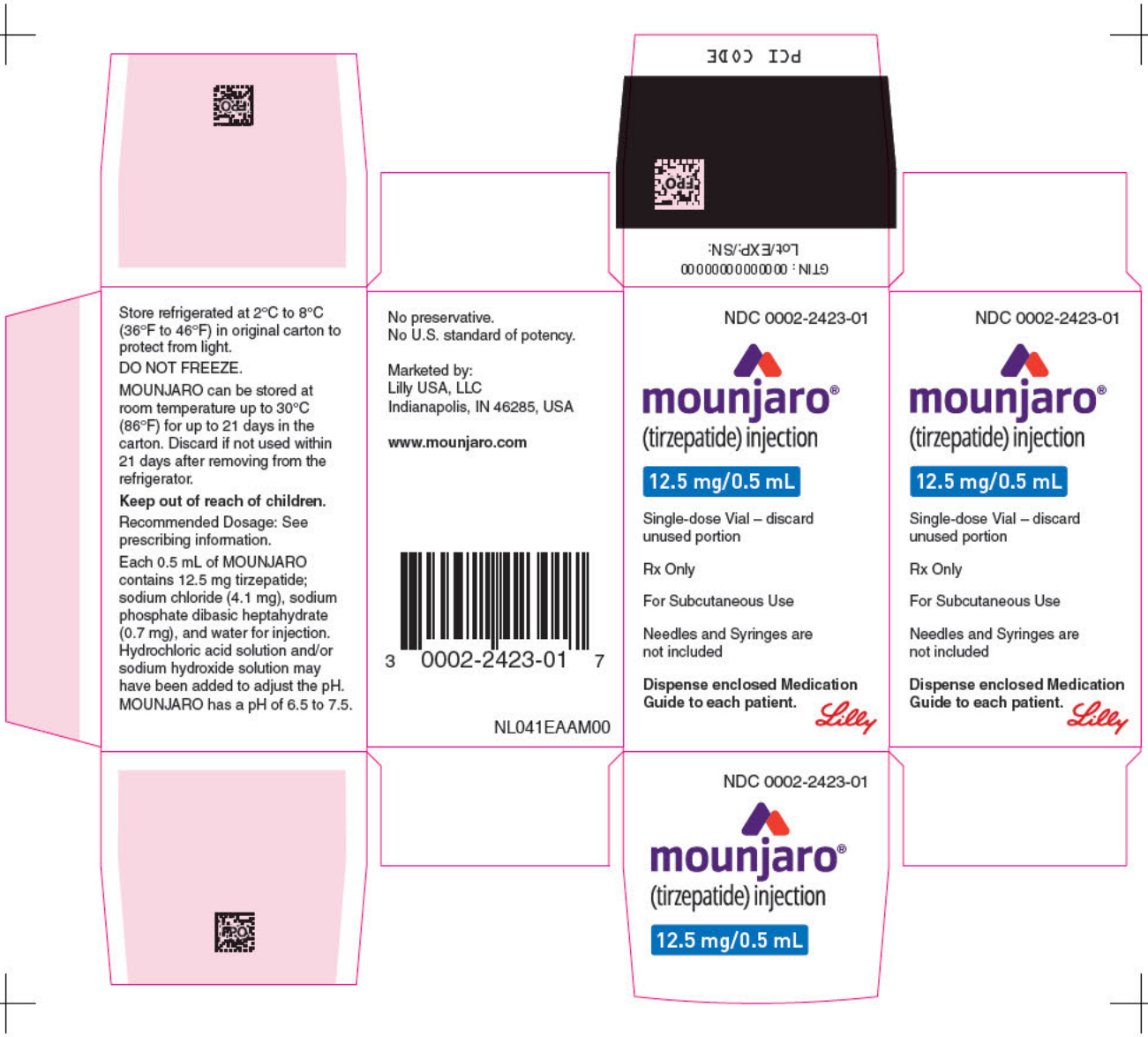
Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.
DO NOT FREEZE.
MOUNJARO can be stored at room temperature up to 30°C (86°F) for up to 21 days in the carton. Discard if not used within 21 days after removing from the refrigerator.
Keep out of reach of children.
Recommended Dosage: See prescribing information.
Each 0.5 mL of MOUNJARO contains 10 mg tirzepatide; sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. MOUNJARO has a pH of 6.5 to 7.5.
No preservative.
No U.S. standard of potency.
Marketed by:
Lilly USA, LLC
Indianapolis, IN 46285, USA
www.mounjaro.com
3 0002-2340-01 7
NL040EAAM00
NDC 0002-2340-01
mounjaro®
(tirzepatide) injection
10 mg/0.5 mL
Single-dose Vial – discard unused portion
Rx Only
For Subcutaneous Use
Needles and Syringes are not included
Dispense enclosed Medication Guide to each patient.
Lilly
NDC 0002-2340-01
mounjaro®
(tirzepatide) injection
10 mg/0.5 mL
Single-dose Vial – discard unused portion
Rx Only
For Subcutaneous Use
Needles and Syringes are not included
Dispense enclosed Medication Guide to each patient.
Lilly
NDC 0002-2340-01
mounjaro®
(tirzepatide) injection
10 mg/0.5 mL

(b) (4)


PCI CODE
GTIN: 00000000000000
Lot/EXP./SN:
Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.
DO NOT FREEZE.
MOUNJARO can be stored at room temperature up to 30°C (86°F) for up to 21 days in the carton. Discard if not used within 21 days after removing from the refrigerator.
Keep out of reach of children.
Recommended Dosage: See prescribing information.
Each 0.5 mL of MOUNJARO contains 12.5 mg tirzepatide; sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. MOUNJARO has a pH of 6.5 to 7.5.
No preservative.
No U.S. standard of potency.
Marketed by:
Lilly USA, LLC
Indianapolis, IN 46285, USA
www.mounjaro.com
3 0002-2423-01 7
NL041EAAM00
NDC 0002-2423-01
mounjaro®
(tirzepatide) injection
12.5 mg/0.5 mL
Single-dose Vial – discard unused portion
Rx Only
For Subcutaneous Use
Needles and Syringes are not included
Dispense enclosed Medication Guide to each patient.
Lilly
NDC 0002-2423-01
mounjaro®
(tirzepatide) injection
12.5 mg/0.5 mL
Single-dose Vial – discard unused portion
Rx Only
For Subcutaneous Use
Needles and Syringes are not included
Dispense enclosed Medication Guide to each patient.
Lilly
NDC 0002-2423-01
mounjaro®
(tirzepatide) injection
12.5 mg/0.5 mL

(b) (4)

Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.

DO NOT FREEZE.

MOUNJARO can be stored at room temperature up to 30°C (86°F) for up to 21 days in the carton. Discard if not used within 21 days after removing from the refrigerator.

Keep out of reach of children.

Recommended Dosage: See prescribing information.

Each 0.5 mL of MOUNJARO contains 15 mg tirzepatide; sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. MOUNJARO has a pH of 6.5 to 7.5.

No preservative.
No U.S. standard of potency.

Marketed by:
Lilly USA, LLC
Indianapolis, IN 46285, USA

www.mounjaro.com

3 0002-3002-01 3

NL042EAAM00

PCI CODE

GTIN: 00000000000000

Lot/EXP:/SN:

NDC 0002-3002-01

mounjaro®
(tirzepatide) injection

15 mg/0.5 mL

Single-dose Vial – discard unused portion

Rx Only

For Subcutaneous Use

Needles and Syringes are not included

Dispense enclosed Medication Guide to each patient.

Lilly

NDC 0002-3002-01

mounjaro®
(tirzepatide) injection

15 mg/0.5 mL

Single-dose Vial – discard unused portion

Rx Only

For Subcutaneous Use

Needles and Syringes are not included

Dispense enclosed Medication Guide to each patient.

Lilly

NDC 0002-3002-01

mounjaro®
(tirzepatide) injection

15 mg/0.5 mL

(b) (4)


NL031EAAM00
Marketed by:
Lilly USA, LLC
www.mounjaro.com
Rx only NDC 0002 11s2 01
mounjaro®
(tirzepatide) injection
2.5 mg/0.5 mL
Single dose Vial
For Subcutaneous Use
PCI CODE
Lot / Exp Date

(b) (4)


NL032EAAM00
Marketed by:
Lilly USA, LLC
www.mounjaro.com
Rx only NDC 0002 1243 01
mounjaro®
(tirzepatide) Injection
5 mg/0.5 mL
Single dose Vial
For Subcutaneous Use
PCI CODE
Lot/ExpDate

(b) (4)


NL033EAAM00
Marketed by:
Lilly USA, LLC
www.mounjaro.com
Rx only NDC 0002 2214 01
mounjaro®
(tirzepatide) injection
7.5 mg/0.5 mL
Single dose Vial
For Subcutaneous Use
PCI CODE
Lot / Exp. Date

(b) (4)


NL034EAAM00
Marketed by:
Lilly USA, LLC
www.mounjaro.com
Rx only NDC 0002 2340 01
mounjaro®
(tirzepatide) injection
10 mg/0.5 mL
Single dose Vial
For Subcutaneous Use
PCI CODE
Lot / Exp Date

(b) (4)


NL035EAAM00
Marketed by:
Lilly USA, LLC
www.mounjaro.com
Rx only NDC 0002 2423 01
mounjaro®
(tirzepatide) Injection
12.5 mg/0.5 mL
Single dose Vial
For Subcutaneous Use
PCI CODE
Lot / Exp Date

(b) (4)


NL036EAAM00
Marketed by:
Lilly USA, LLC
www.mounjaro.com
Rx only NDC 0002 3002 01
mounjaro®
(tirzepatide) Injection
15 mg/0.5 mL
Single dose Vial
For Subcutaneous Use
PCI CODE
Lot / Exp Date

(b) (4)

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/s/

PATRICK ARCHDEACON
07/28/2023 03:50:17 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215866Orig1s002

OTHER REVIEW(S)

Division of Diabetes, Lipid Disorders, and Obesity

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 215866/S-002, NDA 215866/S-006 – Labeling Supplements

Name of Drug: Mounjaro (tirzepatide) injection

Applicant: Eli Lilly and Company

Labeling Reviewed

Submission Date: January 31, 2023 (S-002), April 18, 2023 (S-006)

Receipt Date: January 31, 2023 (S-002), April 18, 2023 (S-006)

Background and Summary Description:

Mounjaro (tirzepatide) is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist that was approved on May 13, 2022, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Mounjaro (tirzepatide) is currently supplied as a clear, colorless to slightly yellow solution in pre-filled single-dose pens, each available in the following strengths:

- 2.5 mg/0.5 mL
- 5 mg/0.5 mL
- 7.5 mg/0.5 mL
- 10 mg/0.5 mL
- 12.5 mg/0.5 mL
- 15 mg/0.5 mL

The approved labeling includes a Prescribing Information, Medication Guide, Instructions for Use document, Quick Reference Guide and carton/container labeling.

On January 31, 2023, Eli Lilly submitted a Prior Approval Supplement (PAS) (S-002) for the addition of a single-use glass vial presentation, the addition (b) (4) as a manufacturing site for the single-use glass vial presentation, the addition of (b) (4) as quality control testing sites, and the addition of (b) (4) as a secondary packaging site for the vial presentation.

On April 18, 2023, Eli Lilly submitted a Changes Being Effected (CBE-0) Supplement (S-006) that provided for updates to Section 4, Section 5.4, Section 6.2 and Section 17 of the Mounjaro

Prescribing Information (PI) to reflect new safety information (anaphylaxis and angioedema).

FDA comments on the proposed labeling for S-002 and S-006 were sent to the Applicant on June 15, 2023, July 6 and July 21, 2023. Final agreed labeling was submitted by the Applicant on July 26 and 27, 2023.

Review

Reviews for S-002 and S-006 were provided by Division of Medication Error Prevention and Analysis (DMEPA)[1,2], Division of Medical Policy Programs (DMPP)[3], Office of Prescription Drug Promotion (OPDP)[4], Office of Surveillance and Epidemiology - Office of Pharmacovigilance and Epidemiology[5] and the Office of Lifecycle Drug Products Division of Post-Marketing Activities[6].

Each piece of proposed labeling was compared to the currently approved version, using the MS Word electronic comparison function and the Adobe PDF Compare Document function. Refer to the attached PDF document for a complete list of all applicable changes.

Labeling Piece	**Currently Approved Labeling and Date**	**Final Labeling Submission Date**
Prescribing Information	NDA 215866, May 13, 2022	July 26 and July 27, 2023
Medication Guide	NDA 215866, May 13, 2022	July 26 and July 27, 2023
Instructions for Use (vial)	N/A – Initial IFU for vial presentation created for S-002	July 26 and July 27, 2023
Carton and Containers (vial)	N/A – Initial C&Cs for vial presentation created for S-002	July 26, 2023

There were no changes to the Quick Reference Guide. The currently approved version, previously approved on May 13, 2022, will be attached to the approval letter.

There were no changes to the IFU (single-dose pen). The currently approved version, previously approved on May 13, 2022, will be attached to the approval letter.

1 Conrad, A. DMEPA Memorandum: Revised Label and Labeling Review. DARRTS Reference ID: 5216205. July 27, 2023
2 Conrad, A. DMEPA Label and Labeling Review. DARRTS Reference ID: 5187490. June 8, 2023
3 Carroll, M. Patient Labeling Review. DARRTS Reference ID: 5211819. July 19, 2023
4 Butler, T. OPDP Labeling Comments for Mounjaro (tirzepatide) injection, Memorandum. DARRTS Reference ID: 5210278. July 17, 2023
5 Dunne, I. Pharmacovigilance Review. DARRTS Reference ID: 5204510. July 10, 2023
6 Zimmermann, S. Review of Chemistry, Manufacturing, and Controls. Refer to review in Panorama. July 20, 2023

Recommendations

An approval letter should be issued for NDA 215866/S-002, NDA 215866/S-006.

Lindsey Kelly	7/27/23
Regulatory Project Manager	Date
Callie Cappel-Lynch/ Elizabeth Solomon	7/27/23
Chief, Project Management Staff	Date

23 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LINDSEY T KELLY
07/27/2023 04:56:22 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 27, 2023
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 215866/S-002
Product Name, Dosage Form, and Strength:	Mounjaro (tirzepatide) injection, 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, 15 mg/0.5 mL
Applicant/Sponsor Name:	Eli Lilly and Company (Lilly)
TTT ID #:	2023-3683-1
DMEPA 1 Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Lilly submitted revised container labels and carton labeling for Mounjaro on July 26, 2023. The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the revised container labels and carton labeling for Mounjaro (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] Lilly provided responses to each of the recommendations and agreed to implement most of them.

