IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

IN RE: GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (GLP-1 RAS) PRODUCTS LIABILITY LITIGATION	:	**CIVIL ACTION**
	:	**MDL No. 3094**
	:	**24-md-3094**
THIS DOCUMENT RELATES TO:	:	
ALL ACTIONS/ALL CASES	:	

POSITION STATEMENT OF DEFENDANTS NOVO NORDISK AND ELI LILLY

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I. Introduction and Litigation Overview

GLP-1RAs are medicines that have revolutionized the treatment of type 2 diabetes and obesity. Numerous clinical studies have shown that GLP-1RAs reduce the risk of death and adverse cardiovascular events, such as heart attacks and strokes. Ongoing studies suggest they may have additional benefits in addressing kidney disease, liver disease, heart failure, and Alzheimer's. The widespread use of GLP-1RAs is a result of their unprecedented efficacy in the treatment of chronic conditions that impact the daily lives of more than 200 million Americans. As leading researchers stated in the American Heart Association's journal, GLP-1RAs have "changed the landscape" and resulted in a "paradigm shift" in treatment guidelines and clinical practice.[1]

The safety profile of GLP-1RAs has been well-established in hundreds of clinical trials, large-scale observational studies, and nearly two decades of real-world use. The known risks associated with these medicines are reflected in their FDA-approved product labeling—which, collectively, FDA has reviewed more than 40 times—and are discussed in textbooks, treatment guidelines, and journals. The most widely reported risks are the gastrointestinal symptoms alleged in the majority of complaints filed to date (*e.g.*, nausea, vomiting, abdominal pain, etc.).

These facts notwithstanding, Plaintiffs allege that Novo Nordisk ("Novo") and/or Eli Lilly ("Lilly") failed to adequately warn about the risk of gastrointestinal side effects with their GLP-1RA medicines. There are currently 88 cases brought by 117 Plaintiffs (100 against Novo Nordisk, 8 against Lilly, and 9 against both), but according to Plaintiffs' counsel, these cases are a tiny fraction of the tens of thousands of claims they plan to file.

The conditions alleged in the complaints can be grouped into four categories: (1) "gastroparesis" (39 Novo, 6 Lilly, 9 both); (2) ileus/intestinal obstruction (12 Novo, 2 Lilly);

[1] Nikolaus Marx et al., *GLP-1 Receptor Agonists for the Reduction of Atherosclerotic Cardiovascular Risk in Patients with Type 2 Diabetes*, 146 Circulation 1882, 1882 (2022), https://tinyurl.com/2p9u6ces.

(3) some form of gallbladder injury (15 Novo, 0 Lilly); and (4) non-specific gastrointestinal symptoms only (40 Novo, 0 Lilly). Each of these categories involves distinct medical conditions, with different diagnostic criteria, risk factors, clinical data, and FDA regulatory histories; for each, strong scientific and legal defenses exist.

Several threshold issues need to be addressed to allow the Parties to efficiently move forward with the litigation. *First*, the Parties are negotiating a Plaintiff Fact Sheet ("PFS") process that will provide Defendants information about injuries, medical conditions, product identification, symptom onset and timing, and medical/pharmacy records. This is particularly important because (1) the complaints include limited information about the alleged injuries; (2) there has been a substantial spike in compounding[2] and counterfeiting of products that claim to contain semaglutide and tirzepatide; (3) many Plaintiffs who allege "gastroparesis" apparently lack an objective diagnosis (raising a question as to their actual alleged injury, given that specific clinical testing is required to distinguish gastroparesis from other conditions that share similar symptoms); and (4) the gastrointestinal symptoms alleged by Plaintiffs are well-known side effects of these medicines. A robust PFS process will also encourage thorough case evaluation prior to filing.

Second, more information is needed regarding the thousands of additional claims Plaintiffs' counsel have collected so that the Parties and the Court can better understand the scope and focus of the litigation, including the specific injuries, products, and defendants at issue. Without such information, it is difficult to efficiently conduct discovery and to make procedural decisions that navigate and potentially narrow the scope of the litigation (such as whether to move the litigation

[2] Compounding is the process of combining, mixing, or altering ingredients to create a medication for an individual patient. Such products are not branded medicines, and FDA does not approve them or verify their safety, effectiveness, or quality. *See* FDA, *Compounding and the FDA* (2022), https://tinyurl.com/4r6paezx.

forward on separate tracks based on injury type or other factors).

Third, Defendants expect to move to dismiss certain claims, such as design defect, manufacturing defect, and fraud. Although these motions may not dispose of entire cases, they will help shape and streamline the scope of discovery. In addition, Defendants expect to move for early summary judgment on several cross-cutting issues, potentially including causation, adequacy of the warnings, preemption, and statute of limitations. Finally, Defendants anticipate moving to exclude any opinion that a Plaintiff has "gastroparesis" in the absence of required objective diagnostic testing, which would make those claims potentially subject to summary judgment.

Below is a brief background on the disease states, medicines, labeling, and the legal issues that Defendants anticipate will arise in this MDL.

II. Background on the Underlying Disease States

Type 2 Diabetes. Diabetes is a chronic medical condition characterized by elevated blood sugar levels. Approximately 38 million Americans (11.6% of the population) suffer from this disease, which is the eighth leading cause of death in the United States. Other complications of diabetes include cardiovascular disease (heart attack and stroke), kidney disease, nerve damage, blindness, and peripheral vascular disease. Patients with diabetes also are at increased risk for developing a range of gastrointestinal conditions, including gastroparesis, gallbladder disease, and intestinal dysfunction; indeed, diabetes itself is the "most common known cause of" gastroparesis.[3] These same conditions are alleged in most Plaintiffs' complaints.

Obesity & Overweight. Obesity is a chronic medical condition that is one of the leading causes of preventable, premature death. Despite efforts at education and lifestyle intervention, more than 40% of Americans suffer from obesity, and the numbers have continued to rise over

[3] Nat'l Inst. of Diabetes & Digestive & Kidney Diseases, *Gastroparesis* (2018) https://tinyurl.com/ye2mnvzb (cited in McDonald Compl. 16 n.37).

time. Obesity and overweight are associated with a wide range of adverse health effects, including an increased risk of death, high blood pressure, high cholesterol, type 2 diabetes, heart disease, stroke, arthritis, cancer, and chronic pain. Obesity also is associated with gallbladder disease and potentially gastroparesis, the very conditions alleged by Plaintiffs in this litigation.

III. GLP-1RA Medicines at Issue

GLP-1RA medicines are considered first-line treatments for type 2 diabetes and obesity and are prominently recommended in guidelines issued by leading medical organizations such as the American Diabetes Association, the American Heart Association, and the American Gastroenterological Association.[4] GLP-1RAs work by a variety of mechanisms, including by stimulating insulin secretion from the pancreas, slowing gastric emptying, and decreasing appetite or food intake. They are widely recognized for their efficacy and safety, which has been established in hundreds of studies and in millions of patients treated under real-world conditions. Public health economists have estimated that GLP-1RA use will save billions of dollars in healthcare associated with disease-related morbidity and mortality.[5]

A. Novo Nordisk's Semaglutide Medicines

Novo's medicines Ozempic®, Wegovy®, and Rybelsus® all share the same active pharmaceutical ingredient, semaglutide. Each medicine has its own approved clinical uses (or indications), recommended dosing, prescribing information, titration schedules, data, delivery

[4] Am. Diabetes Ass'n Pro. Prac. Comm., *Pharmacologic Approaches to Glycemic Treatment*, 47 Diabetes Care S158, S164 (2024), https://tinyurl.com/yvcnbzfc; Joshua J. Joseph et al., *Comprehensive Management of Cardiovascular Risk Factors for Adults with Type 2 Diabetes*, 145 Circulation e722, e738 (2022), https://tinyurl.com/48dezwec; Eduardo Grunvald et al., *AGA Clinical Practice Guideline on Pharmacological Interventions for Adults with Obesity*, 163 Gastroenterology 1198, 1200 (2022), https://tinyurl.com/t2kz2vzk; Marc-André Cornier, *A Review of Current Guidelines for the Treatment of Obesity*, Am. J. Managed Care (Dec. 14, 2022), https://tinyurl.com/37cjbyep.

[5] Dana Goldman et al., *Want Lower Obesity Drug Costs? Medicare Holds the Key*, MedPage Today (2023), https://tinyurl.com/44hztehj.

forms, and product labeling. The products are not interchangeable and should not be used outside of their approved indications.

Ozempic® is a once-weekly injectable formulation of semaglutide that FDA first approved in 2017 for the treatment of type 2 diabetes. In 2020, FDA approved an additional use for reduction of cardiovascular complications. This was based on data from a large-scale trial showing that, compared with placebo, Ozempic® reduced the risk of non-fatal heart attacks in patients with type 2 diabetes and of non-fatal stroke. A recent study also has demonstrated that Ozempic® helps prevent progression of kidney disease in patients with type 2 diabetes.

Wegovy® is a once-weekly injectable formulation of semaglutide approved by FDA in 2021 for chronic weight management. In March 2024, FDA approved an additional use for reduction of major adverse cardiovascular events. This was based on a large clinical trial that found Wegovy® reduced the risk of major adverse cardiovascular events, death, and developing type 2 diabetes. Wegovy® is the first and only FDA-approved anti-obesity medicine that has been shown to reduce the risk of obesity-related complications, such as heart attack, stroke, death, and diabetes. Recent data also suggests that Wegovy® can improve heart failure symptoms in patients with diabetes and obesity.

Rybelsus® is the first and only FDA-approved oral GLP-1 medicine. Rybelsus® has been FDA-approved since 2019 for the treatment of type 2 diabetes and offers patients an alternative to an injection. Results of the Rybelsus® cardiovascular trial are expected later this year.

B. Lilly's Dulaglutide and Tirzepatide Medicines

Trulicity® and Mounjaro® are the two Lilly medicines at issue in this litigation, both of which are FDA-approved to treat type 2 diabetes. Lilly does not promote use of these medicines outside of their approved indications.

Trulicity® is a GLP-1RA medicine approved by FDA in 2014 for treatment of type 2

diabetes. Trulicity® was the first injectable GLP-1RA medication requiring only once-weekly dosing through a unique pre-filled pen delivery device that did not require mixing or needle attachment. In 2020, Trulicity® also became the first medicine approved to reduce the risk of major adverse cardiovascular events in patients with type 2 diabetes. The active ingredient in Trulicity® is dulaglutide. The effects of Trulicity® have been widely studied, with the National Institutes of Health registering at least 100 completed or ongoing clinical research studies involving dulaglutide (including dozens sponsored by Lilly), along with widespread commercial use for nearly a decade.

FDA approved Mounjaro® in 2022, with the active ingredient tirzepatide, as a once-weekly injectable medicine for the treatment of type 2 diabetes. In approving Mounjaro®, FDA described it as "a first-in-class" medication.[6] Unlike Trulicity® and other GLP-1RA medicines, Mounjaro® is a dual-agonist, meaning it activates not only the GLP-1 receptor but also the Glucose-dependent Insulinotropic Polypeptide ("GIP") hormone receptor. GIP is a separate hormone that affects the body's secretion of insulin, which is involved in blood sugar control.

As provided in the Mounjaro® FDA-approved label, in adult patients with type 2 diabetes, "treatment with MOUNJARO produced a statistically significant reduction from baseline in HbA1c [blood sugar level] compared to placebo."[7]

IV. Plaintiffs' Alleged Injuries

A. Gastroparesis

The largest quantity of current claims alleged by Plaintiffs have been characterized as "gastroparesis." Gastroparesis is a relatively rare gastrointestinal condition that is estimated to affect approximately 100,000 persons in the United States.

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[6] *See* FDA, *New Drug Therapy Approvals 2022*, https://tinyurl.com/mr2nnm3t.

[7] In November 2023, FDA approved Zepbound® for chronic weight management in adults with obesity (BMI greater than or equal to 30) or who are overweight (BMI greater than or equal to 27) with certain weight-related conditions. There are no pending cases involving Zepbound®.

Symptoms of gastroparesis—including nausea, vomiting, dyspepsia (indigestion), abdominal fullness, bloating, and reflux—are shared with numerous other conditions. Studies show that approximately **80%** of patients with clinical symptoms of gastroparesis ***do not*** actually have gastroparesis.[8] For this reason, symptoms alone are not sufficient to diagnose gastroparesis.

Instead, objective diagnostic testing is required to confirm that a person in fact has gastroparesis, including evidence of delayed gastric emptying by an appropriate gastric emptying study and radiological testing confirming absence of mechanical obstruction.[9] Only 8 of 54 cases asserting gastroparesis allege confirmatory testing of any kind (8 for Novo; none for Lilly). Absent such testing, these alleged injuries amount to non-specific gastrointestinal symptoms. Defendants expect to challenge whether Plaintiffs have reliable evidence of gastroparesis supported by objective diagnostic testing.

Further confounding Plaintiffs' claims, gastroparesis is a known complication of type 2 diabetes (the condition that Ozempic®, Rybelsus®, Trulicity®, and Mounjaro® are approved to treat) and may be linked to obesity (the condition that Wegovy® is approved to treat). Other known causes of gastroparesis include injury to the vagus nerve, hypothyroidism, and certain autoimmune diseases, nervous system diseases, and viral infections. A substantial percentage of gastroparesis

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[8] David Cangemi et al., *Misdiagnosis of Gastroparesis Is Common*, 21 Clinical Gastroenterology & Hepatology 2670 (2023) (abstract), https://tinyurl.com/bdf9e83b.

[9] Michael Camilleri et al., *ACG Clinical Guideline: Gastroparesis*, 117 Am. J. of Gastroenterology 1197 (2022), https://tinyurl.com/8ccj2unz; Children's Hospital of Philadelphia, *Gastroparesis*, https://tinyurl.com/4ffz48sb; Yale Medicine, *Gastroparesis*, https://tinyurl.com/5825kk2u. The Society of Nuclear Medicine and Molecular Imaging and the American Neurogastroenterology and Motility Society hold out gastric emptying scintigraphy (a nuclear imaging test measuring how long it takes food to empty from the stomach into the small intestine) as the gold standard for the diagnosis of gastroparesis. A. Shin et al., *Diagnostic Assessment of Diabetic Gastroparesis*, 62 *Diabetes* 2667 (2013), https://tinyurl.com/4ajfeyrs; Haider Ghazanfar et al., *Diagnostic Modalities Used in Diagnosing Gastroparesis*, 14 Cureus e30540, at *2 (2022), https://tinyurl.com/3ttfysrk; Yan Wang et al., *Diagnostic Methods for Evaluation of Gastric Motility*, 13 Diagnostics 803, 803, 808 (2023), https://tinyurl.com/ndefnxkc.

cases are idiopathic, meaning that no cause is known. Defendants are not aware of any randomized, controlled study reporting an increased risk of confirmed gastroparesis with semaglutide or tirzepatide. As such, even where Plaintiffs have a reliable diagnosis of gastroparesis, causation will be a key issue.