Of note, in response to our comment regarding their proposal to package one single-dose vial per carton, Lilly stated that the "*proposed labeling is sufficiently clear that each carton contains a single-dose vial and as such, helps mitigate against medication errors. Prescriptions will be based on quantity sufficient to fill a volume (for example, 2.0 mL being equivalent to a one-month supply), number of presentations (for example, 4 single-dose pens or vials), or duration of therapy (for example, one-month supply). As the dose-strength is the same between the currently approved single-dose pen and the proposed single-dose vial, the quantity sufficient for a one-month supply will be the same. Pharmacists will dispense a quantity sufficient to meet the prescription.* (b) (4)

[a] Conrad, A. Label and Labeling Review for Mounjaro (NDA 215866/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Jun 8. TTT ID No.: 2023-3683.

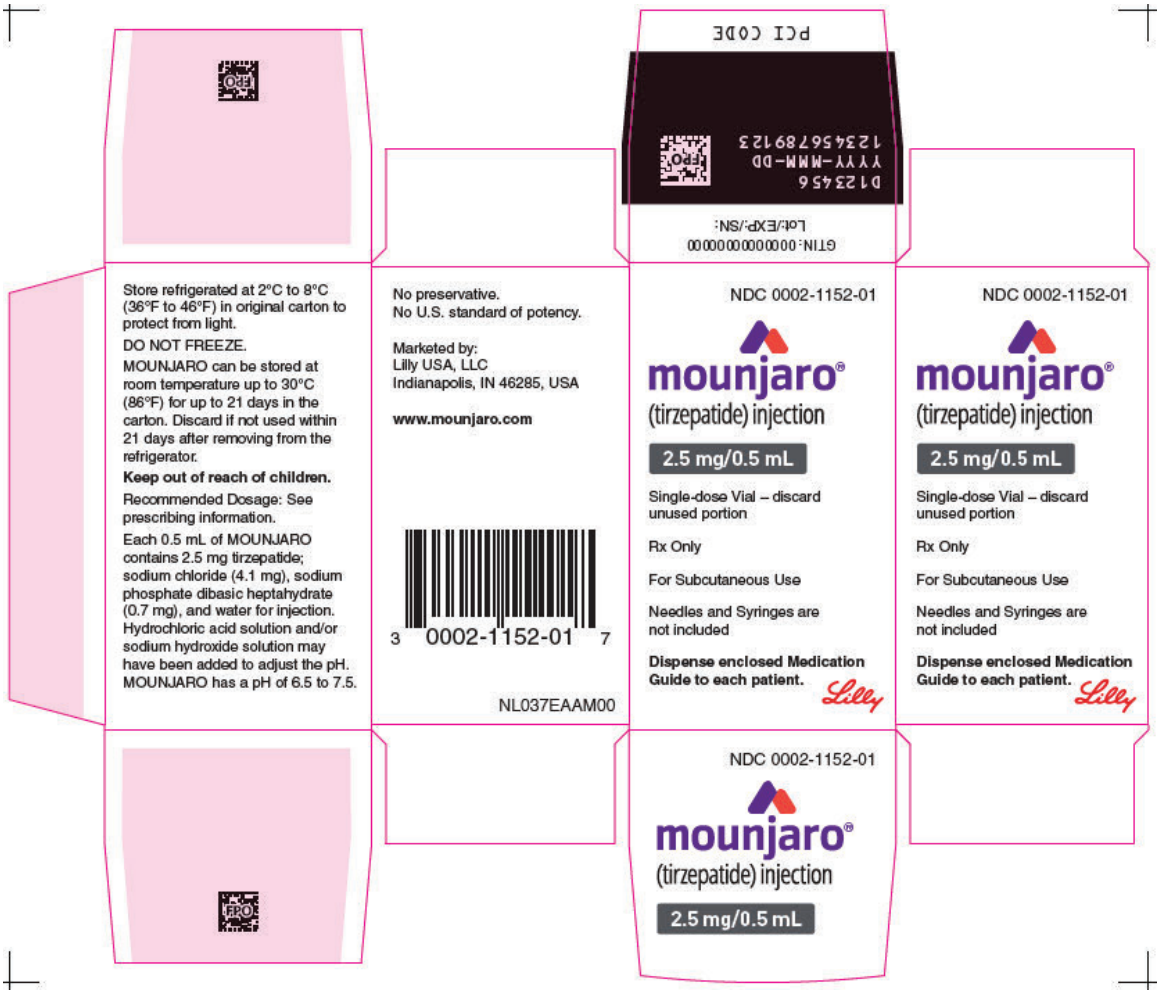
(b) (4) Thus, they determined that it was not feasible to revise their proposed (b) (4)

2 CONCLUSION

Lilly addressed our recommendations for the proposed cartons and container labels, and we find them to be acceptable from a medication error perspective. We have no additional recommendations at this time.

APPEARS THIS WAY ON ORIGINAL

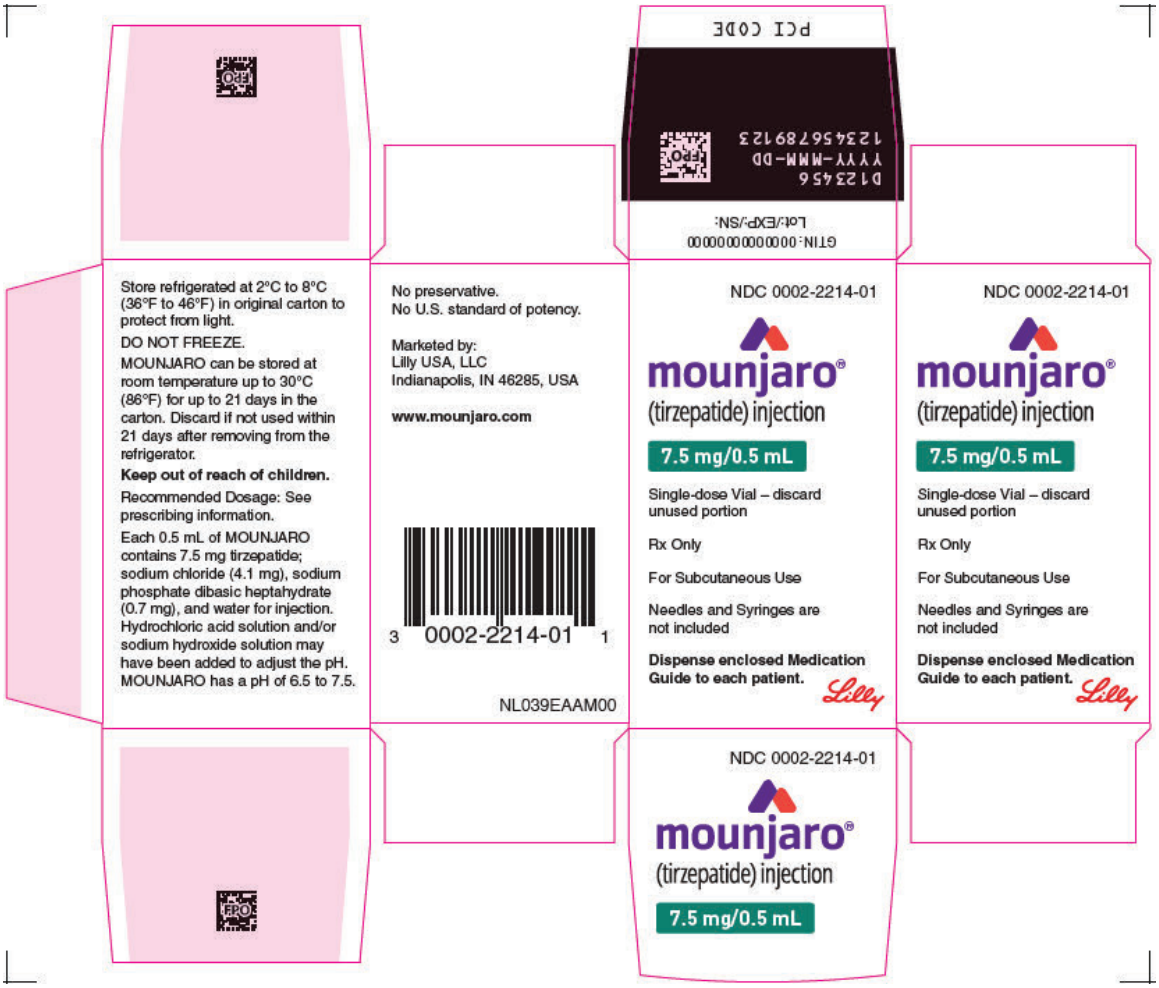
APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JULY 26, 2023




NL032EAAM00
Marketed by:
Lilly USA, LLC
www.mounjaro.com
Rx only NDC 0002-1243-01
mounjaro®
(tirzepatide) injection
5 mg/0.5 mL
Single-dose Vial
For Subcutaneous Use
PCI CODE
Lot / Exp Date
D123456
YYYY-MMM-DD

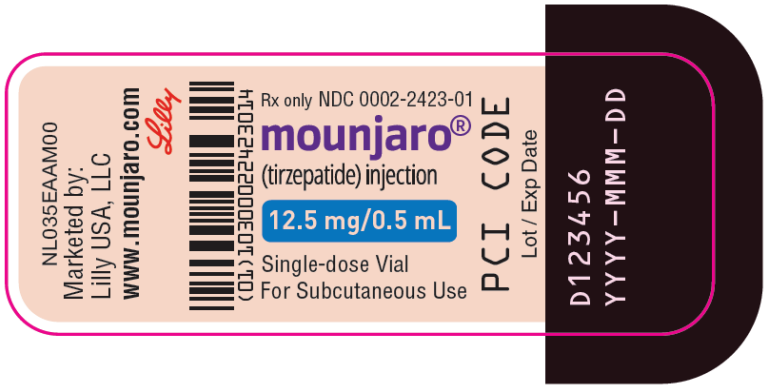

Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.
DO NOT FREEZE.
MOUNJARO can be stored at room temperature up to 30°C (86°F) for up to 21 days in the carton. Discard if not used within 21 days after removing from the refrigerator.
Keep out of reach of children.
Recommended Dosage: See prescribing information.
Each 0.5 mL of MOUNJARO contains 5 mg tirzepatide; sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. MOUNJARO has a pH of 6.5 to 7.5.
No preservative.
No U.S. standard of potency.
Marketed by:
Lilly USA, LLC
Indianapolis, IN 46285, USA
www.mounjaro.com
3 0002-1243-01 2
NL038EAAM00
PCI CODE
D123456
YYYY-MMM-DD
123456789123
GTIN: 00000000000000
Lot/EXP/SN:
NDC 0002-1243-01
mounjaro®
(tirzepatide) injection
5 mg/0.5 mL
Single-dose Vial – discard unused portion
Rx Only
For Subcutaneous Use
Needles and Syringes are not included
Dispense enclosed Medication Guide to each patient.
NDC 0002-1243-01
mounjaro®
(tirzepatide) injection
5 mg/0.5 mL
Single-dose Vial – discard unused portion
Rx Only
For Subcutaneous Use
Needles and Syringes are not included
Dispense enclosed Medication Guide to each patient.
NDC 0002-1243-01
mounjaro®
(tirzepatide) injection
5 mg/0.5 mL

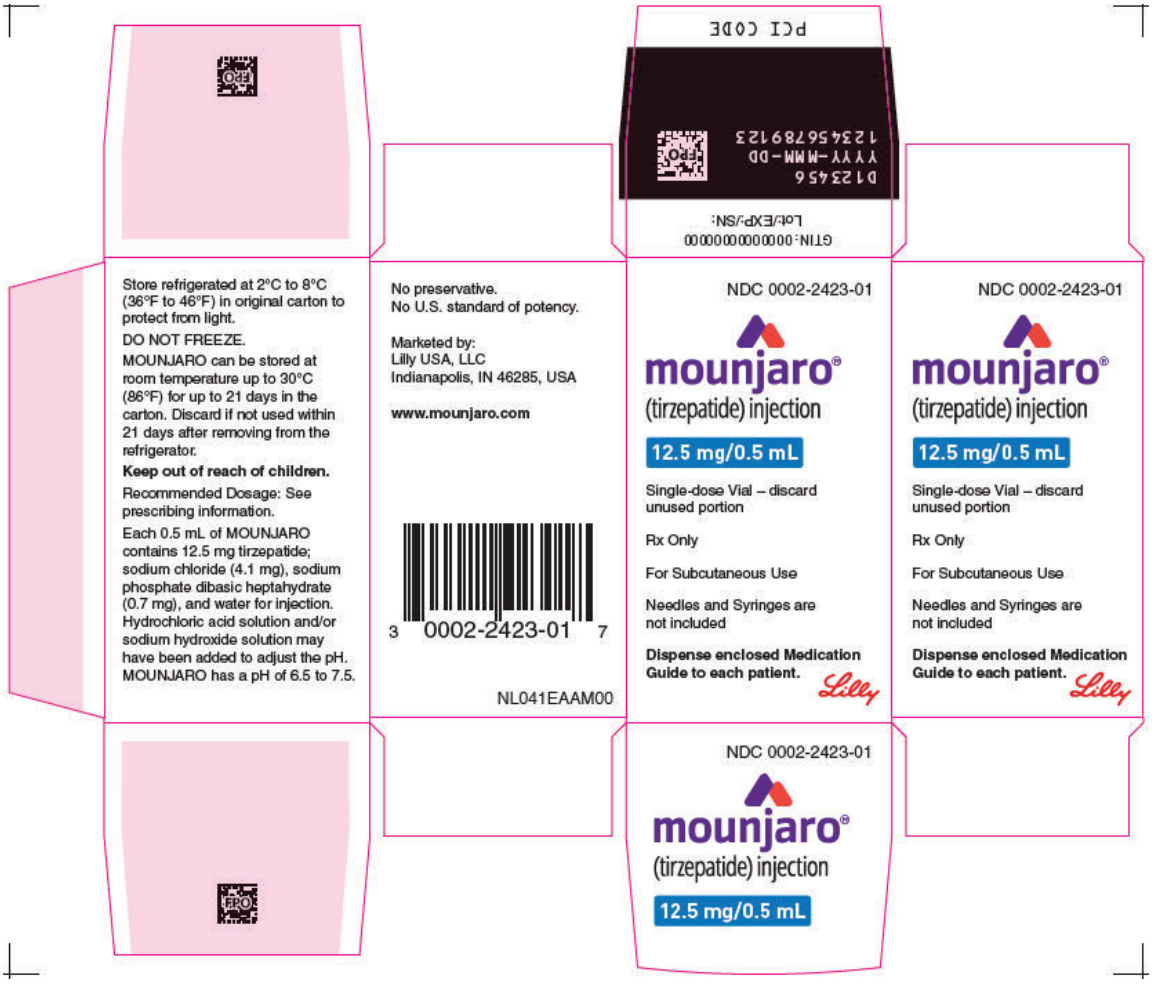

NL033EAAM00
Marketed by:
Lilly USA, LLC
www.mounjaro.com
Rx only NDC 0002-2214-01
mounjaro®
(tirzepatide) injection
7.5 mg/0.5 mL
Single-dose Vial
For Subcutaneous Use
PCI CODE
Lot / Exp Date
D123456
YYYY-MMM-DD


Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.
DO NOT FREEZE.
MOUNJARO can be stored at room temperature up to 30°C (86°F) for up to 21 days in the carton. Discard if not used within 21 days after removing from the refrigerator.
Keep out of reach of children.
Recommended Dosage: See prescribing information.
Each 0.5 mL of MOUNJARO contains 7.5 mg tirzepatide; sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. MOUNJARO has a pH of 6.5 to 7.5.
No preservative.
No U.S. standard of potency.
Marketed by:
Lilly USA, LLC
Indianapolis, IN 46285, USA
www.mounjaro.com
3 0002-2214-01 1
NL039EAAM00
PCI CODE
D123456
YYYY-MMM-DD
NDC 0002-2214-01
mounjaro®
(tirzepatide) injection
7.5 mg/0.5 mL
Single-dose Vial – discard unused portion
Rx Only
For Subcutaneous Use
Needles and Syringes are not included
Dispense enclosed Medication Guide to each patient.
Lilly
NDC 0002-2214-01
mounjaro®
(tirzepatide) injection
7.5 mg/0.5 mL
Single-dose Vial – discard unused portion
Rx Only
For Subcutaneous Use
Needles and Syringes are not included
Dispense enclosed Medication Guide to each patient.
Lilly
NDC 0002-2214-01
mounjaro®
(tirzepatide) injection
7.5 mg/0.5 mL


NL034EAAM00
Marketed by:
Lilly USA, LLC
www.mounjaro.com
Rx only NDC 0002-2340-01
mounjaro®
(tirzepatide) injection
10 mg/0.5 mL
Single-dose Vial
For Subcutaneous Use
PCI CODE
Lot / Exp Date
D123456
YYYY-MMM-DD


Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.
DO NOT FREEZE.
MOUNJARO can be stored at room temperature up to 30°C (86°F) for up to 21 days in the carton. Discard if not used within 21 days after removing from the refrigerator.
Keep out of reach of children.
Recommended Dosage: See prescribing information.
Each 0.5 mL of MOUNJARO contains 10 mg tirzepatide; sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. MOUNJARO has a pH of 6.5 to 7.5.
No preservative.
No U.S. standard of potency.
Marketed by:
Lilly USA, LLC
Indianapolis, IN 46285, USA
www.mounjaro.com
3 0002-2340-01 7
NL040EAAM00
PCI CODE
D123456
YYYY-MMM-DD
GTIN: 00000000000000
Lot:/EXP:/SN:
NDC 0002-2340-01
mounjaro®
(tirzepatide) injection
10 mg/0.5 mL
Single-dose Vial – discard unused portion
Rx Only
For Subcutaneous Use
Needles and Syringes are not included
Dispense enclosed Medication Guide to each patient.
NDC 0002-2340-01
mounjaro®
(tirzepatide) injection
10 mg/0.5 mL
Single-dose Vial – discard unused portion
Rx Only
For Subcutaneous Use
Needles and Syringes are not included
Dispense enclosed Medication Guide to each patient.
NDC 0002-2340-01
mounjaro®
(tirzepatide) injection
10 mg/0.5 mL


NL035EAAM00
Marketed by:
Lilly USA, LLC
www.mounjaro.com
Rx only NDC 0002-2423-01
mounjaro®
(tirzepatide) injection
12.5 mg/0.5 mL
Single-dose Vial
For Subcutaneous Use
PCI CODE
Lot / Exp Date
D123456
YYYY-MMM-DD


Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.
DO NOT FREEZE.
MOUNJARO can be stored at room temperature up to 30°C (86°F) for up to 21 days in the carton. Discard if not used within 21 days after removing from the refrigerator.
Keep out of reach of children.
Recommended Dosage: See prescribing information.
Each 0.5 mL of MOUNJARO contains 12.5 mg tirzepatide; sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. MOUNJARO has a pH of 6.5 to 7.5.
No preservative.
No U.S. standard of potency.
Marketed by:
Lilly USA, LLC
Indianapolis, IN 46285, USA
www.mounjaro.com
3 0002-2423-01 7
NL041EAAM00
PCI CODE
GTIN: 00000000000000
Lot/EXP/SN:
D123456
YYYY-MMM-DD
1234567891 23
NDC 0002-2423-01
mounjaro®
(tirzepatide) injection
12.5 mg/0.5 mL
Single-dose Vial – discard unused portion
Rx Only
For Subcutaneous Use
Needles and Syringes are not included
Dispense enclosed Medication Guide to each patient.
NDC 0002-2423-01
mounjaro®
(tirzepatide) injection
12.5 mg/0.5 mL
Single-dose Vial – discard unused portion
Rx Only
For Subcutaneous Use
Needles and Syringes are not included
Dispense enclosed Medication Guide to each patient.
NDC 0002-2423-01
mounjaro®
(tirzepatide) injection
12.5 mg/0.5 mL


NL036EAAM00
Marketed by:
Lilly USA, LLC
www.mounjaro.com
Rx only NDC 0002-3002-01
mounjaro®
(tirzepatide) injection
15 mg/0.5 mL
Single-dose Vial
For Subcutaneous Use
PCI CODE
Lot / Exp Date
D123456
YYYY-MMM-DD


Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.
DO NOT FREEZE.
MOUNJARO can be stored at room temperature up to 30°C (86°F) for up to 21 days in the carton. Discard if not used within 21 days after removing from the refrigerator.
Keep out of reach of children.
Recommended Dosage: See prescribing information.
Each 0.5 mL of MOUNJARO contains 15 mg tirzepatide; sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. MOUNJARO has a pH of 6.5 to 7.5.
No preservative.
No U.S. standard of potency.
Marketed by:
Lilly USA, LLC
Indianapolis, IN 46285, USA
www.mounjaro.com
3 0002-3002-01 3
NL042EAAM00
PCI CODE
GTIN: 00000000000000
Lot/EXP/SN:
D123456
YYYY-MMM-DD
1234567891 23
NDC 0002-3002-01
mounjaro®
(tirzepatide) injection
15 mg/0.5 mL
Single-dose Vial – discard unused portion
Rx Only
For Subcutaneous Use
Needles and Syringes are not included
Dispense enclosed Medication Guide to each patient.
Lilly
NDC 0002-3002-01
mounjaro®
(tirzepatide) injection
15 mg/0.5 mL
Single-dose Vial – discard unused portion
Rx Only
For Subcutaneous Use
Needles and Syringes are not included
Dispense enclosed Medication Guide to each patient.
Lilly
NDC 0002-3002-01
mounjaro®
(tirzepatide) injection
15 mg/0.5 mL

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/s/

ARIANE O CONRAD
07/27/2023 11:31:24 AM

IDALIA E RYCHLIK
07/27/2023 12:23:15 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 19, 2023
To:	Lindsey Kelly, Pharm.D. Regulatory Project Manager **Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Tierra Butler, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: (Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	MOUNJARO (tirzepatide)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 215866
Supplement Number:	S-002
Applicant:	Eli Lilly and Company

1 INTRODUCTION

On January 31, 2023, Eli Lilly and Company submitted for the Agency's review a Prior Approval Supplement (PAS) – Labeling for their approved New Drug Application (NDA) 215866/S-002 MOUNJARO (tirzepatide) injection, for subcutaneous use. This supplemental application is seeking approval for an additional container closure system, a single-use glass vial.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) on February 15, 2023 and February 13, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for MOUNJARO (tirzepatide) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft MOUNJARO (tirzepatide) MG and IFU received on January 31, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 6, 2023.
- Draft MOUNJARO (tirzepatide) Prescribing Information (PI) received on January 31, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 6, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

We find the proposed MG received on February 23, 2023 to be acceptable. The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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LASHAWN M GRIFFITHS
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 17, 2023

To: Lindsey Kelly, PharmD, Regulatory Project Manager, Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Frank Pucino, MD, Clinical Reviewer, DDLO

Melinda Wilson, PharmD, MPH, Associate Director for Labeling, DDLO

From: Tierra Butler, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for MOUNJARO (tirzepatide) injection, for subcutaneous use

NDA: 215866, S-002 and S-006

Background:

In response to DDLO's consult request dated February 13, 2023 and May 4, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide/Instructions for Use (IFU), and carton and container labeling for supplement 002 and 006 for Mounjaro. Supplement 002 includes creation of a new IFU for an additional container closure system, a single-use glass vial, and supplement 006 updates the PI with additional new safety language for anaphylactic reactions based on post-marketing safety surveillance.

PI/Medication Guide/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on July 6, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide/IFU, and comments will be sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on July 13, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Tierra Butler at 301-796-1368 or tierra.butler@fda.hhs.gov.

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 8, 2023
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 215866/S-002
Product Name, Dosage Form, and Strength:	Mounjaro (tirzepatide) injection, 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, 15 mg/0.5 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eli Lilly and Company (Lilly)
FDA Received Date:	January 31, 2023
TTT ID #:	2023-3683
DMEPA 1 Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

Eli Lilly and Company submitted a Chemistry Manufacturing and Controls (CMC) Supplement for Mounjaro (tirzepatide) injection under NDA 215866/S-002. The supplement proposes to introduce new single-dose vial presentations for each of the approved dosage presentations of Mounjaro. The original NDA for Mounjaro included six single-dose prefilled pens (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, and 15 mg/0.5 mL) and was approved on May 13, 2022.

Subsequently, the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the revised Mounjaro prescribing information (PI) and the proposed Instructions for Use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	C

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the revised prescribing information (PI) and proposed Instructions for Use (IFU), container labels, and carton labeling for Mounjaro to identify areas of vulnerability that may lead to medication errors and other areas of improvement. Of note, Lilly proposes to introduce single-dose vial presentations for each of the approved doses of Mounjaro; (b) (4)

(b) (4)

(b) (4)

(b) (4) We also identified other areas of concern for the PI, IFU, container labels, and carton labeling, and our recommendations are noted below in Section 4.1 for the Division and Section 4.2 for Lilly.

4 CONCLUSION & RECOMMENDATIONS

The proposed labels and labeling for Mounjaro are not acceptable from a medication error perspective and we have provided recommendations to improve clarity below in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR DIVISION OF DIABETES, LIPID DISORDERS, AND OBESITY (DDLO)

A. Prescribing Information

1. Dosage and Administration Section 2

a. (b) (4)

b. Recommendations for Section 2.2 are noted in track changes below:

[a] (b) (4) (b) (4) \\CDSESUB1\EVSPROD\nda215866\0286\m1\us\regulatory-response--ifu-fda-may-2023-.pdf.

2.2 Important Administration Instructions

- (b) (4)
- Administer MOUNJARO once weekly, any time of day, with or without meals.
- Inject MOUNJARO subcutaneously in the abdomen, thigh, or upper arm.
- Rotate injection sites with each dose.
- Inspect MOUNJARO visually before use. It should appear clear and colorless to slightly yellow. Do not use MOUNJARO if particulate matter or discoloration is seen.
- When using MOUNJARO with insulin, administer as separate injections and never mix. It is acceptable to inject MOUNJARO and insulin in the same body region, but the injections should not be adjacent to each other.

2. How Supplied/Storage and Handling Section 16

   a. For improved readability and clarity, we recommend revising the section to appears as follows:

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

MOUNJARO is a clear, colorless to slightly yellow solution available in cartons containing 4 pre-filled single-dose pens or 1 single-dose vial as follows:

Total Strength per Total Volume	(b) (4)	(b) (4) Pen NDC	(b) (4)	(b) (4) Vial NDC
2.5 mg/0.5 mL		0002-1506-80		0002-1152-01
5 mg/0.5 mL		0002-1495-80		0002-1243-01
7.5 mg/0.5 mL		0002-1484-80		0002-2214-01
10 mg/0.5 mL		0002-1471-80		0002-2340-01
12.5 mg/0.5 mL		0002-1460-80		0002-2423-01
15 mg/0.5 mL		0002-1457-80		0002-3002-01

B. Instructions for Use

1. (b) (4)

2. Replace (b) (4) with an image of the actual vial and ensure that this image aligns with the approved vial label for improved clarity.

3. We note that the instructions to attach separately supplied needles to the syringe are provided. However, the image of the needle provided appears to be inconsistent with the instructions provided because (b) (4)

[redacted] For improved clarity of this image and alignment with your instructions, we recommend revising the image to include separate images of the needle and syringe with each of the parts labeled, which is consistent with Lilly's format in the Humalog KwikPen IFU (for example, "Syringe Parts" and "Needle Parts (Needles not included)".

4. As [redacted] Failure to provide this information may lead to administrations errors or delay in therapy, therefore, we recommend adding the statement "Needles and Syringes are not included" to the IFU.

4.2 RECOMMENDATIONS FOR ELI LILLY AND COMPANY

We recommend the following be implemented prior to approval of this NDA Supplement:

A. General Comments (Container labels & Carton Labeling)

1. Add the placeholder for the expiration date in accordance with USP General Chapter <7>. We recommend you ensure that there are no other numbers located near the expiration date. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date.

2. We note that you [redacted] however, [redacted] In addition, we note that this [redacted] We are concerned that this inconsistency will introduce the potential for medication errors resulting in dosing and omission errors. [redacted]

B. Container Labels

1. We note that the [redacted] accordingly, increase the prominence [redacted]

In addition, we note that the established name does not appear to be at least half the size of the proprietary name. Revise the established name to be in accordance with 21 CFR 201.10(g)(2). Also, you can consider making the box around the product strength smaller to improve readability of other information on the label.

2. Consider decreasing the prominence of the statement [redacted] (b) (4) by relocating the statement to the bottom of the label as this information appears more prominent than the established name on the principal display panel.
3. To ensure consistency with the Prescribing Information, add the statement "Recommended Dosage: See prescribing information" to the side panel.
4. Consider revising the net quantity statement to read "0.5 mL single-dose vial" for improved clarity. However, if there is excess volume in the vials (i.e., greater than 0.5 mL), please clarify and revise the statement to read "single-dose vial – discard unused portion" instead. Inclusion of this discard statement helps minimize the risk of the entire contents of the vial being given as a single dose. See Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018).
5. We note that the [redacted] (b) (4) appear to be presented on the [redacted] (b) (4) which could lead to confusion. To ensure that there are no other numbers located near the expiration date that could be confused with the expiration date, we recommend that you consider moving the lot number and serial number to separate lines.