During the past year, FDA requested information from manufacturers on the effects of GLP-1RAs on aspiration, including data on gastric motility, and the results of FDA's review are still pending.[10] FDA's findings may be relevant to both causation and preemption defenses.

B. Ileus and Intestinal Obstruction

Fourteen Plaintiffs assert "ileus" and/or "intestinal obstruction." While both affect the intestinal tract, they are different conditions with different clinical presentation and features. Ileus refers to a temporary decrease in bowel motility.[11] Symptoms of ileus include bloating, abdominal pain, nausea, vomiting, constipation, loss of appetite, and diarrhea. The most common cause is abdominal surgery. Other causes include some medications (particularly opiates and commonly used anticholinergic medicines such as Benadryl), infections, and kidney failure. Treatment typically involves food restriction, with symptom resolution generally occurring in 1 to 3 days.

Intestinal obstruction refers to a mechanical blockage of the small or large bowel.[12] Symptoms include abdominal pain, bloating, vomiting, constipation, and diarrhea. The most common causes of intestinal obstruction are prior abdominal or pelvic surgery, hernia, certain tumors, diverticulitis, and severe constipation. Defendants are not aware of controlled studies reporting a risk of intestinal obstruction with semaglutide or tirzepatide.

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[10] FDA, *Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS)* (2023), https://tinyurl.com/mr9skym6.
[11] Parswa Ansari, *Ileus*, Merck Manual (2023), https://tinyurl.com/369fewxk.
[12] Parswa Ansari, *Intestinal Obstruction*, Merck Manual (2023), https://tinyurl.com/vpzrr26k.

C. Gallbladder Injury

Fifteen Plaintiffs assert gallbladder injury while taking either Ozempic® or Rybelsus®. (No current cases against Lilly allege gallbladder injuries.) The nature of the gallbladder injuries is unclear, but they likely involve cholelithiasis or cholecystitis. Cholelithiasis refers to gallstones (hardened bile deposits) in the gallbladder. About 15% of the U.S. population has gallstones and, in most cases, they are asymptomatic. Risk factors include female gender, age, overweight, pregnancy, diet, family history, diabetes, liver disease and, importantly, rapid weight loss.

Cholecystitis is inflammation of the gallbladder. Typical symptoms of cholecystitis include abdominal pain, nausea, vomiting, and fever. Gallstones are the most common causes of cholecystitis; other causes include biliary disease, cancer, and infection. Defendants are not aware of any controlled studies reporting a significantly increased risk of cholecystitis with semaglutide.

D. Gastrointestinal Symptoms (Including Severe or Prolonged Symptoms)

Another 40 Plaintiffs allege only non-specific gastrointestinal issues (currently all against Novo, none against Lilly). As discussed below, such gastrointestinal issues (including nausea, vomiting, and diarrhea) are the most common and well-understood side effects associated with GLP-1RA medications—and are described in the FDA-approved product labeling, treatment guidelines, review articles, and textbooks. These gastrointestinal issues are associated with many conditions, including diabetes and obesity, the very conditions for which GLP-1RAs are indicated. These claims may be dismissed on adequacy of warnings, learned intermediary, and other grounds.

V. FDA-Approved Label Warnings[13]

Like all medicines, GLP-1RAs have certain side effects. By far, the most common are gastrointestinal symptoms. These gastrointestinal side effects are reflected in each medicine's

[13] Exhibits A, B, and C include a summary of the Novo labeling, as well as Lilly labels with relevant provisions highlighted.

FDA-approved product labeling (discussed below) and have been recognized in the medical and scientific communities for many years, including in treatment guidelines, review articles, and textbooks relied on by healthcare professionals ("HCPs"). HCPs weigh the risks and benefits of GLP-1RAs (and all medicines) in making treatment decisions for their patients, and these decisions are based on their education, experience, and the specific clinical situation. While Defendants do not promote medicines for off-label uses (*i.e.*, outside the FDA-approved uses), the FDA permits HCPs to use their clinical judgment to prescribe medicines for uses beyond the approved label.

A. Novo's FDA-Approved Label Warnings

Gastrointestinal Symptoms. The FDA-approved product labels for Ozempic®, Wegovy®, and Rybelsus® state in numerous parts that patients may experience gastrointestinal side effects—including nausea, vomiting, diarrhea, abdominal pain, and constipation—and that, in clinical trials, approximately 3% to 8% of patients stopped taking the medicines due to adverse gastrointestinal effects. Ex. A, at 1-2, 5-6, 8-9. The Patient Guide provided with the labeling also notes that "the most common side effects" of these medicines include: "nausea," "stomach (abdominal) pain," "diarrhea," "vomiting," and "constipation," and recommends that patients contact their HCPs if these symptoms persist. *Id.* at 3, 7, 10.

Gallbladder Disease. The Wegovy® label has warned of a risk of Acute Gallbladder Disease since its commercial launch. For Ozempic® and Rybelsus®, the labels always have stated in the Adverse Reactions section that cholelithiasis (gallstones) were reported more frequently in patients treated with these medicines. In 2022, a warning regarding Acute Gallbladder Disease was added to the labeling for Ozempic® and Rybelsus® after FDA completed its review of post-marketing reports of gallbladder-related events in patients taking GLP-1RA medicines.

Ileus/Intestinal Obstruction. In 2022, FDA initiated a review of reports of intestinal obstruction with GLP-1RA medicines. Upon completion of the review, FDA specifically requested

that the term "ileus," *but not intestinal obstruction*, be added to the Adverse Reactions section of the product labeling for all GLP-1RA medicines, including Ozempic®, Wegovy®, and Rybelsus®.

B. Lilly's FDA-Approved Label Warnings

Gastrointestinal Issues. The Trulicity® and Mounjaro® labels have warned since launch that these medicines may be associated with "severe" gastrointestinal reactions—*i.e.*, the very injuries that Plaintiffs assert against Lilly. In the "WARNINGS AND PRECAUTIONS" sections, both labels state: "*Severe Gastrointestinal Disease*: Use may be associated with gastrointestinal adverse reactions, ***sometimes severe***." Ex. B, at 1; Ex. C, at 1 (emphasis added). Both labels also always warned in the same section that these medicines have "not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and [are] therefore not recommended in these patients." Ex. B, at 4; Ex. C, at 4. The Medication Guides further state that Trulicity® and Mounjaro® "**may cause serious side effects, including: . . . severe stomach problems**." Ex. B, at 33; Ex. C, at 21.

In addition, both the Mounjaro® and Trulicity® labels repeatedly warn of vomiting, diarrhea, constipation, dyspepsia (indigestion), and abdominal (stomach) pain, which are listed as the "most common adverse reactions" and the "most common side effects" of Trulicity® and/or Mounjaro®. The "Adverse Reactions" section of the Mounjaro® label, for example, includes the following information: "The most common adverse reactions, reported in >5% of all patients treated with MOUNJARO are: nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain." Ex. B, at 1; Ex. C, at 1. Both labels also state that these medicines "slow[]" and "delay[] gastric emptying." Ex. B, at 1, 8, 10, 11, 14; Ex. C, at 1, 7, 10, 11.

Ileus. In 2022 and 2023, respectively, the Trulicity® and Mounjaro® labels added "ileus" as a post-approval reported adverse reaction. Ex. B, at 8; Ex. C, at 7.

Gallbladder. No Plaintiff alleges gallbladder injuries from Trulicity® or Mounjaro®. Both

labels warn: "*Acute Gallbladder Disease:* Has occurred in clinical trials. If cholelithiasis is suspected, gallbladder studies and clinical follow-up are indicated." Ex. B, at 5; Ex. C, at 4. "Acute Gallbladder Disease" is listed as a potential "serious adverse reaction[]." Ex. B, at 5; Ex. C, at 5.

VI. Preliminary Roadmap

One of the primary efficiencies of the MDL process is the potential resolution of dispositive issues that can narrow or eliminate categories of claims. *See, e.g.*, *In re Asbestos Prods. Liab. Litig. (No. VI)*, 718 F.3d 236, 240-41, 247-49 (3d Cir. 2013). Considering the public health benefits of these medicines and the well-known and labeled risks, it is important to develop a case structure that streamlines and facilitates rigorous evaluation of the legal and scientific viability of Plaintiffs' claims. Defendants propose the following potential sequencing for the identification, categorization, and resolution of key legal, scientific, and factual issues.

A. Step One: Plaintiff Fact Sheets and Docket Metrics

The Parties are negotiating a PFS process that will provide data points on critical dispositive issues, including product identification, causation, statute of limitations, and learned intermediary. By providing information about injuries, medical conditions, product identification, symptom onset and timing, and medical/pharmacy records, the PFS process will permit the Parties and the Court to categorize claims. This will include identifying claim categories that are candidates for early motion practice, targeted discovery, and expert work to ripen cross-cutting summary judgment (and related Rule 702) motions. The PFSs will help balance the asymmetry of case specific information that tilts in favor of Plaintiffs at the beginning of this litigation.

For example, about half of all filed claims in this MDL allege symptoms of gastroparesis. Early identification of which Plaintiffs among the group have gastroparesis diagnoses confirmed by objective testing will be an important case management tool, especially because gastroparesis presents nonspecific symptoms like nausea and vomiting. Claims lacking a confirmed, objective

gastroparesis diagnosis will be candidates for early summary judgment motions to dismiss both the gastroparesis claims (based on no reliable diagnosis) and any claims for other alleged symptom (like vomiting, nausea) because they are well-known and warned-of risks of the medicines.

Further, Plaintiffs' counsel has represented to the Court that they have inventories of, and expect to file, more than 10,000 claims. But they have filed less than 1% of that number, raising questions about the complexion of the ultimate docket. To appropriately focus discovery and identify which legal, scientific, and factual issues will cut across significant numbers of claims, Defendants request that the Court consider making informal inquiries regarding the general complexion of claims that are not yet on file (*e.g.*, types of injuries, confirmatory testing, breakdown by products and defendants, percentage of cases involving hospitalization, etc.) and encourage that Plaintiffs file cases that reflect the array of cases in inventory.

B. Step Two: Early Elimination of Meritless Claims

The PFS process will also provide a tool to advance early resolution of a significant number of cases. *First*, the PFS process may help discourage the filing of meritless claims. *Second*, as is the case with virtually every major personal-injury MDL, some claimants will fail to comply with PFS requirements (whether because their claims lack merit or they choose not to participate in the litigation). *Third*, the sworn responses to PFS questions and required medical, pharmacy, or other records may present candidates for early summary judgment or docket-control show cause orders because, for example, the PFS shows their claims are invalid. For example:

***Product Identification*.** Plaintiffs may not sue Defendants for injuries allegedly caused by counterfeit or compounded products that Defendants did not manufacture, supply ingredients for, or sell. Early production of product identification records and certification of branded product use will allow the Court to dispose of claims lacking product identification at the outset.

***Timing of Injury*.** The timing of Plaintiffs' alleged symptom onset and injury diagnoses

will also be important. Given that many of the injuries alleged in the litigation are associated with the very medical conditions (diabetes and obesity) that are treated by GLP-1RAs, Defendants anticipate that many Plaintiffs may have had those symptoms (in particular gastroparesis and other gastrointestinal disease) before they started using Defendants' medicines—which Lilly's labels warn against. A robust PFS will help identify those claims that are subject to causation, learned intermediary, and other defenses. Date of symptom onset will also be important to assess the relevant statute(s) of limitations, especially since some of these medicines were first commercialized in the United States in 2014 (Trulicity®) and 2017 (Ozempic®).

Other MDL courts have implemented procedures to identify and dismiss claims based primarily on PFS deficiencies. *See, e.g.*, *In re Taxotere (Docetaxel) Prods. Liab. Litig.*, 966 F.3d 351, 356-57 (5th Cir. 2020) (affirming dismissal for failure to serve completed PFS); *In re Paraquat Prods. Liab. Litig.*, 2023 WL 10478347, at *2 (S.D. Ill. Mar. 15, 2023) (implementing docket control orders based on concerns about cases "that present implausible or far-fetched theories of liability, and therefore would not have been filed but for the availability of" the MDL).

Further, Defendants expect to move to dismiss certain legal claims (such as manufacturing and design defect, which are pled against Novo but not Lilly) that are extraneous to the litigation or are adequately addressed in the current product label. Facially meritless claims that are allowed to languish would complicate the resolution of the remaining claims. Although these motions may not dispose of entire cases, they will shape and narrow the scope of discovery, thus streamlining discovery and positioning remaining claims for potential resolution on summary judgment.

C. Step Three: Accelerated Cross-Cutting Summary Judgment Motions

The case management structures described above will set the stage for accelerated targeted discovery, expert work, and summary judgment or other dispositive motion practice that will impact and likely dispose of entire categories of claims. For example:

Gastroparesis Claims Lacking Objective Confirmatory Testing. Defendants anticipate a threshold issue will be whether Plaintiffs have a valid gastroparesis diagnosis. Accelerated discovery and expert work intended to address whether Plaintiffs have reliable evidence of gastroparesis may result in the disposition of many claims and impact the scope and merits of others. *See, e.g.*, *In re Zostavax (Zoster Vaccine Live) Prods. Liab. Litig.*, No. MDL 2848, 2022 WL 17477553, at *2-5 (E.D. Pa. Dec. 6, 2022) (applying earlier summary judgment and Rule 702 orders to dismiss with prejudice 1,189 claims that lacked required confirmatory laboratory testing).

Learned Intermediary/Warnings. Many of the complaints allege gastrointestinal symptoms like nausea, vomiting, constipation, etc. As discussed above, these are well-known, labeled risks of GLP1-RAs and are common knowledge among HCPs to whom the duty to warn runs under the learned intermediary doctrine. "In the MDL context, transferee courts have issued omnibus orders" where, as here, "a drug label [is] adequate as a matter of law" (or because there was no duty to warn of known risks). *See In re Taxotere (Docetaxel) Prods. Liab. Litig.*, 462 F. Supp. 3d 650, 652-53 (E.D. La. 2020) (granting summary judgment on nearly 200 warning claims by chemotherapy patients where label warned of risk of permanent alopecia).

D. Step Four: Notice of Other Potential Early Motions

Defendants also expect to file, at the appropriate time, other motions that may cut across large numbers of cases. These may include:

***General Causation*.** Defendants anticipate bringing motions for summary judgment on at least some alleged injuries because Plaintiffs do not have reliable evidence that the medicines are capable of causing the injury in question. Fed. R. Evid. 702; *see generally In re Acetaminophen - ASD-ADHD Prods. Liab. Litig.*, — F. Supp. 3d —, 2023 WL 8711617 (S.D.N.Y. Dec. 18, 2023) (excluding under Rule 702 general causation experts' opinions that prenatal exposure to acetaminophen causes autism and/or attention deficit disorder); *In re Zantac (Ranitidine) Prods.*

Liab. Litig., 644 F. Supp. 3d 1075, 1278 (S.D. Fla. 2022) (granting summary judgment on certain cancer claims after excluding plaintiffs' general causation experts under Rule 702).