C. Carton Labeling

1. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.
2. Revise the net quantity statement to read "One 0.5 mL single-dose vial" for improved clarity. However, if there is excess volume in the vials (i.e., greater than 0.5 mL), please clarify and revise the statement to read "single-dose vial – discard unused portion" instead. Inclusion of this discard statement helps

minimize the risk of the entire contents of the vial being given as a single dose. See Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018).

3. As currently presented, the principal display panel (b) (4)

(b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

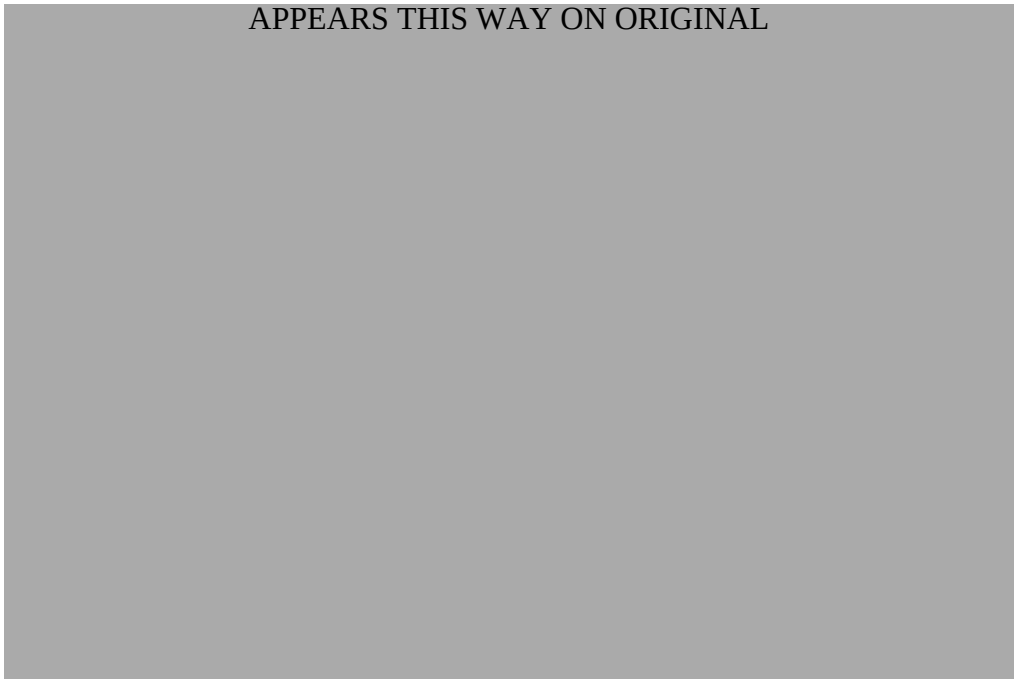
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Mounjaro received on January 31, 2023 from Eli Lilly and Company.

Table 2. Relevant Product Information for Mounjaro	
Initial Approval Date	May 13, 2022
Active Ingredient	tirzepatide
Indication	an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Route of Administration	subcutaneous
Dosage Form	injection
Strength	2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, 15 mg/0.5 mL
Dose and Frequency	• The recommended starting dosage is 2.5 mg injected subcutaneously once weekly. After 4 weeks, increase to 5 mg injected subcutaneously once weekly. • If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose. The maximum dosage is 15 mg subcutaneously once weekly
How Supplied	2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, 15 mg/0.5 mL in a prefilled pen or single-dose vial
Storage	refrigerate at 2°C to 8°C (36°F to 46°F).
Container Closure	single-dose pen or single-dose vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 25, 2023, we searched for previous DMEPA reviews relevant to this current review using the term, Mounjaro. Our search identified 4 previous reviews[b], and we considered our previous recommendations to see if they are applicable for this current review.



[b] Kumar, N. Review of Revised Label and Labeling Memorandum for Mounjaro (NDA 215866). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 May 13. RCM No.: 2021-1827-1.

Conrad, A. Review of Revised Label and Labeling Memorandum for Mounjaro (NDA 215866). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 May 13. RCM No.: 2021-1828-1.

Kumar, N. Human Factors Study Report Review for Mounjaro (NDA 215866). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Feb 15. RCM No.: 2021-1827.

Conrad, A. Label and Labeling Review for Mounjaro (NDA 215866). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Feb 9. RCM No.: 2021-1828.

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Mounjaro labels and labeling submitted by Eli Lilly and Company.

- Container label received on January 31, 2023
- Carton labeling received on January 31, 2023
- Instructions for Use received on January 31, 2023, available from \\CDSESUB1\EVSPROD\nda215866\0193\m1\us\mounjaro-vial-ifu-draft.docx
- Prescribing Information received on January 31, 2023, available from \\CDSESUB1\EVSPROD\nda215866\0193\m1\us\mounjaro-uspi-draft-clean.docx
- Medication Guide received on January 31, 2023, available from \\CDSESUB1\EVSPROD\nda215866\0193\m1\us\mounjaro-mg-draft-clean.docx

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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HUMAN FACTORS STUDY REPORT REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 15, 2022
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 215866
Drug Constituent Name and Strength	Mounjaro[a] (tirzepatide), 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, and 15 mg/0.5 mL
Product Type:	Combination Product (Drug-Device)
Device Constituent:	Autoinjector
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eli Lilly and Company (Eli Lilly)
FDA Received Date:	September 15, 2021, October 29, 2021, January 3, 2022, January 10, 2022
OSE RCM #:	2021-1827
DMEPA 1 Human Factors Evaluator:	Neha Kumar, PharmD
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

[a] The proprietary name, Mounjaro, was found conditionally acceptable on December 2, 2021

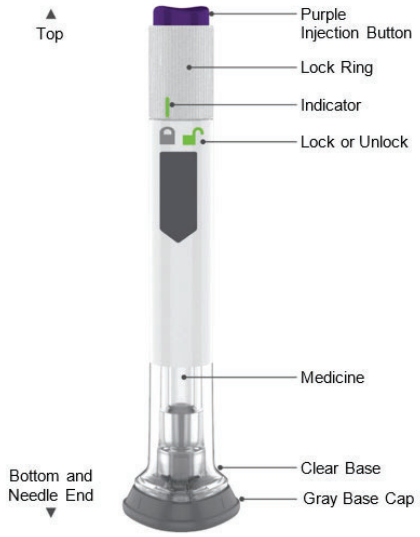
1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study reports submitted under NDA 215866 for tirzepatide injection.

1.1 PRODUCT DESCRIPTION

This is a combination product with a proposed single-use autoinjector (AI) device constituent part that is intended as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and to be administered once weekly. The carton contains 4 AIs, medication guide, instructions for use (IFU), and quick reference guide (QRG). Each AI contains a (b) (4) glass prefilled syringe (b) (4) needle for subcutaneous administration. For additional product information, see Table 5 in Appendix A.

Figure 1. Image of the tirzepatide autoinjector



1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVEOPMENT PROGRAM

- On December 21, 2020, the Applicant submitted a Type C meeting package under IND 128801 which included human factors related questions.[b] Since we were in the process of reviewing the Applicant's HF validation study protocol, submitted on December 18,

[b] Type C Meeting Briefing Document: Justification for Human Factors Differentiation for Tirzepatide Delivery Devices (IND 128801, Tirzepatide). Indianapolis (IN): Eli Lilly and Company; 2020 DEC 21. Available from: \\CDSESUB1\evsprod\ind128801\0134\m1\us\ly3298176-general-bd--type-c-fda-human-factors-dec-2020-.pdf.

2020, we denied the meeting request. We provided our responses to the Applicant's questions submitted under the Type C meeting request in our review of the Applicant's HF validation study protocol. We reviewed the protocol and provided recommendations to the Applicant.[c] The Applicant implemented our recommendations.

- On September 15, 2021, the Applicant submitted NDA 215866 to seek approval for tirzepatide. As such, the NDA submission included the results of their HF validation study for adults to support their marketing application, which is the subject of this review.

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Human Factors Validation Study Report	C
Information Requests Issued During the Review	D
Labels and Labeling	E

[c] Bhalodia A. Human Factors Protocol Review for Tirzepatide (IND 128801). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 22. RCM No.: 2020-2692

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed, and our analysis to determine if the results indicate that the user interface has been optimized to support the safe and effective use of the proposed product.

2.1 SUMMARY OF HF VALIDATION DESIGN

Table 2 presents a summary of the HF validation study design. See Appendix C for more details on the study design.

Table 2. Study Methodology for Human Factors (HF) Validation Study

Study Design Elements	Details
Participants	See nested table below
Training	No training was provided to the test participants.
Study Environment	Per the Applicant, the test room sufficiently represented the basic characteristics of the intended use environments (e.g., a private room in a patient's home or office, inpatient/outpatient facilities, and community settings). The room was equipped with a table, chairs, refrigerator, and trash can.
Sequence of Study	Simulated use scenario Root cause analysis Knowledge assessment Root cause analysis

User groups	Number of injection experienced participants	Number of injection naïve participants	Total number of participants
Untrained Type 2 Diabetes Mellitus Adult Patients	15	15	30
Untrained Adult Caregivers	15	15	30
Healthcare professionals (HCPs)	15	N/A	15

2.1.1 METHODOLGY DISCUSSION OF HF VALIDATION STUDY

Our review of the HF validation study methodology finds that the knowledge assessment included leading language. Specifically, the participants were instructed to point out information in the IFU. The use of leading language may impact study participant performance and the study results. However, we noted that all critical tasks, except for store device and inspect device before use were observed during the simulated use scenario.

Additionally, we noted that of the 15 injection naïve caregiver participants recruited, 5 participants were injection naïve, but not caregivers. We issued an information request for the Applicant's justification of their rationale and recruitment efforts to attempt to recruit injection naïve caregivers (see Appendix D). The Applicant stated that due to COVID-19, ultimately only 10 injection naïve caregivers, in addition to 5 injection naïve participants, were recruited. Based on the aforementioned considerations, we find the Applicant's rationale for including 10 injection naïve caregivers acceptable.

2.2 SUMMARY OF SUPPLEMENTAL HF STUDY DESIGN

Table 3 presents a summary of the supplemental HF study design. See Appendix C for more details on the study design.

Table 3. Study Methodology for Supplemental Human Factors (HF) Study

Study Design Elements	Details
Objective	The objective is to provide supplemental evidence to validate the safe and effective use of the tirzepatide autoinjector (AI) for the intended use, by the intended users, and in the intended use environment. The scope of this study was limited to evaluating the post-validation user interface changes associated with the critical task, "Place device at injection site". The changes included: • AI injection button color was changed (b) (4) to purple to introduce contrast to help identify the button from the gray base cap • The AI label was modified to add a color-coded arrow graphic as a background to the concentration listed on the container label; the arrow shape points to the device bottom and needle end • The IFU and QRG were updated to add a visual element and clarify text instructions that identify the AI bottom and needle end • IFU and QRG images, IFU Guide to parts, and text instructions were updated as necessary to be consistent with the modifications described above and represent the final design • The carton AI image was updated to reflect the final design (i.e., AI label modification and purple injection button)

<table>
<tr><td>Participants</td><td>
<table>
<tr><th>User groups</th><th>Number of injection experienced participants</th><th>Number of injection naïve participants</th><th>Total number of participants</th></tr>
<tr><td>Untrained Type 2 Diabetes Mellitus Adult Patients</td><td>15</td><td>15</td><td>30</td></tr>
<tr><td>Untrained Adult Caregivers</td><td>15</td><td>15</td><td>30</td></tr>
<tr><td>Healthcare professionals (HCPs)</td><td>15</td><td>N/A</td><td>15</td></tr>
</table>
</td></tr>
<tr><td>Training</td><td>No training was provided to the test participants.</td></tr>
<tr><td>Study Environment</td><td>Per the Applicant, the test room was sufficiently representative of the intended use environment with respect to lighting, sound levels, and temperature/humidity. The test room sufficiently represented the basic characteristics of the intended use environments (e.g., a private room in a patient’s home or office, inpatient/outpatient facilities, and community settings). The room was equipped with a table, chairs, and trash can. Participants sat at a table with a session moderator while being monitored remotely by the sponsor and/or other study personnel.</td></tr>
<tr><td>Sequence of Study</td><td>Simulated use scenario
Root cause analysis</td></tr>
</table>

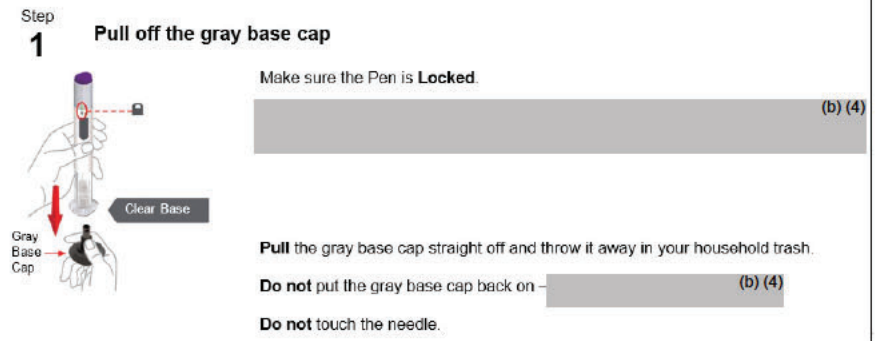
2.2.1 METHODLOGY DISCUSSION OF SUPPLEMENTAL HF STUDY

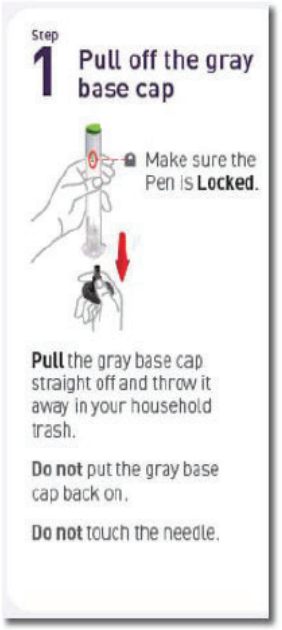
We noted in the supplemental HF study, of the 15 injection naïve caregiver participants recruited, 9 participants were injection naïve, but not caregivers. We issued an information request for the Applicant’s justification of their rationale and recruitment efforts to attempt to recruit injection naïve caregivers (see Appendix D). The Applicant stated that due to COVID-19, ultimately only 6 injection naïve caregivers, in addition to 9 injection naïve participants, were recruited for the supplemental HF validation study. Based on the above considerations, we find the Applicant’s rationale for including 6 injection naïve caregivers acceptable.