Preemption. The impact of FDA-approved labeling (and FDA's ongoing review of GLP-1RA medicines in the ordinary course) will be important and may provide opportunities to dismiss certain claims based on preemption. For example, the Court should grant summary judgment where the record shows: (1) Defendants did not have "newly acquired information" supporting a unilateral labeling change or (2) "clear evidence" shows that FDA would have rejected the proposed warning. *See, e.g.*, *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, 593 F. Supp. 3d 96, 143-45 (D. N.J. 2022); *In re Incretin-Based Therapies Prods. Liab. Litig.*, 524 F. Supp. 3d 1007, 1033 (S.D. Cal. 2021). Defendants will promptly notify the Court and the parties if FDA-related events or certain claims provide grounds for early preemption motions.

Statute of Limitations. In light of the well-established association between GLP-1RA medicines and gastrointestinal side effects, some claims may be time-barred based on the date of onset of the alleged symptoms. Statute of limitations defenses are particularly important here because gastrointestinal symptoms typically occur shortly after starting GLP-1RA therapies and are well-known and discoverable.

Case Specific Defenses. Finally, if the litigation reaches the bellwether stage, Defendants expect to have other defenses, including specific causation and warnings causation.

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Respectfully Submitted,

/s/ Loren H. Brown

Loren H. Brown
Lucas P. Przymusinski
DLA PIPER LLP (US)
1251 Avenue of the Americas
27th Floor
New York, NY 10020-1104
Telephone: (212) 335-4846
Facsimile: (212) 335-4501
loren.brown@us.dlapiper.com
lucas.przymusinski@us.dlapiper.com

Ilana H. Eisenstein (PA Bar No. 94907)
Raymond M. Williams (PA Bar No. 90771)
Rachel A.H. Horton (PA Bar No. 316482)
DLA PIPER LLP (US)
1650 Market Street, Suite 5000
Philadelphia, PA 19103
Telephone: (215) 656-3300
Facsimile: (215) 606-3301
ilana.eisenstein@us.dlapiper.com
raymond.williams@us.dlapiper.com
rachel.horton@us.dlapiper.com

Matthew A. Holian
Katherine W. Insogna
DLA PIPER LLP (US)
33 Arch Street, 26th Floor
Boston, MA 02110
Telephone: (617) 406-6000
Facsimile: (617) 406-6100
matt.holian@us.dlapiper.com
katie.insogna@us.dlapiper.com

Attorneys for Novo Nordisk A/S, Novo Nordisk North America Operations A/S, Novo Nordisk US Holdings, Inc., Novo Nordisk US Commercial Holdings, Inc., Novo Nordisk, Inc., Novo Nordisk Research Center Seattle, Inc., and Novo Nordisk Pharmaceutical Industries, LP

-and-

/s/ Samuel W. Silver
Samuel W. Silver (PA Bar No. 56596)
Catherine M. Recker (PA Bar No. 56813)
Bruce P. Merenstein (PA Bar No. 82609)
Abigail T. Burton (PA Bar No. 334450)
Welsh & Recker, P.C.
306 Walnut Street
Philadelphia, PA 19106
Telephone: (215) 972-6430
Facsimile: (985) 617-1021
ssilver@welshrecker.com
cmrecker@welshrecker.com
bmerenstein@welshrecker.com
aburton@welshrecker.com

James F. Hurst, P.C.
Renee D. Smith
Diana M. Watral, P.C.
Kirkland & Ellis LLP
300 North LaSalle
Chicago, IL 60654
Telephone: (312) 862-2000
Facsimile: (312) 862-2200
james.hurst@kirkland.com
renee.smith@kirkland.com
diana.watral@kirkland.com

Attorneys for Defendant Eli Lilly and Company

Exhibit A

OZEMPIC®
Last revised: September 2023

Section	Excerpts of Relevant GI Labeling Language
Highlights of Prescribing Information	**WARNINGS AND PRECAUTIONS** Acute Kidney Injury: Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions (5.6). Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated (5.8).
	ADVERSE REACTIONS The most common adverse reactions, reported in ≥5% of patients treated with OZEMPIC are: nausea, vomiting, diarrhea, abdominal pain and constipation (6.1).
	DRUG INTERACTIONS Oral medications: OZEMPIC delays gastric emptying. May impact absorption of concomitantly administered oral medications. Use with caution (7.2).
Warnings and Precautions	**5.2 – Pancreatitis** After initiation of OZEMPIC, 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, OZEMPIC should be discontinued and appropriate management initiated; if confirmed, OZEMPIC should not be restarted.
	5.6 - Acute Kidney Injury There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis, in patients treated with GLP-1 receptor agonists. 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 OZEMPIC in patients reporting severe adverse gastrointestinal reactions.
	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 placebo-controlled trials, cholelithiasis was reported in 1.5% and 0.4% of patients-treated with OZEMPIC 0.5 mg and 1 mg, respectively. Cholelithiasis was not reported in placebo-treated patients. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.
Adverse Reactions 6.1 - Clinical Trials Experience	**Table 1. Adverse Reactions in Placebo-Controlled Trials Reported in ≥5% of OZEMPIC-Treated Patients with Type 2 Diabetes Mellitus** (listing adverse reaction rates for Nausea, Vomiting, Diarrhea, Abdominal Pain, and Constipation).

Section	Excerpts of Relevant GI Labeling Language
	Gastrointestinal Adverse Reactions In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving OZEMPIC than placebo (placebo 15.3%, OZEMPIC 0.5 mg 32.7%, OZEMPIC 1 mg 36.4%). The majority of reports of nausea, vomiting, and/or diarrhea occurred during dose escalation. More patients receiving OZEMPIC 0.5 mg (3.1%) and OZEMPIC 1 mg (3.8%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.4%). In the trial with OZEMPIC 1 mg and 2 mg, gastrointestinal adverse reactions occurred more frequently among patients receiving OZEMPIC 2 mg (34.0%) vs OZEMPIC 1 mg (30.8%). In addition to the reactions in Table 1, the following gastrointestinal adverse reactions with a frequency of <5% were associated with OZEMPIC (frequencies listed, respectively, as: placebo; 0.5 mg; 1 mg): dyspepsia (1.9%, 3.5%, 2.7%), eructation (0%, 2.7%, 1.1%), flatulence (0.8%, 0.4%, 1.5%), gastroesophageal reflux disease (0%, 1.9%, 1.5%), and gastritis (0.8%, 0.8%, 0.4%).
	Cholelithiasis In placebo-controlled trials, cholelithiasis was reported in 1.5% and 0.4% of patients-treated with OZEMPIC 0.5 mg and 1 mg, respectively. Cholelithiasis was not reported in placebo-treated patients.
Adverse Reactions 6.3 - Postmarketing Experience	The following adverse reactions have been reported during post-approval use of semaglutide, the active ingredient of OZEMPIC. 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. *Gastrointestinal Disorders*: Ileus. *Hypersensitivity*: anaphylaxis, angioedema, rash, urticaria. *Hepatobiliary*: cholecystitis, cholecystectomy.
Drug Interactions	OZEMPIC causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, semaglutide did not affect the absorption of orally administered medications to any clinically relevant degree *[see Clinical Pharmacology (12.3)]*. Nonetheless, caution should be exercised when oral medications are concomitantly administered with OZEMPIC.
Clinical Pharmacology	Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated, and glucagon secretion is inhibited. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase.
	Gastric emptying Semaglutide causes a delay of early postprandial gastric emptying, thereby reducing the rate at which glucose appears in the circulation postprandially.
	Drug Interaction Studies The delay of gastric emptying with semaglutide may influence the absorption of concomitantly administered oral medicinal products.