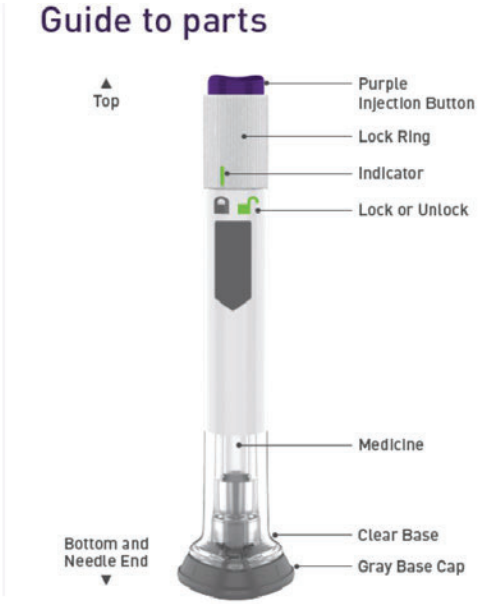
3 RESULTS AND ANALYSES

Table 4 describes the study results, the Applicant’s analyses of the results, and DMEPA 1’s analyses and recommendations.

Table 4: Identified Issues and DMEPA's Findings		
	Identified Issue and Rationale for Concern	**DMEPA's Analysis and Findings**
1.	For the task (b) (4) **injection site"**, there were three use errors and one close call during the first injection attempt. The subjective data and the Applicant's root cause analysis indicated: • Perception error – failure to see visual information (three participants overlooked the "Choose your injection site" section in the instructions for use (IFU) or the quick reference guide (QRG) and went directly to Step 1; one participant folded the IFU in a way in which they could not see the section, "Choose your injection site", that comes before Steps 1-3 • Cognitive error – knowledge-based mistake (one participant had seen doctors inject in the bicep in the past) • Test artifact – context for use (two participants assumed that selecting the correct injection site did not matter since this study is just an "experiment") Based on the use-related risk analysis (URRA), if the injection is past subcutaneous tissue and is an intramuscular injection, there is risk that the patient experiences some discomfort, but therapeutic effects remain the same. Based on the URRA, if the injection is too shallow and is an intradermal injection, this will most likely lead to the same therapeutic effect, potential pain, and possible wheal at injection site. The Applicant did not propose any risk mitigation strategies for these use errors and close call.	Our review of the study results identified subjective feedback that indicated that multiple use errors were due to the participants not noticing the "Choose your injection site" section in the IFU and QRG. Our review of the labels and labeling (user interface, etc.) finds that the IFU and QRG can be improved. We noted that the task to "Choose your injection site" is not numbered and that the IFU must be fully unfolded to see this task. **We provide a recommendation in Table A to address this concern**. We have determined that this change can be implemented without additional HF validation testing to be submitted for review.
2.	For the task **"** (b) (4) **base cap"**, there were three use errors and one close call during the first injection attempt.	Our review of the study results identified subjective feedback that indicated that two of the use errors were due to negative transfer and

	• one participant actuated the autoinjector (AI) while removing the gray base cap
	• one participant actuated the AI with the gray base cap on
	• one participant reattached the gray base cap before injection attempt
	• one participant attempted to inject with the gray base cap on, but self-corrected
	
	The subjective data and the Applicant's root cause analysis indicated:
	Cognitive error – knowledge-based mistake in which participant's action were intended but did not achieve the intended outcome due to:
	• inexperience, prior experience with other injection devices, and knowledge deficits, based on two participants' thought processes that the needle is at the "top" (b) (4) injection button) instead of at the base, and one participant's attempt to inject with the gray base cap on, referring to the QRG, and then removing the gray base cap
	• incomplete or inaccurate mental model of how the AI should operate based on one participant misinterpreting the QRG instruction to pull off the gray base cap and expecting the cap to twist off instead
	
	Based on the URRA, if the user:
	• actuates the AI while removing the gray base cap this may result in
	  ○ no dose or underdose and there is risk of mild, symptomatic or asymptomatic hyperglycemia
	  ○ exposed needle, the potential to inject someone other than the patient, and if
		the mental model that the needle is at the "top" (i.e., (b) (4) injection button) instead of at the base.
		
		Our review of the study results also identified subjective feedback that a participant misinterpreted the QRG and said that he expected the gray base cap to twist off easily. Our review of the study results indicated that the root cause analysis was incomplete because the Applicant did not identify why the participant misinterpreted the QRG and thought the cap should be twisted off.
		
		Our review of the labels and labeling (user interface, etc.) finds that the IFU and QRG contain text and illustration on how to remove the gray base cap by pulling straight off and shows a directional arrow to indicate the direction to pull. See Figure 2 and Figure 3 below.
		
		Figure 2. IFU instructions to pull off the gray base cap
		 

	overdose > 2.5 mg, there is risk of adverse event in a child ○ drug product coming in contact with patient or caregiver eye and risk of eye irritation or injury • actuates the AI with the gray base cap on, user is unable to deliver dose, there is risk of underdose that may result in mild, symptomatic or asymptomatic hyperglycemia • removes and reattaches the gray base cap and needle is damaged, there is risk of excess injection site trauma and/or underdose that may lead to mild, symptomatic or asymptomatic hyperglycemia The Applicant did not propose any risk mitigation strategies for these use errors and close call.	**Figure 3**. QRG instruction to pull off the gray base cap  We have not identified additional changes to the user interface to further reduce the risks associated with these use errors and close call. We find that the residual risk in this case is acceptable.
3.	For the task **"place** (b) (4) **",** there were eight use errors during the first attempt. Participants placed/actuated the AI upside down on the injection site. The subjective data and the Applicant's root cause analysis indicated: • Information overload during the task at hand (one participant may have created information overload by trying to simulate their typical patient interaction using	Our review of both HF study results indicates that several use errors were due to negative transfer and the mental model that the needle is at the "top" (i.e., (b) (4) injection button) instead of at the base. Our review of the study results also indicates the that the Applicant's root cause analysis was incomplete because it blames the participant for information overload for one of the use errors and does not identify elements of the user interface that may have contributed to the use error.

	an unfamiliar device for the first time in an artificial setting) • Failure to see visual information (one participant stated that they are a "visual learner" and "just looked at the pictures and surmised what to do") • Cognitive error - reverting to established habits and routines, inadequate or incorrect mental models (eight participants thought that the needle is at the "top" (i.e., (b) (4) injection button) instead of at the base) The Applicant implemented mitigation strategies to address these use errors. These mitigations strategies included: • AI injection button color was changed from (b) (4) to purple to introduce contrast to help identify the button from the gray base cap • The AI label was modified to add a color-coded arrow graphic as a background to the concentration listed on the container label; the arrow shape points to the device bottom and needle end • The IFU and QRG were updated to add a visual element and clarify text instructions that identify the AI bottom and needle end • IFU and QRG images, IFU Guide to parts, and text instructions were updated as necessary to be consistent with the modifications described above and represent the final design • The carton AI image was updated to reflect the final design (i.e., AI label modification and purple injection button) Based on the mitigation strategies implemented above, the Applicant conducted a supplemental HF validation study assessing these mitigations for use errors associated with the task, "Place (b) (4)	Our review of the labels and labeling (user interface, etc.), including the Applicant's mitigations, finds that the IFU and QRG illustrations and text in Steps 2-3 indicate how to appropriately place the AI at the injection site. The IFU Guide to parts section (see Figure 4) indicates the location of the injection button and needle end. However, our review finds that the post HF validation change to include the arrow pointing to the needle end on the container label can be improved. **We provide a recommendation in Table A to address this concern.** We have determined that this change can be implemented without additional HF validation testing to be submitted for review. **Figure 4**. Guide to parts section in IFU 

	Supplemental HF study result For the task "**place** [redacted] (b) (4) **"** there was one use error. On the first try the participant actuated the AI before placing on the injection pad, which prevented evaluation of the task, "place [redacted] (b) (4) The moderator allowed the participant to administer a second injection, during which the participant placed and actuated the AI upside down on the injection pad. The subjective data and the Applicant's root cause analysis indicated: conflicting mental model/negative transfer (participant only focused on the QRG text and not the QRG graphics; the participant did not fully process the proper steps and subsequently reverted to previously learned behavior using syringes). Upon looking at the QRG again, the participant realized her error, and stated that the QRG "could not have been more clear" on how to place the AI. Based on the URRA, if the user places/actuates the AI upside down on the injection site this may lead to: • injection of an incorrect site, such as the thumb, and there is risk of pain, injury • injection of someone other than the patient and there is risk of hypoglycemia, nausea, diarrhea, vomiting • drug expelled in the wrong direction and there is risk of mild, symptomatic or asymptomatic hyperglycemia • drug product coming in contact with patient or caregiver eye and risk of eye irritation or injury The Applicant did not propose any risk mitigation strategies for the use error seen in the supplemental study.	
4.	For the task [redacted] (b) (4) **"** there was one use error and two close calls during the first attempt, and one close call during a second attempt. For the use error, the participant did not	We disagree with the Applicant's clinical impact of use errors associated with the task to "[redacted] (b) (4) ". If the patient does not receive a

	unlock the AI, pressed the (b) (4) injection button, held the AI for 10 seconds, and disposed of the AI. For the close calls, the participants placed the locked AI on the injection pad, pressed the (b) (4) injection button, received no device feedback, and self-corrected by unlocking the AI.
	
	The subjective data and the Applicant's root cause analysis indicated:
	• Perception error - failure to see visual information
	  ○ One participant who had a use error only read the bolded header of Steps 1, 2, 3. The Step 2 bolded header states "Place on skin and unlock", but the participant only read the "Place on skin" portion of the header.
	  ○ One participant stated that the text in the QRG was too small, but self-corrected.
	  ○ One participant referred to the QRG but did not see the unlock instruction because "he rushed through it" and eventually self-corrected.
	• Cognitive error – memory failure (one participant was used to vial and syringe, but eventually self-corrected)
	
	The Applicant also states that all three participants who experienced close calls self-corrected when they realized that they could not press the (b) (4) injection button.
	
	Based on the URRA, if this task is omitted or not performed correctly this may lead to no dose with no perceptible clinical impact. Additionally, based on the URRA, since a locked device cannot be actuated, this may lead to excessive manipulation of the AI and result in pain.
		dose due to a locked AI, then the patient would also not receive the intended therapeutic benefit.
		
		Our review of the study results identified subjective feedback that indicated that one use error was due to negative transfer as the participant was accustomed to using a vial and a syringe. Additionally, our review of the study results indicates that the root cause analysis was incomplete because the Applicant did not identify why the participant only read the "Place on skin" portion of the "Place on skin, then unlock" bolded header.
		
		Our review of the labels and labeling (user interface, etc.) finds that the IFU and QRG contain text and illustrations on unlocking the AI. The AI displays lock and unlock symbols that align with the lock ring control. Additionally, we note that the AI will not provide its normal informative feedback, including injection button movement, audible clicks, and gray plunger movement, if the AI is not unlocked when the user attempts to press the injection button. It appears that the absence of informative feedback when the AI is locked may inform the user that the AI may be locked. However, based on subjective feedback that the QRG is too small, **we provide a recommendation in Table A to address this concern.** We have determined that this change can be implemented without additional HF validation testing to be submitted for review.

	The Applicant did not propose any risk mitigation strategies for these close calls and use error.	
5.	For the task (b) (4), there were two use errors during the first attempt and one use error during the second attempt. The subjective data and the Applicant's root cause analysis indicated: • Cognitive error - knowledge-based mistake (one participant who did not refer to the QRG or IFU, and another participant who "kind of looked at the pictures" in Steps 2 and 3, lifted after the first click) • Perception error – failure to see visual information (one participant, had "preconceived notions about how basic [the injection would be]", decided to only look at the text below the header of Step 3 "Press and hold up to 10 seconds" in the QRG and lifted after the first click) Based on the URRA, if the task is omitted or not performed correctly this may lead to underdose and there is risk of mild, symptomatic or asymptomatic hyperglycemia. Additionally, based on the URRA, if the injection is too shallow or is an intradermal injection then this would most likely lead to the same therapeutic effect, but potentially cause pain or wheals at injection site. Unintended needle movement may lead to excess injection site trauma. The Applicant did not propose any risk mitigation strategies for these use errors.	Our review of the study results identified subjective feedback that indicated that use errors were due to participants misinterpreting the first click as injection completion. On October 27, 2021, we issued an information request (IR) to the Applicant to provide the time required for the AI to complete the delivery of the drug and the time each participant held the AI at the injection site during Step 3 "Press and hold up to 10 seconds". On October 29, 2021, the Applicant responded, stating that the injection time required for the AI to complete the delivery of the drug is 2 seconds. The Applicant also stated that the injection time (i.e., time (in seconds) from when the participant pressed the injection button until the AI injected the drug product and automatically retracted and locked the semi-finished syringe and needle) was 2 seconds for each participant who had a use error. See Appendix D for more information. Based on this information, for the three use errors, participants received the full dose from holding the AI for 2 seconds. Additionally, our review of the identified subjective feedback indicated that one participant only looked at the text under the bolded header "Press and Hold for up to 10 seconds" for Step 3 in the QRG. This text first states "**Press and Hold** the purple injection button" and does not state the appropriate hold time of 10 seconds. **We provide a recommendation in Table A to address this concern.** We have determined that this change can be implemented without additional HF validation testing to be submitted for review.
6.	For the task **"dispose**", there were nine use errors and five close calls during the first attempt and two use errors and one close call during the second attempt. For the use errors, five participants threw the used AI in the trash can, three	We disagree with the Applicant that instances in which participants disposed of the used AI into the trash and then later attempted to self-correct would be considered close calls. These instances should be

	participants placed the used AI on the table, and three participants put the used AI back in the carton. For the close calls, participants threw the used AI in the trash, tried to self-correct, but were stopped by the moderator.
	
	The subjective data and the Applicant's root cause analysis indicated:
	• Perception errors – failure to see visual information (eleven participants did not notice the disposal instructions in the QRG or IFU)
	• Cognitive errors – memory failure and knowledge-based mistake
	  ○ Two participants stated that at home they throw injectable products, or certain parts of injectable products, in the household trash
	  ○ One participant did not understand the term "sharps container" in the IFU statement "After your injection, place the used Pen in a sharps container".
	  ○ Two participants did not see the disposal instructions and were unclear of the number of doses per AI or thought that there was more than one dose in the AI
	  ○ Test artifact – context for use (one participant stated, "[I] wasn't sure if the sharps container was real because I was using an example pen.")
	
	Based on the URRA, if this task is omitted or not performed correctly and the user disposes the used AI in household trash then there is risk of pain and injury due to broken glass.
	
	The Applicant did not propose any risk mitigation strategies for these use errors and close calls.
		considered use errors, because in this case the use error has already occurred.
		
		Our review of the study results identified subjective feedback that indicated that the use errors were due to participants not noticing disposal instructions in the IFU or QRG and negative transfer from participants disposing injectable products in the household trash at home.
		