Section	Excerpts of Relevant GI Labeling Language
Patient Counseling Information	Pancreatitis Inform patients of the potential risk for pancreatitis. Instruct patients to discontinue OZEMPIC promptly and contact their physician 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)]*.
	Acute Kidney Injury Advise patients treated with OZEMPIC 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 acute kidney injury occurs *[see Warnings and Precautions (5.6)]*.
	Acute Gallbladder Disease Inform patients of the potential risk for cholelithiasis or cholecystitis. Instruct patients to contact their physician if cholelithiasis or cholecystitis is suspected for appropriate clinical follow-up *[see Warnings and Precautions (5.8)]*.
Medication Guide	**What are the possible side effects of OZEMPIC? OZEMPIC may cause serious side effects, including:** • **inflammation of your pancreas (pancreatitis)**. Stop using OZEMPIC 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. • **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. • **gallbladder problems.** Gallbladder problems have happened in some people who take OZEMPIC. Tell your healthcare provider right away if you get symptoms of gallbladder problems which may include: pain in your upper stomach (abdomen), yellowing of skin or eyes (jaundice), fever, or clay-colored stools **The most common side effects of OZEMPIC may include** nausea, vomiting, diarrhea, stomach (abdominal) pain, and constipation. Talk to your healthcare provider about any side effect that bothers you or does not go away.

WEGOVY®
Last revised: March 2024

Section	Excerpts of Relevant GI Labeling Language
Highlights of Prescribing Information	**WARNINGS AND PRECAUTIONS** Acute Gallbladder Disease: Has occurred in clinical trials. If cholelithiasis is suspected, gallbladder studies and clinical follow-up are indicated (5.3) Acute Kidney Injury: Has occurred. Monitor renal function when initiating or escalating doses of WEGOVY in patients reporting severe adverse gastrointestinal reactions or in those with renal impairment reporting severe adverse gastrointestinal reactions (5.5).
	ADVERSE REACTIONS Most common adverse reactions (incidence ≥ 5%) in adults or pediatric patients aged 12 years and older are: nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distension, eructation, hypoglycemia in patients with type 2 diabetes, flatulence, gastroenteritis, gastroesophageal reflux disease, and nasopharyngitis (6.1).
	DRUG INTERACTIONS WEGOVY delays gastric emptying. May impact absorption of concomitantly administered oral medications. Use with caution (7.2).
Warnings and Precautions	**5.2 – Acute Pancreatitis** After initiation of WEGOVY, observe patients carefully for signs and symptoms of acute pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, and which may or may not be accompanied by vomiting). If acute pancreatitis is suspected, WEGOVY should promptly be discontinued, and appropriate management should be initiated. If acute pancreatitis is confirmed, WEGOVY should not be restarted.
	5.3 – Acute Gallbladder Disease Treatment with WEGOVY is associated with an increased occurrence of cholelithiasis and cholecystitis. The incidence of cholelithiasis and cholecystitis was higher in WEGOVY-treated pediatric patients aged 12 years and older than in WEGOVY-treated adults. In randomized clinical trials in adult patients, cholelithiasis was reported by 1.6% of WEGOVY-treated patients and 0.7% of placebo-treated patients. Cholecystitis was reported by 0.6% of WEGOVY-treated adult patients and 0.2% of placebo-treated patients. In a clinical trial in pediatric patients aged 12 years and older, cholelithiasis was reported by 3.8% of WEGOVY-treated patients and 0% placebo-treated patients. Cholecystitis was reported by 0.8% of WEGOVY-treated pediatric patients and 0% placebo-treated patients *[see Adverse Reactions (6.1)]*. Substantial or rapid weight loss can increase the risk of cholelithiasis; however, the incidence of acute gallbladder disease was greater in WEGOVY-treated patients than in placebo-treated patients, even after accounting for the degree of weight loss. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.
	5.5 - Acute Kidney Injury There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which have in some cases required hemodialysis, in patients treated with semaglutide. Patients with renal impairment may be at greater risk of acute kidney injury, but some of these events have been reported in patients

Section	Excerpts of Relevant GI Labeling Language
	without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, or diarrhea, leading to volume depletion *[see Adverse Reactions (6)]*. Monitor renal function when initiating or escalating doses of WEGOVY in patients reporting severe adverse gastrointestinal reactions. Monitor renal function in patients with renal impairment reporting any adverse reactions that could lead to volume depletion.
Adverse Reactions 6.1 - Clinical Trials Experience	**Table 3. Adverse Reactions (≥2% and Greater Than Placebo) in WEGOVY-treated Adults with Obesity or Overweight.** (listing adverse reaction rates for Nausea, Diarrhea, Vomiting, Constipation, Abdominal Pain, Headache, Fatigue, Dyspepsia, Dizziness, Abdominal Distention, Eructation, Hypoglycemia in T2DM, Flatulence, Gastroenteritis, Gastroesophageal Reflux Disease, Gastritis, Gastroenteritis Viral, Hair Loss, and Dysesthesia).
	Acute Gallbladder Disease In WEGOVY clinical trials in adults, cholelithiasis was reported by 1.6% of WEGOVY-treated patients and 0.7% of placebo-treated patients. Cholecystitis was reported by 0.6% of WEGOVY-treated adult patients and 0.2% of placebo-treated patients. In a clinical trial in pediatric patients aged 12 years and older *[see Clinical Studies (14.3)]*, cholelithiasis was reported by 3.8% of WEGOVY-treated patients and 0% placebo-treated patients. Cholecystitis was reported by 0.8% of WEGOVY-treated pediatric patients and 0% placebo-treated patients.
	Acute Kidney Injury Acute kidney injury occurred in clinical trials in 7 adult patients (0.4 cases per 100 patient years) receiving WEGOVY versus 4 patients (0.2 cases per 100 patient years of exposure) receiving placebo. Some of these adverse reactions occurred in association with gastrointestinal adverse reactions or dehydration. In addition, 2 patients treated with WEGOVY had acute kidney injury with dehydration in other clinical trials.
	Hypotension and Syncope Adverse reactions related to hypotension (hypotension, orthostatic hypotension, and decreased blood pressure) were reported in 1.3% of WEGOVY-treated adult patients versus 0.4% of placebo-treated patients and syncope was reported in 0.8% of WEGOVY-treated patients versus 0.2% of placebo-treated patients. Some reactions were related to gastrointestinal adverse reactions and volume loss associated with WEGOVY.
	Gastrointestinal Adverse Reactions In clinical trials in adults, 73% of WEGOVY-treated patients and 47% of patients receiving placebo reported gastrointestinal adverse reactions, including severe reactions that were reported more frequently among patients receiving WEGOVY (4.1%) than placebo (0.9%). The most frequently reported reactions were nausea (44% vs. 16%), vomiting (25% vs. 6%), and diarrhea (30% vs. 16%). Other reactions that occurred at a higher incidence among WEGOVY-treated adult patients included dyspepsia, abdominal pain, abdominal distension, eructation, flatulence, gastroesophageal reflux disease, gastritis, hemorrhoids, and hiccups. These reactions increased during dose escalation.