		Our review of the labels and labeling (user interface, etc.) finds that the IFU and QRG can be improved. In the QRG and the front of the IFU, at the end of Step 3 "Press and Hold up to 10 seconds", the statements, "Put used Pen in a sharps container" and "After your injection, place the use Pen in sharps container", respectively, lack prominence and clarity. See Figure 5 and Figure 6 below. Additionally, the full details of the disposal instructions are on the back of the IFU and users may not realize this, as indicated by subjective feedback in which participants stated that they did not see disposal instructions in the IFU. **We provide a recommendation in Table A to address this concern.** We have determined that this change can be implemented without additional HF validation testing to be submitted for review.

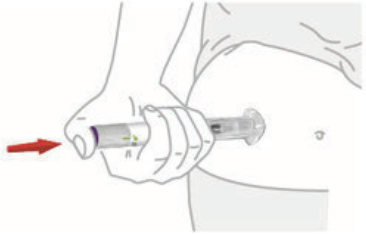
		Figure 5. "Put used Pen in a sharps container" instruction in the QRG Step **3 Press and Hold up to 10 seconds**  **Press and Hold** the purple injection button. **Listen** for: • First click = injection started • Second click = injection completed Injection is complete when you see the gray plunger.  Put used Pen in a sharps container.

		Figure 6. "After your injection, place the use Pen in sharps container" instruction in the IFU 
7.	For the knowledge-based question, **"What do the instructions say you should do if a pen has been frozen?"** there were four "unsuccessful answers". The subjective data and the Applicant's root cause analysis indicated: • Perception error – failure to see visual information (three participants could not find the instruction to not use a frozen pen, but they did not provide a reason for why they could not find the correct information) • Cognitive error – knowledge-based mistake (one participant misunderstood the question and interpreted the word "frozen" to mean a frozen mechanism (i.e., injection button was stuck). The	Our review of the study results identified subjective feedback that indicated that the Applicant's root cause analyses is incomplete, since the Applicant did not further probe the participants who stated that they did not see the relevant information. Our review of the labels and labeling (user interface, etc.) finds that the "Storage and handling" section of the IFU states, "**Do not** freeze your Pen. If the Pen has been frozen, throw the Pen away and use a new Pen." Additionally, the carton states, "DO NOT FREEZE". We did not identify additional changes to the user interface that may address the "unsuccessful answers" and we find the residual risk acceptable.

	Applicant states that the moderator did not redirect the participant to the correct question. Based on the URRA, if the user stores the AI in a freezer this can lead to: • degraded drug/loss of potency and there is risk of mild, symptomatic or asymptomatic hyperglycemia • loss of potency by less than 50%, which does not have clinical impact • non-retraction of needle due to freezing and there is risk of needle stick, including potential infection from contaminated needle stick • injection of particulate and there is risk of pain, injury, capillary embolism, granuloma, or immune response The Applicant did not propose any risk mitigation strategies for these "unsuccessful answers".	
8.	For the knowledge-based question, **"What do the instructions say about inspecting the device before use?"** there was one "unsuccessful answer". The subjective data and the Applicant's root cause analysis indicated: perception errors – failure to see visual information (participant did not see the relevant information in the IFU). Based on the URRA, if the user omits or does not inspect the device before use then there is risk of: • pain, injury, capillary embolism, granuloma, toxicity, immune response, possibly requiring medication treatment • mild symptomatic or asymptomatic hyperglycemia • needle stick and possible infection	Our review of the study results identified subjective feedback that indicated that the Applicant's root cause analyses is incomplete, since the Applicant did not further probe the participant who stated that they did not see the relevant information in the IFU. Our review of the labels and labeling (user interface, etc.) finds that the "Preparing to inject Mounjaro" section of the IFU states, "Inspect the Pen to make sure that it is not damaged. Make sure the medication is not frozen, not cloudy, colorless to slightly yellow, does not have particles". However, this section is not numbered as a step that is to be performed upon each use of the AI and thus may be overlooked. As such, our review of the IFU finds that the "Preparing to inject Mounjaro" section can be numbered as a step a user should complete. **We provide a recommendation in Table A to address this concern.** We have determined that this change can be implemented without additional HF validation testing to be submitted for review.

	The Applicant did not propose any risk mitigation strategies for this "unsuccessful answer".	
9.	For the knowledge-based question, **"According to these materials, how should these devices be stored?"** there was one "unsuccessful answer". The subjective data and the Applicant's root cause analysis indicated: perception error – failure to see visual information (participant did not read information under the "Storage and handling section" and stated that they only glanced at the information instead of reading it thoroughly because they are familiar with similar devices; therefore, the participant thought they already knew what information would be provided in the IFU). Based on the URRA, if the task is omitted or not performed there is risk of: • toxicity, immune response • mild, symptomatic, or asymptomatic hyperglycemia in some users • pain, injury The Applicant did not propose any risk mitigation strategies for this "unsuccessful answer".	Our review of the study results identified subjective feedback that indicated that the participant did not notice the relevant information in the IFU. Our review of the label and labeling (user interface, etc.) finds that the "Storage and handling" section of the IFU states, "Store your Pen in the refrigerator between 36°F to 46°F (2°C to 8°C)." and "You may store your Pen at room temperature (b) (4) 86°F (30°C) for up to (b) (4) 21 days." Additionally, the carton states, "Store refrigerated at 36°F to 46°F (2°C to 8°C) in original carton to protect from light." and "Mounjaro can be stored at room temperature up to 86°F (30°C) for up to 21 days in the carton. (b) (4) Discard if not used within 21 days after removing from the refrigerator." We did not identify additional changes to the user interface that may address this "unsuccessful answer" and we find the residual risk acceptable.
10.	For the knowledge-based question, **"What do the instructions say about checking the pen label before use?"** there were thirteen "unsuccessful answers". The subjective data and the Applicant's root cause analysis indicated: • Perception error – failure to see visual information (eleven participants focused on the "Important information you need to know before injecting	Our review of the study results identified subjective feedback that indicated that the participants expected to see the relevant information in the "Important information you need to know before injecting Mounjaro" which is the section that precedes the "Preparing to inject Mounjaro" section that contains information on checking the pen label. Our review of the labels and labeling (user interface, etc.) indicated that the "Preparing to inject Mounjaro" section of the IFU states, "Check the Pen label to make sure you have the right medicine and dose and that it

	Mounjaro" section preceding the "Preparing to inject Mounjaro" section of the IFU, which instructs the user to check the pen label) • Cognitive error – knowledge-based mistake due to misunderstanding or misinterpreting the question due to an incorrect mental model or knowledge deficit (two participants did not understand what "pen label" meant) Based on the URRA, if the task is omitted or not performed there is risk of toxicity, immune response. The Applicant did not propose any risk mitigation strategies for these "unsuccessful answers".	has not expired." Additionally, next to this task is an illustration indicating the location of the expiration date on the AI (see Figure 7 below). However, the IFU "Preparing to inject Mounjaro" section is not numbered as a step that is to be completed when using each AI and thus may be overlooked. **We provide a recommendation in Table A to address this concern.** We have determined that this change can be implemented without additional HF validation testing to be submitted for review. **Figure 7**. Illustration indicating expiration date location in the "Preparing to inject Mounjaro" section of the IFU 

3.1 LABELS AND LABELING

Tables A below includes the identified medication error issues with the submitted label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table A: Identified Issues and Recommendations for Eli Lilly (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Autoinjector (AI) label			
1.	The added color-coded arrow graphic (see below) on the AI label is not labeled to indicate that it is pointing to the needle end. 	We are concerned that if the user places/actuates the autoinjector upside down on the injection site this may lead to: • injection of an incorrect site, such as the thumb, and there is risk of pain, injury • injection of someone other than the patient and there is risk of hypoglycemia, nausea, diarrhea, vomiting • drug expelled in the wrong direction and there is risk of mild, symptomatic or asymptomatic hyperglycemia • drug product coming in contact with patient or caregiver eye and there is risk of eye irritation or injury	We recommend that you consider adding text to the autoinjector label to indicate to the user which end is the needle-end.
Instructions for Use (IFU) and Quick Reference Guide (QRG)			
1.	The step “Preparing to inject Mounjaro” is not numbered as a step that is to be completed when using each autoinjector and thus may be overlooked.	We are concerned that if a user omits or does not perform the tasks associated with “Preparing to inject Mounjaro” there is risk of pain, injury, capillary embolism, granuloma, toxicity, immune response, mild, symptomatic or asymptomatic	We recommend you number the step “Preparing to inject Mounjaro” in the IFU.

		hyperglycemia, and infection from needle stick. The human factors (HF) validation study results identified subjective feedback that indicated that participants did not notice the "Preparing to inject Mounjaro" step in the IFU. Several participants thought that relevant information would be stated in the preceding "Important information you need to know before injecting Mounjaro".	
2.	The step "Choose your injection site" is not numbered as a step that is to be completed when using each autoinjector and thus may be overlooked.	We are concerned that if a user injects at the wrong injection site there is risk of pain, injury, wheals at injection site. The HF validation study results identified subjective feedback that indicated that participants did not notice the "Choose your injection site" step. Instead, participants proceeded to "Step 1 Pull off the gray base cap", which is the task listed immediately after "Choose your injection site".	We recommend you number the step "Choose your injection site" in the IFU and QRG.
3.	The IFU and QRG text under (b) (4) Press and Hold up to 10 seconds" states "Press and Hold the purple injection button" but does not state the appropriate hold time of 10 seconds.	We are concerned that if this task is omitted or not performed correctly this may lead to mild, symptomatic or asymptomatic hyperglycemia. The HF validation study results identified a participant who overlooked the bolded header for (b) (4) and only read the text	We recommend that you make the following change to (b) (4) Press and Hold up to 10 seconds" of the QRG and IFU: Change the statement, "Press and Hold the purple injection button" to "Press and Hold the purple injection button for up to 10 seconds".

		underneath which states, “Press and Hold the purple injection button”.	
4.	The instructions “After your injection, place the used Pen in a sharps container” in the IFU and “Put used Pen in a sharps container” in the QRG lack prominence and clarity.	We are concerned that if a user omits or does not perform the disposal task then there is risk of injury. The HF validation study results identified several participants who did not see the disposal instruction. In the IFU the full disposal instructions, “Disposing of your used Pen” is the only task that is on the back of the IFU. Additionally, some participants who referred to the QRG did not know to dispose of the autoinjector after each injection.	• We recommend you revise the QRG statement, “Put used Pen in a sharps container” to align with the IFU and state the following: “After your injection, place the used Pen in a sharps container”. • We recommend that you make the aforementioned disposal instructions in the IFU and QRG more prominent. • We recommend that in IFU Step 3, after the statement, “After your injection, place the used Pen in a sharps container”, include instructions for the user to flip the IFU to the back to see the “Disposing of your used Pen” step. • We recommend you number the step “Disposing of your used Pen” in the IFU.
5.	The QRG text and illustrations may not be large enough for users to read or see.	We are concerned that patients with diabetes mellitus who are visually impaired may have difficulty reading the QRG due to small text size and illustrations.	We recommend that you increase the QRG text and illustration size.

4 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation studies demonstrated several use errors with critical tasks that may result in harm. Based on our review of the available participants' subjective feedback, and root cause analysis, we identified additional risk mitigations to address the use errors. Above, we have provided recommendations in Table A for the Applicant. We ask that the Division of Diabetes, Lipid Disorders and Obesity (DDLO) convey Table A in its entirety to the Applicant. These changes can be implemented without submitting additional HF validation testing data for Agency review.

4.1 RECOMMENDATION FOR ELI LILLY

Our evaluation of the results of your human factors (HF) validation studies indicates that there are additional mitigations that can be implemented to address use errors that occurred with critical tasks. We provide recommendations in Table A and we recommend that you implement these recommendations and submit the revised label and labeling for our review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for tirzepatide that Eli Lilly submitted on September 15, 2021.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist
Active Ingredient (Drug or Biologic)	Tirzepatide
Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	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, and 15 mg/0.5 mL
Dose and Frequency	• Start at 2.5 mg once weekly. After 4 weeks, increase the dose to 5 mg once weekly. • If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose, up to 15 mg. • If a dose is missed administer within 4 days of missed dose
How Supplied	Tirzepatide a clear, colorless to slightly yellow solution available in pre-filled single-dose autoinjectors. Each autoinjector contains 0.5 mL of solution. <u>Carton of 4 Single-Dose Autoinjectors</u> • 2.5 mg/0.5 mL • 5 mg/0.5 mL • 7.5 mg/0.5 mL • 10 mg/0.5 mL • 12.5 mg/0.5 mL • 15 mg/0.5 mL
Storage	• Store tirzepatide in a refrigerator at 36°F to 46°F (2°C to 8°C).

	• If needed, each single-dose autoinjector can be stored unrefrigerated at temperatures not to exceed 86ºF (30ºC) for up to 21 days. • Do not freeze. Do not use if frozen. • Store in the original carton to protect from light.
Container Closure/Device Constituent	Single-dose, prefilled injection device enclosing a syringe containing the medication.
Intended Users	• Adult patients • Caregivers • Healthcare professionals
Intended Use Environment	Home or medical setting

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On October 22, 2021, we searched the L:drive and AIMS using the terms tirzepatide, IND 128801 and NDA 215866 to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified one previous review[d], and we confirmed that our previous recommendations were implemented.

[d] Bhalodia A. Human Factors Protocol Review for tirzepatide (IND 128801). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 DEC MAR 21. RCM No.: 2020-2692.

APPENDIX C. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:
\\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\(b) (6)-other-stud-rep\human-factors-engineering-report\human-factors-engineering-report.pdf

APPENDIX D. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On October 27, 2021, we issued an Information Request (IR) to obtain:

- the protocols for the human factors validation study and human factors supplemental study referenced in the Tirzepatide Autoinjector Human Factors Engineering Report
- information on time required to for the autoinjector to complete drug delivery, actual time that each participant held the autoinjector at the injection site, time for the gray plunger to be visible in the viewing window

The Applicant provided an acceptable response on October 29, 2021 that can be accessible in EDR via:

\\CDSESUB1\evsprod\nda215866\0012\m1\us\reg-response-oct-21.pdf

\\CDSESUB1\evsprod\nda215866\0012\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\(b) (6)-other-stud-rep\human-factors-engineering-report\prt-92277-tirzepatide-autoinjector-human-factors-validation-.pdf

\\CDSESUB1\evsprod\nda215866\0012\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\(b) (6)-other-stud-rep\human-factors-engineering-report\prt-93365-tirzepatide-autoinjector-supplemental-human-factor.pdf

On December 29, 2021, we issued an IR to obtain:

- clarification on the reported hold times for 65 participants
- information on why a patient choosing and injecting in the back of the arm is considered successful, when the IFU states that patients should inject in their thigh or abdomen
- information on why the injection naïve caregivers were substituted with injection naïve laypersons

The Applicant provided an acceptable response on January 3, 2022 that can be accessible in EDR via:

\\CDSESUB1\evsprod\nda215866\0031\m1\us\reg-response-jan-2022.pdf

On January 7, 2022, we issued an IR to obtain:

- clarification on whether there were 10 or 14 participants who had use errors during first injection attempt
- the subjective feedback and root cause analyses for the use errors seen in the first injection attempts

- subjective feedback and root cause analyses for use errors seen in the human factors validation study for the task “place device at injection site”

The Applicant provided an acceptable response on January 10, 2022 that can be accessible in EDR via:

\\CDSESUB1\evsprod\nda215866\0022\m1\us\reg-response-jan-2022.pdf

APPENDIX E. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following tirzepatide labels and labeling submitted by Eli Lilly.

- Container labels received on September 15, 2021
- Carton labeling received on September 15, 2021
- Instructions for Use (image not shown) received on September 15, 2021, available from \\CDSESUB1\evsprod\nda215866\0001\m1\us\proposed-usermanual-clean.docx
- Quick Reference Guide (image now shown) received on September 15, 2021, available from: \\CDSESUB1\evsprod\nda215866\0001\m1\us\proposed-quickguide-clean.docx

E.2 Labels and Labeling Images

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NEHA KUMAR
02/15/2022 12:24:14 PM

OLUWAMUREWA OGUNTIMEIN
02/15/2022 12:33:20 PM

JASON A FLINT
02/15/2022 01:09:38 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215866Orig1s002

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

From: Kelly, Lindsey
Sent: Tue, 25 Jul 2023 21:32:25 +0000
To: John J Kaiser
Cc: Linda S Kelly;Sally L Anliker
Subject: RE: [EXTERNAL] RE: NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments
Attachments: proposed-vial-usermanual-clean.docx, proposed-medguide-clean.docx, proposed-uspi-clean.docx, proposed-vial-usermanual.docx, carton-vial-12pt5mg.pdf, carton-vial-15mg.pdf, contain-vial-2pt5mg.pdf, contain-vial-5mg.pdf, contain-vial-7pt5mg.pdf, contain-vial-10mg.pdf, contain-vial-12pt5mg.pdf, contain-vial-15mg.pdf, carton-vial-2pt5mg.pdf, carton-vial-5mg.pdf, carton-vial-10mg.pdf, carton-vial-7pt5mg.pdf

Hi John,

We accept your revisions dated July 24, 2023. You may now formally submit the labeling to the NDA (including the agreed upon carton/container labeling provided on 6/23/23, attached)

We just remind you to update the revision dates for the PI, MG and IFU.

Thanks!

Lindsey Kelly, Pharm.D.
Regulatory Project Manager

Diabetes, Lipid Disorders, and Obesity
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Lindsey.Kelly@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: John J Kaiser <kaiser_john_joseph@lilly.com>
Sent: Monday, July 24, 2023 4:45 PM
To: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: [EXTERNAL] RE: NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments

Hi Lindsey,

Please find attached Lilly's response to FDA's Round 3 comments on the draft PI (combined S-002 and S-006 changes), and S-002 MG and IFU labeling. You should have attached the following:

- USPI & Med Guide: clean word version
- IFU: clean and tracked word versions

We have accepted all changes for the USPI and Med Guide. The IFU contains Lilly comments and edits as requested. Please let me know if there are any questions.

Thank you!
John

John J. Kaiser, PharmD, RPh
Sr. Director, Global Regulatory Affairs - North America, Diabetes
Eli Lilly and Company
317.277.5906 (Office) | 317.672.8901 (Mobile)
jkaiser@lilly.com | www.lilly.com

From: Ruth M. Belin <belin_ruth_m@lilly.com>
Sent: Friday, July 21, 2023 3:57 PM
To: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Cc: John J Kaiser <kaiser_john_joseph@lilly.com>; Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>

Subject: RE: [WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED]RE: [EXTERNAL] RE: NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments

Lindsey, Thanks so much for forwarding the documents to me.
Confirming receipt.
All the best, Ruth

Ruth Belin, MD, MPH
Vice President
Diabetes, Obesity, and Cardiovascular Regulatory Affairs – North America
Eli Lilly and Company
Lilly Corporate Center, Indianapolis IN 46285 U.S.A.
+1 317.748.1542 (mobile)
belinrm@lilly.com | www.lilly.com

From: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Sent: Friday, July 21, 2023 2:55 PM
To: Ruth M. Belin <belin_ruth_m@lilly.com>
Cc: John J Kaiser <kaiser_john_joseph@lilly.com>; Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker

<anliker_sally_l@lilly.com>

Subject: FW: ﻵ[WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED]RE: [EXTERNAL] RE: NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments

Hi Ruth,

Please see the email below. I am forwarding in John Kaiser's absence.

Thank you,

Lindsey Kelly, Pharm.D.
Regulatory Project Manager

Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-837-7654
Lindsey.Kelly@fda.hhs.gov

From: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Sent: Friday, July 21, 2023 2:39 PM
To: John J Kaiser <kaiser_john_joseph@lilly.com>
Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>

Subject: RE: ﻵ[WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED]RE: [EXTERNAL] RE: NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments

Hi John,

In regard to NDA 215866 (tirzepatide) S-002 received on January 31, 2023, and S-006, received on April 18, 2023 , please see the attached round 3 FDA comments on the draft PI (combined S-002 and S-006 changes), and S-002 MG and IFU labeling. We have decided to do a combined action for both of these supplements. We remind you that these edits do not reflect the final regulatory decision for this application and that portions of the label are still under review. We have no additional edits to the C/C labels at this time, but we request that you wait to formally submit them to the NDA until all the labeling is agreed upon.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. When you add a comment bubble, please state " Lilly response to FDA change" or "Lilly comment."

We ask that you complete your review and return comments **as soon as possible or by EOB on Monday, July 24, 2023**. You can return the updated labels via email as the updated versions of the label need not be submitted to the NDA until final agreed labeling has been reached.

Please confirm receipt of this email and let me know if you have any questions.

Thank you,

Lindsey Kelly, Pharm.D.
Regulatory Project Manager

Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
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Lindsey.Kelly@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: John J Kaiser <kaiser_john_joseph@lilly.com>
Sent: Wednesday, July 12, 2023 3:49 PM
To: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: [WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED]RE: [EXTERNAL] RE: NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments
Importance: High

Hi Lindsey,

Please find attached our responses to FDA's Round 2 labeling comments for S-002 & S-006 . You should have track change and clean copies of the USPI, MG, and IFU (6 word documents in total).

Notably:

- All FDA comments have been accepted

- The only Lilly comment bubble in the tracked med guide should have been deleted as these changes were incorporated from Round 1.
- The IFU contains 2 newly proposed images, added for clarity.

Please let me know if you have any additional questions.

Thank you and have a great night!
John

John J. Kaiser, PharmD, RPh
Sr. Director, Global Regulatory Affairs - North America, Diabetes
Eli Lilly and Company
317.277.5906 (Office) | 317.672.8901 (Mobile)
jkaiser@lilly.com | www.lilly.com

From: John J Kaiser <kaiser_john_joseph@lilly.com>
Sent: Thursday, July 6, 2023 6:12 PM
To: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: Re: [EXTERNAL] RE: NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments

Hi Lindsey,

Confirming receipt. I have no immediate questions.

Thank you and have a great night.

John

Get Outlook for iOS

From: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Sent: Thursday, July 6, 2023 4:29:19 PM
To: John J Kaiser <kaiser_john_joseph@lilly.com>
Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: [WARNING: UNSCANNABLE EXTRACTION FAILED]RE: [EXTERNAL] RE: NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments

Hi John,

In regard to NDA 215866 (tirzepatide) S-002 received on January 31, 2023, and S-006, received on April 18, 2023 , please see the attached round 2 FDA comments on the draft PI (combined S-002 and S-006 changes), and S-002 MG and IFU labeling. We have decided to do a combined action for both of these supplements. We remind you that these edits do not reflect the final regulatory decision for this application and that portions of the label are still under review. We have no additional edits to the C/C labels at this time, but we request that you wait to formally submit them to the NDA until all the labeling is agreed upon.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. When you add a comment bubble, please state " Lilly response to FDA change" or "Lilly comment."

We ask that you complete your review and return comments **as soon as possible or by EOB on Thursday, July 13, 2023**. You can return the updated labels via email as the updated versions of the label need not be submitted to the NDA until final agreed labeling has been reached.

Please confirm receipt of this email and let me know if you have any questions.

Thank you,
Lindsey

Lindsey Kelly, Pharm.D.
Regulatory Project Manager

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Tel: 301-837-7654
Lindsey.Kelly@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: John J Kaiser <kaiser_john_joseph@lilly.com>
Sent: Friday, June 23, 2023 1:23 PM
To: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: [EXTERNAL] RE: NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments
Importance: High

Hi Lindsey,

Please find attached our responses to the carton/container labeling comments for S-002 (6 PDFs for carton and 6 PDFs for container). Also attached is a regulatory response document which provides more information and context for the labels. I will submit the regulatory response formally to the NDA on Monday.

Thank you and have a great weekend!
John

John J. Kaiser, PharmD, RPh
Sr. Director, Global Regulatory Affairs - North America, Diabetes
Eli Lilly and Company
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jkaiser@lilly.com | www.lilly.com

From: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Sent: Friday, June 23, 2023 11:02 AM
To: John J Kaiser <kaiser_john_joseph@lilly.com>
Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: RE: [WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED]RE: [EXTERNAL] [WARNING: UNSCANNABLE EXTRACTION FAILED]NDA 215866 S-002 & S-006 Mounjaro (t
Importance: High

Hi John,

Thank you for your email, I am confirming receipt.

Have a great weekend!

Lindsey Kelly, Pharm.D.
Regulatory Project Manager

Diabetes, Lipid Disorders, and Obesity
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Lindsey.Kelly@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

From: John J Kaiser <kaiser_john_joseph@lilly.com>
Sent: Thursday, June 22, 2023 3:37 PM
To: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: [WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED]RE: [EXTERNAL] [WARNING: UNSCANNABLE EXTRACTION FAILED]NDA 215866 S-002 & S-006 Mounjaro (ti...

Hi Lindsey,

Thank you for the flexibility!

Please find attached our responses to the prescribing information, medication guide, and IFU for S-002 and S-006. These documents have been provided in both clean and track-change versions. As previously mentioned, we will be slightly delayed in responding to the carton/container labeling, which I hope to send Monday or Tuesday at the latest.

If possible, please confirm receipt of this email and let me know if you have any questions.

Thank you!
John

John J. Kaiser, PharmD, RPh
Sr. Director, Global Regulatory Affairs - North America, Diabetes
Eli Lilly and Company
317.277.5906 (Office) | 317.672.8901 (Mobile)
jkaiser@lilly.com | www.lilly.com

From: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Sent: Thursday, June 22, 2023 2:07 PM

To: John J Kaiser <kaiser_john_joseph@lilly.com>
Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: RE: [EXTERNAL] [WARNING: UNSCANNABLE EXTRACTION FAILED]NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments
Importance: High

Hi John,

Thank you for the update, it is appreciated. Your plan sounds reasonable.

Thanks!

Lindsey Kelly, Pharm.D.
Regulatory Project Manager

Diabetes, Lipid Disorders, and Obesity
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Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-837-7654
Lindsey.Kelly@fda.hhs.gov

From: John J Kaiser <kaiser_john_joseph@lilly.com>
Sent: Wednesday, June 21, 2023 4:14 PM
To: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: RE: [EXTERNAL] [WARNING: UNSCANNABLE EXTRACTION FAILED]NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments

Hi Lindsey,

I wanted to provide you with a quick update on our planned response. We may have the USPI, Med Guide, and IFU back to you tomorrow afternoon but certainly Friday. There is a possibility that the carton/container labeling might be delayed to Monday of next week. We are working diligently to make the requested timeline and I hope to know more about our timing of the carton/container tomorrow afternoon. If there are any immediate concerns about a Monday, June 26 response for the carton/container please let me know.

Thank you!
John

John J. Kaiser, PharmD, RPh
Sr. Director, Global Regulatory Affairs - North America, Diabetes
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jkaiser@lilly.com | www.lilly.com

From: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Sent: Friday, June 16, 2023 9:43 AM
To: John J Kaiser <kaiser_john_joseph@lilly.com>
Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: RE: [EXTERNAL] [WARNING: UNSCANNABLE EXTRACTION FAILED]NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments
Importance: High

Hi John,

Thank you for confirming receipt, I'll be sure to do so.

Have a great weekend,

Lindsey Kelly, Pharm.D.
Regulatory Project Manager

Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations, Office of New Drugs
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Lindsey.Kelly@fda.hhs.gov

From: John J Kaiser <kaiser_john_joseph@lilly.com>
Sent: Thursday, June 15, 2023 5:21 PM
To: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: RE: [EXTERNAL] [WARNING: UNSCANNABLE EXTRACTION FAILED]NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments

Hi Lindsey,

Confirming receipt. We will work to provide a response no later than 23 June as requested.

If possible, please also include me in future correspondences on these supplements. I will reach out if there are any questions.

Thank you!

John

John J. Kaiser, PharmD, RPh
Sr. Director, Global Regulatory Affairs - North America, Diabetes
Eli Lilly and Company
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jkaiser@lilly.com | www.lilly.com

From: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Sent: Thursday, June 15, 2023 4:57 PM
To: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: [EXTERNAL] [WARNING: UNSCANNABLE EXTRACTION FAILED]NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments

Hi Linda and Sally,

In regard to NDA 215866 (tirzepatide) S-002 received on January 31, 2023, and S-006, received on April 18, 2023 , please see the attached round 1 FDA comments on the draft PI (combined S-002 and S-006

changes), and S-002 MG, IFU and carton/container labeling. We have decided to do a combined action for both of these supplements. We remind you that these edits do not reflect the final regulatory decision for this application and that portions of the label are still under review.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. When you add a comment bubble, please state " Lilly response to FDA change" or "Lilly comment."

We ask that you complete your review and return comments **as soon as possible or by EOB on Friday, June 23, 2023**. You can return the updated labels and c/c comments via email as the updated versions of the label need not be submitted to the NDA until final agreed labeling has been reached.

Please confirm receipt of this email and let me know if you have any questions.

Thank you,
Lindsey

Lindsey Kelly, Pharm.D.
Regulatory Project Manager

Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
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Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-837-7654
Lindsey.Kelly@fda.hhs.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LINDSEY T KELLY
07/25/2023 08:35:10 PM
See source document for attachments.