Section	Excerpts of Relevant GI Labeling Language
	In the pediatric clinical trial, 62% of WEGOVY-treated patients and 42% of placebo-treated patients reported gastrointestinal disorders. The most frequently reported reactions were nausea (42% vs. 18%), vomiting (36% vs. 10%), and diarrhea (22% vs. 19%). Other gastrointestinal-related reactions that occurred at a higher incidence than placebo among WEGOVY-treated pediatric patients included abdominal pain, constipation, eructation, gastroesophageal reflux disease, dyspepsia, and flatulence. Permanent discontinuation of treatment as a result of a gastrointestinal adverse reaction occurred in 4.3% of WEGOVY-treated adult patients versus 0.7% of placebo-treated patients. In a pediatric clinical trial, 2.3% of patients treated with WEGOVY versus 1.5% of patients who received placebo discontinued treatment as a result of gastrointestinal adverse reactions.
Adverse Reactions 6.2 - Postmarketing Experience	The following adverse reactions have been reported during post-approval use of semaglutide, the active ingredient of WEGOVY. 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. *Gastrointestinal Disorders:* acute pancreatitis and necrotizing pancreatitis, sometimes resulting in death; ileus. *Hypersensitivity*: anaphylaxis, angioedema, rash, urticaria. *Renal and Urinary Disorders*: acute kidney injury.
Drug Interactions	WEGOVY causes a delay of gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials with semaglutide 1 mg, semaglutide did not affect the absorption of orally administered medications *[see Clinical Pharmacology (12.3)]*. Nonetheless, monitor the effects of oral medications concomitantly administered with WEGOVY.
Clinical Pharmacology	Gastric Emptying Semaglutide delays gastric emptying.
	Drug Interaction Studies The delay of gastric emptying with semaglutide may influence the absorption of concomitantly administered oral medications *[see Drug Interactions (7.2)]*.
Patient Counseling Information	Acute Pancreatitis Inform patients of the potential risk for acute pancreatitis. Instruct patients to discontinue WEGOVY promptly and contact their physician 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)]*.
	Acute Gallbladder Disease Inform patients of the risk of acute gallbladder disease. Advise patients that substantial or rapid weight loss can increase the risk of gallbladder disease, but that gallbladder disease may also occur in the absence of substantial or rapid weight loss. Instruct patients to contact their healthcare provider for appropriate

Section	Excerpts of Relevant GI Labeling Language
	clinical follow-up if gallbladder disease is suspected *[see Warnings and Precautions (5.3)]*.
	Dehydration and Renal Impairment Advise patients treated with WEGOVY 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)]*.
Medication Guide	**What are the possible side effects of WEGOVY? WEGOVY may cause serious side effects, including:** • **inflammation of your pancreas (pancreatitis)**. Stop using WEGOVY 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. • **gallbladder problems.** WEGOVY may cause gallbladder problems including gallstones. Some gallbladder problems need surgery. Call your healthcare provider if you have any of the following symptoms: pain in your upper stomach (abdomen), yellowing of skin or eyes (jaundice), fever, or clay-colored stools • **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. **The most common side effects of WEGOVY in adults or children aged 12 years and older may include:** nausea, diarrhea, vomiting, constipation, stomach (abdomen) pain, headache, tiredness (fatigue), upset stomach, dizziness, feeling bloated, belching, low blood sugar in people with type 2 diabetes, gas, stomach flu, heartburn, runny nose or sore throat. Talk to your healthcare provider about any side effect that bothers you or does not go away.

RYBELSUS®
Last revised: January 2024

Section	Excerpts of Relevant GI Labeling Language
Highlights of Prescribing Information	**WARNINGS AND PRECAUTIONS** Acute Kidney Injury: Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions (5.5). Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated (5.7)
	ADVERSE REACTIONS Most common adverse reactions (incidence ≥5%) are nausea, abdominal pain, diarrhea, decreased appetite, vomiting and constipation (6.1).
	DRUG INTERACTIONS Oral Medications: RYBELSUS delays gastric emptying. Instruct patients to closely follow RYBELSUS administration instructions (7.2).
Warnings and Precautions	**5.2 – Pancreatitis** After initiation of RYBELSUS, 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, RYBELSUS should be discontinued and appropriate management initiated; if confirmed, RYBELSUS should not be restarted.
	5.5 - Acute Kidney Injury There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis, in patients treated with GLP-1 receptor agonists, including semaglutide. 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 RYBELSUS in patients reporting severe adverse gastrointestinal reactions.
	5.7 - 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 placebo-controlled trials, cholelithiasis was reported in 1% of patients treated with RYBELSUS 7 mg. Cholelithiasis was not reported in RYBELSUS 14 mg or placebo-treated patients. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated *[see Adverse Reactions (6.2)]*.
Adverse Reactions 6.1 - Clinical Trials Experience	**Table 1. Adverse Reactions in Placebo-Controlled Trials Reported in ≥5% of RYBELSUS-Treated Patients with Type 2 Diabetes Mellitus** (listing adverse reaction rates for Nausea, Abdominal Pain, Diarrhea, Decreased Appetite, Vomiting, and Constipation).

Section	Excerpts of Relevant GI Labeling Language
	Gastrointestinal Adverse Reactions In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving RYBELSUS than placebo (placebo 21%, RYBELSUS 7 mg 32%, RYBELSUS 14 mg 41%). The majority of reports of nausea, vomiting, and/or diarrhea occurred during dose escalation. More patients receiving RYBELSUS 7 mg (4%) and RYBELSUS 14 mg (8%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (1%). In addition to the reactions in Table 1, the following gastrointestinal adverse reactions with a frequency of <5% were associated with RYBELSUS (frequencies listed, respectively, as placebo; 7 mg; 14 mg): abdominal distension (1%, 2%, 3%), dyspepsia (0.6%, 3%, 0.6%), eructation (0%, 0.6%, 2%), flatulence (0%, 2%, 1%), gastroesophageal reflux disease (0.3%, 2%, 2%), and gastritis (0.8%, 2%, 2%).
	Cholelithiasis In placebo-controlled trials, cholelithiasis was reported in 1% of patients treated with RYBELSUS 7 mg. Cholelithiasis was not reported in RYBELSUS 14 mg or placebo-treated patients.
Adverse Reactions 6.2 - Postmarketing Experience	The following adverse reactions have been reported during post-approval use of semaglutide, the active ingredient of RYBELSUS. 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. *Gastrointestinal*: ileus *Hypersensitivity*: anaphylaxis, angioedema, rash, urticaria *Hepatobiliary*: cholecystitis, cholelithiasis requiring cholecystectomy *Nervous system disorders*: dizziness, dysgeusia.
Drug Interactions	RYBELSUS causes a delay of gastric emptying, and thereby has the potential to impact the absorption of other oral medications. Levothyroxine exposure was increased 33% (90% CI: 125-142) when administered with RYBELSUS in a drug interaction study *[see Clinical Pharmacology (12.3)]*.
Clinical Pharmacology	Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase.
	Gastric emptying Semaglutide causes a delay of early postprandial gastric emptying, thereby reducing the rate at which glucose appears in the circulation postprandially.
	Drug Interaction Studies The delay of gastric emptying with semaglutide may influence the absorption of concomitantly administered oral medicinal products.

Section	Excerpts of Relevant GI Labeling Language
Patient Counseling Information	Pancreatitis Inform patients of the potential risk for pancreatitis. Instruct patients to discontinue RYBELSUS promptly and contact their physician 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)]*.
	Dehydration and Renal Failure Advise patients treated with RYBELSUS 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)]*.
	Acute Gallbladder Disease Inform patients of the potential risk for cholelithiasis or cholecystitis. Instruct patients to contact their physician if cholelithiasis or cholecystitis is suspected for appropriate clinical follow-up *[see Warnings and Precautions (5.7)]*.
Medication Guide	**What are the possible side effects of OZEMPIC? OZEMPIC may cause serious side effects, including:** • **inflammation of your pancreas (pancreatitis)**. Stop using RYBELSUS 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. • **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. • **gallbladder problems.** Gallbladder problems have happened in some people who take RYBELSUS. Tell your healthcare provider right away if you get symptoms of gallbladder problems, which may include: pain in your upper stomach (abdomen), yellowing of skin or eyes (jaundice), fever, or clay-colored stools **The most common side effects of RYBELSUS may include** nausea, stomach (abdominal) pain, diarrhea, decreased appetite, vomiting and constipation. Nausea, vomiting and diarrhea are most common when you first start RYBELSUS. Talk to your healthcare provider about any side effect that bothers you or does not go away.