From: Kelly, Lindsey
Sent: Fri, 21 Jul 2023 18:39:17 +0000
To: John J Kaiser
Cc: Linda S Kelly;Sally L Anliker
Subject: RE: [WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED]RE: [EXTERNAL] RE: NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments
Attachments: 7.21.23 mounjaro-proposed-mg.docx, 7.21.23 mounjaro-proposed-uspi.docx, 7.21.23 mounjaro-proposed-vial-ifu.docx

Hi John,

In regard to NDA 215866 (tirzepatide) S-002 received on January 31, 2023, and S-006, received on April 18, 2023 , please see the attached round 3 FDA comments on the draft PI (combined S-002 and S-006 changes), and S-002 MG and IFU labeling. We have decided to do a combined action for both of these supplements. We remind you that these edits do not reflect the final regulatory decision for this application and that portions of the label are still under review. We have no additional edits to the C/C labels at this time, but we request that you wait to formally submit them to the NDA until all the labeling is agreed upon.

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We ask that you complete your review and return comments **as soon as possible or by EOB on Monday, July 24, 2023**. You can return the updated labels via email as the updated versions of the label need not be submitted to the NDA until final agreed labeling has been reached.

Please confirm receipt of this email and let me know if you have any questions.

Thank you,

Lindsey Kelly, Pharm.D.
Regulatory Project Manager

Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-837-7654
Lindsey.Kelly@fda.hhs.gov

From: John J Kaiser <kaiser_john_joseph@lilly.com>
Sent: Wednesday, July 12, 2023 3:49 PM
To: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: [WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED]RE: [EXTERNAL] RE: NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments
Importance: High

Hi Lindsey,

Please find attached our responses to FDA's Round 2 labeling comments for S-002 & S-006 . You should have track change and clean copies of the USPI, MG, and IFU (6 word documents in total).

Notably:

- All FDA comments have been accepted
- The only Lilly comment bubble in the tracked med guide should have been deleted as these changes were incorporated from Round 1.
- The IFU contains 2 newly proposed images, added for clarity.

Please let me know if you have any additional questions.

Thank you and have a great night!
John

John J. Kaiser, PharmD, RPh
Sr. Director, Global Regulatory Affairs - North America, Diabetes
Eli Lilly and Company
317.277.5906 (Office) | 317.672.8901 (Mobile)
jkaiser@lilly.com | www.lilly.com

From: John J Kaiser <kaiser_john_joseph@lilly.com>
Sent: Thursday, July 6, 2023 6:12 PM
To: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: Re: [EXTERNAL] RE: NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments

Hi Lindsey,

Confirming receipt. I have no immediate questions.

Thank you and have a great night.

John

Get Outlook for iOS

From: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Sent: Thursday, July 6, 2023 4:29:19 PM
To: John J Kaiser <kaiser_john_joseph@lilly.com>
Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: [WARNING: UNSCANNABLE EXTRACTION FAILED]RE: [EXTERNAL] RE: NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments

Hi John,

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Thank you,
Lindsey

Lindsey Kelly, Pharm.D.

Regulatory Project Manager

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Subject: [EXTERNAL] RE: NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments
Importance: High

Hi Lindsey,

Please find attached our responses to the carton/container labeling comments for S-002 (6 PDFs for carton and 6 PDFs for container). Also attached is a regulatory response document which provides more information and context for the labels. I will submit the regulatory response formally to the NDA on Monday.

Thank you and have a great weekend!
John

John J. Kaiser, PharmD, RPh
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jkaiser@lilly.com | www.lilly.com

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Sent: Friday, June 23, 2023 11:02 AM
To: John J Kaiser <kaiser_john_joseph@lilly.com>
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Importance: High

EXTERNAL EMAIL: Use caution before replying, clicking links, and opening attachments.

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Have a great weekend!

Lindsey Kelly, Pharm.D.
Regulatory Project Manager

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FDA U.S. FOOD & DRUG ADMINISTRATION

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To: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
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Hi Lindsey,

Thank you for the flexibility!

Please find attached our responses to the prescribing information, medication guide, and IFU for S-002 and S-006. These documents have been provided in both clean and track-change versions. As previously

mentioned, we will be slightly delayed in responding to the carton/container labeling, which I hope to send Monday or Tuesday at the latest.

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Thank you!
John

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Subject: RE: [EXTERNAL] [WARNING: UNSCANNABLE EXTRACTION FAILED]NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments
Importance: High

Hi John,

Thank you for the update, it is appreciated. Your plan sounds reasonable.

Thanks!

Lindsey Kelly, Pharm.D.
Regulatory Project Manager

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Lindsey.Kelly@fda.hhs.gov

From: John J Kaiser <kaiser_john_joseph@lilly.com>
Sent: Wednesday, June 21, 2023 4:14 PM
To: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: RE: [EXTERNAL] [WARNING: UNSCANNABLE EXTRACTION FAILED]NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments

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Thank you!
John

John J. Kaiser, PharmD, RPh
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jkaiser@lilly.com | www.lilly.com

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To: John J Kaiser <kaiser_john_joseph@lilly.com>
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Subject: RE: [EXTERNAL] [WARNING: UNSCANNABLE EXTRACTION FAILED]NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments
Importance: High

Hi John,

Thank you for confirming receipt, I'll be sure to do so.

Have a great weekend,

Lindsey Kelly, Pharm.D.
Regulatory Project Manager

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Lindsey.Kelly@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

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Sent: Thursday, June 15, 2023 5:21 PM
To: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: RE: [EXTERNAL] [WARNING: UNSCANNABLE EXTRACTION FAILED]NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments

Hi Lindsey,

Confirming receipt. We will work to provide a response no later than 23 June as requested.

If possible, please also include me in future correspondences on these supplements. I will reach out if there are any questions.

Thank you!

John

John J. Kaiser, PharmD, RPh
Sr. Director, Global Regulatory Affairs - North America, Diabetes
Eli Lilly and Company

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jkaiser@lilly.com | www.lilly.com

From: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Sent: Thursday, June 15, 2023 4:57 PM
To: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: [EXTERNAL] [WARNING: UNSCANNABLE EXTRACTION FAILED]NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments

Hi Linda and Sally,

In regard to NDA 215866 (tirzepatide) S-002 received on January 31, 2023, and S-006, received on April 18, 2023 , please see the attached round 1 FDA comments on the draft PI (combined S-002 and S-006 changes), and S-002 MG, IFU and carton/container labeling. We have decided to do a combined action for both of these supplements. We remind you that these edits do not reflect the final regulatory decision for this application and that portions of the label are still under review.

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Thank you,
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Lindsey.Kelly@fda.hhs.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LINDSEY T KELLY
07/24/2023 03:46:18 PM
See source document for attachments

From: Kelly, Lindsey
Sent: Thu, 6 Jul 2023 20:29:19 +0000
To: John J Kaiser
Cc: Linda S Kelly;Sally L Anliker
Subject: RE: [EXTERNAL] RE: NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments
Attachments: 7.6.23 proposed-medguide.docx, 7.6.23 proposed-uspi.docx, 7.6.23 proposed-vial-IFU.docx

Hi John,

In regard to NDA 215866 (tirzepatide) S-002 received on January 31, 2023, and S-006, received on April 18, 2023 , please see the attached round 2 FDA comments on the draft PI (combined S-002 and S-006 changes), and S-002 MG and IFU labeling. We have decided to do a combined action for both of these supplements. We remind you that these edits do not reflect the final regulatory decision for this application and that portions of the label are still under review. We have no additional edits to the C/C labels at this time, but we request that you wait to formally submit them to the NDA until all the labeling is agreed upon.

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Thank you,
Lindsey

Lindsey Kelly, Pharm.D.
Regulatory Project Manager

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Subject: [EXTERNAL] RE: NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments
Importance: High

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Please find attached our responses to the carton/container labeling comments for S-002 (6 PDFs for carton and 6 PDFs for container). Also attached is a regulatory response document which provides more information and context for the labels. I will submit the regulatory response formally to the NDA on Monday.

Thank you and have a great weekend!
John

John J. Kaiser, PharmD, RPh
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jkaiser@lilly.com | www.lilly.com

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Cc: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>
Subject: RE: [WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED][WARNING: UNSCANNABLE EXTRACTION FAILED]RE: [EXTERNAL] [WARNING: UNSCANNABLE EXTRACTION FAILED]NDA 215866 S-002 & S-006 Mounjaro (t
Importance: High

Hi John,

Thank you for your email, I am confirming receipt.

Have a great weekend!

Lindsey Kelly, Pharm.D.
Regulatory Project Manager

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Importance: High

Hi John,

Thank you for the update, it is appreciated. Your plan sounds reasonable.

Thanks!

Lindsey Kelly, Pharm.D.
Regulatory Project Manager

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Importance: High

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Lindsey Kelly, Pharm.D.
Regulatory Project Manager

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Thank you!

John

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To: Linda S Kelly <kelly_linda_s@lilly.com>; Sally L Anliker <anliker_sally_l@lilly.com>

Subject: [EXTERNAL] [WARNING: UNSCANNABLE EXTRACTION FAILED]NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments

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Tel: 301-837-7654
Lindsey.Kelly@fda.hhs.gov

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/s/

LINDSEY T KELLY
07/06/2023 04:43:13 PM
see source document for attachments

From: Kelly, Lindsey
Sent: Thu, 15 Jun 2023 20:56:42 +0000
To: Linda S Kelly;Sally L Anliker
Subject: NDA 215866 S-002 & S-006 Mounjaro (tirzepatide): Labeling Comments
Attachments: NDA 215866 S-002 Carton & Container Labeling - Comments.docx, NDA 215866 S-002 mounjaro-mg-draft-comments.docx, NDA 215866 S-002 mounjaro-vial-ifu-draft-comments.docx, NDA 215866 S-002, S-006 proposed-uspi .docx

Hi Linda and Sally,

In regard to NDA 215866 (tirzepatide) S-002 received on January 31, 2023, and S-006, received on April 18, 2023 , please see the attached round 1 FDA comments on the draft PI (combined S-002 and S-006 changes), and S-002 MG, IFU and carton/container labeling. We have decided to do a combined action for both of these supplements. We remind you that these edits do not reflect the final regulatory decision for this application and that portions of the label are still under review.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. When you add a comment bubble, please state " Lilly response to FDA change" or "Lilly comment."

We ask that you complete your review and return comments **as soon as possible or by EOB on Friday, June 23, 2023**. You can return the updated labels and c/c comments via email as the updated versions of the label need not be submitted to the NDA until final agreed labeling has been reached.

Please confirm receipt of this email and let me know if you have any questions.

Thank you,
Lindsey

Lindsey Kelly, Pharm.D.
Regulatory Project Manager

Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-837-7654
Lindsey.Kelly@fda.hhs.gov

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LINDSEY T KELLY
06/15/2023 05:04:02 PM
Please see source document for attachments

From: Kelly, Lindsey
Sent: Thu, 11 May 2023 15:00:53 +0000
To: Sally L Anliker
Subject: RE: [EXTERNAL] NDA 215866/S-002: Mounjaro PAS

Hi Sally,

Please refer to your January 31, 2023 labeling submission for Mounjaro (NDA 215866/S-002). We request that you provide a written response to this inquiry by **Friday, May 19, 2023**.

(b) (4)

(b) (4)

The needle and syringe recommended by your healthcare provider may look different than the needle and syringe in this INSTRUCTIONS FOR USE.

Please confirm receipt.

Thank you!

Lindsey Kelly, Pharm.D.
Regulatory Project Manager

Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-837-7654
Lindsey.Kelly@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

From: Sally L Anliker <anliker_sally_l@lilly.com>
Sent: Monday, February 13, 2023 2:52 PM
To: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Subject: RE: [EXTERNAL] NDA 215866/S-002: Mounjaro PAS

Hello Lindsey,

I confirm receipt of this communication. Thanks!

Sally L. Anliker

Associate Vice President
Global Regulatory Affairs – CMC
Eli Lilly and Company
317-695-2653

From: Kelly, Lindsey <Lindsey.Kelly@fda.hhs.gov>
Sent: Monday, February 13, 2023 2:43 PM
To: Sally L Anliker <anliker_sally_l@lilly.com>
Subject: [EXTERNAL] NDA 215866/S-002: Mounjaro PAS

Hello Sally,

Please see attached for the Acknowledgment Letter for NDA 215866 Supplement 002. Please confirm receipt and let us know if you have any questions.

Thank you,

Lindsey Kelly, Pharm.D.
Regulatory Project Manager

Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations, Office of New Drugs
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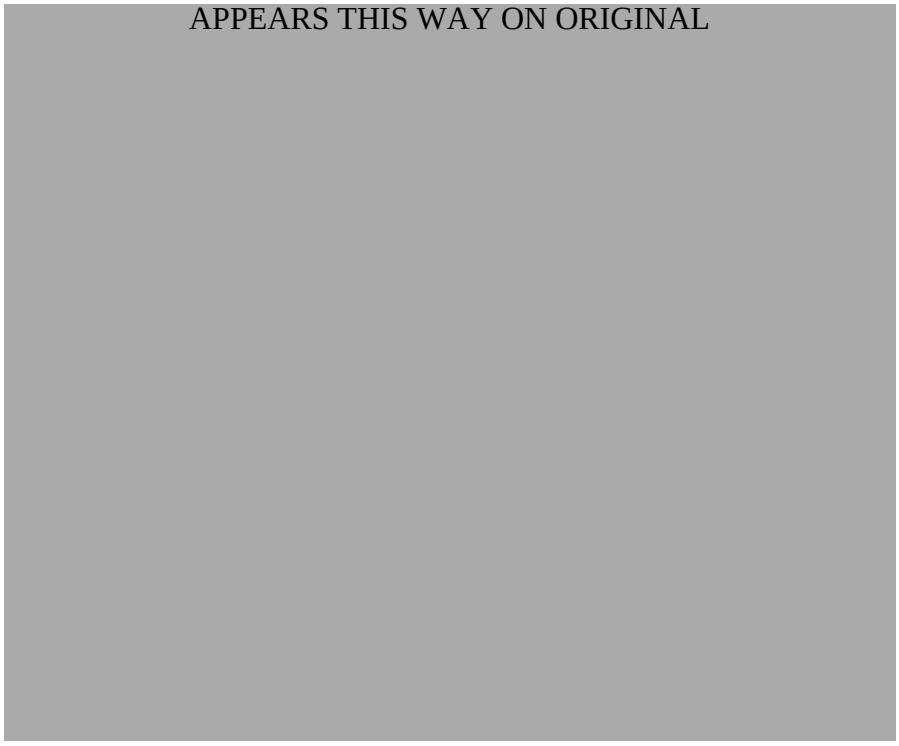
U.S. Food and Drug Administration
Tel: 301-837-7654
Lindsey.Kelly@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

APPEARS THIS WAY ON ORIGINAL



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LINDSEY T KELLY
05/11/2023 11:17:17 AM