Exhibit B

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

TRULICITY (dulaglutide) injection, for subcutaneous use
Initial U.S. Approval: 2014

WARNING: RISK OF THYROID C-CELL TUMORS
See full prescribing information for complete boxed warning.

- **Dulaglutide causes thyroid C-cell tumors in rats. It is unknown whether TRULICITY causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of dulaglutide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).**
- **TRULICITY is contraindicated in patients with a personal or family history of MTC and 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 ----------

Indications and Usage (1)	11/2022
Dosage and Administration (2.2)	11/2022
Warnings and Precautions (5.8)	6/2022

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

TRULICITY® is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated (1):

- As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus.
- To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors.

Limitations of Use:

- Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in these patients (1, 5.2).
- Not for treatment of type 1 diabetes mellitus (1).
- Not recommended in patients with severe gastrointestinal disease, including severe gastroparesis (1, 5.6).

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

Adult Dosage (2.1)

- Recommended starting dosage is 0.75 mg injected subcutaneously once weekly.
- Increase dosage to 1.5 mg once weekly for additional glycemic control.
- If additional glycemic control is needed, increase dosage in 1.5 mg increments after at least 4 weeks on the current dosage.
- Maximum recommended dosage is 4.5 mg injected subcutaneously once weekly.

Pediatric Dosage (2.2)

- Recommended starting dosage is 0.75 mg injected subcutaneously once weekly.
- If additional glycemic control is needed, increase dosage to the maximum recommended dosage of 1.5 mg once weekly after at least 4 weeks on the 0.75 mg dosage.

Recommendations Regarding Missed Dose (2.3)

- If a dose is missed, administer the missed dose as soon as possible if there are at least 3 days (72 hours) until the next scheduled dose.

Important Administration Instructions (2.4)

- Administer once weekly at any time of day with or without food.
- Inject subcutaneously in the abdomen, thigh, or upper arm.

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

- Injection: 0.75 mg/0.5 mL solution in a single-dose pen (3)
- Injection: 1.5 mg/0.5 mL solution in a single-dose pen (3)
- Injection: 3 mg/0.5 mL solution in a single-dose pen (3)
- Injection: 4.5 mg/0.5 mL solution in a single-dose pen (3)

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

- Patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4, 5.1).
- Patients with a serious hypersensitivity reaction to dulaglutide or any of the product components (4, 5.4).

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

- *Thyroid C-cell Tumors:* See Boxed Warning (5.1).
- *Pancreatitis:* Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed (5.2).
- *Hypoglycemia:* Concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing the dose of insulin secretagogue or insulin may be necessary (5.3).
- *Hypersensitivity Reactions:* Serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) have occurred. Discontinue TRULICITY 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:* Have been reported in a cardiovascular outcomes trial. Monitor patients with a history of diabetic retinopathy (5.7).
- *Acute Gallbladder Disease:* If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated (5.8).

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

Most common adverse reactions (incidence ≥5%) are nausea, diarrhea, vomiting, abdominal pain, and decreased appetite (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 ----------

Oral Medications: Delays gastric emptying and has the potential to reduce the rate of absorption of concomitantly administered oral medications (7.1, 12.3).

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

Pregnancy: Should be used during pregnancy only if the potential benefit justifies the potential risk to fetus (8.1).

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

Revised: 11/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

- **In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. It is unknown whether TRULICITY causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of dulaglutide-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions (5.1), and Nonclinical Toxicology (13.1)]*.**
- **TRULICITY is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC with use of TRULICITY and inform them of symptoms of thyroid tumors (e.g., 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 TRULICITY *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

TRULICITY® is indicated:

- As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus.
- To reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors.

Limitations of Use

TRULICITY:

- Has not been studied in patients with a history of pancreatitis *[see Warnings and Precautions (5.2)]*. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Should not be used in patients with type 1 diabetes mellitus.
- Has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis and is therefore not recommended in these patients *[see Warnings and Precautions (5.6)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosage

- The recommended starting dosage of TRULICITY is 0.75 mg injected subcutaneously once weekly.
- Increase the dosage to 1.5 mg once weekly for additional glycemic control.

- If additional glycemic control is needed, increase the dosage in 1.5 mg increments after at least 4 weeks on the current dosage.
- The maximum recommended dosage is 4.5 mg injected subcutaneously once weekly.

2.2 Pediatric Dosage

- The recommended starting dosage of TRULICITY is 0.75 mg injected subcutaneously once weekly.
- If additional glycemic control is needed, increase the dosage to the maximum recommended dosage of 1.5 mg once weekly after at least 4 weeks on the 0.75 mg dosage.

2.3 Recommendations Regarding Missed Dose

- If a dose is missed, instruct patients to administer the dose as soon as possible if there are at least 3 days (72 hours) until the next scheduled dose. If less than 3 days remain before the next scheduled dose, 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 last dose was administered 3 or more days before the new day of administration.

2.4 Important Administration Instructions

- Prior to initiation, train patients and caregivers on proper injection technique *[see Instructions for Use]*.
- Administer TRULICITY once weekly, any time of day, with or without food.
- Inject TRULICITY subcutaneously in the abdomen, thigh, or upper arm.
- Rotate injection sites with each dose.
- Inspect TRULICITY visually before use. It should appear clear and colorless. Do not use TRULICITY if particulate matter or coloration is seen.
- When using TRULICITY with insulin, administer as separate injections and never mix. It is acceptable to inject TRULICITY and insulin in the same body region, but the injections should not be adjacent to each other.

3 DOSAGE FORMS AND STRENGTHS

Injection: TRULICITY is a clear and colorless solution available as:

- 0.75 mg/0.5 mL solution in a single-dose pen
- 1.5 mg/0.5 mL solution in a single-dose pen
- 3 mg/0.5 mL solution in a single-dose pen
- 4.5 mg/0.5 mL solution in a single-dose pen

4 CONTRAINDICATIONS

TRULICITY is contraindicated in patients with:

- 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)]*.
- Serious hypersensitivity reaction to dulaglutide or to any of the product components. Serious hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with TRULICITY *[see Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-cell Tumors

In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure *[see Nonclinical Toxicology (13.1)]*. Glucagon-like peptide-1 (GLP-1) receptor agonists have induced thyroid C-cell adenomas and carcinomas in mice and rats at clinically relevant exposures. It is unknown whether TRULICITY will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of dulaglutide-induced rodent thyroid C-cell tumors has not been determined.

One case of MTC was reported in a patient treated with TRULICITY in a clinical trial. This patient had pretreatment calcitonin levels approximately 8 times the upper limit of normal (ULN). An additional case of C-cell hyperplasia with elevated calcitonin levels following treatment was reported in the cardiovascular outcomes trial (REWIND). Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans.

TRULICITY 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 TRULICITY 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 TRULICITY. 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

In a pooled analysis from the original registration studies, 12 (3.4 cases per 1000 patient years) pancreatitis-related adverse reactions were reported in patients exposed to TRULICITY versus 3 in non-incretin comparators (2.7 cases per 1000 patient years). An analysis of adjudicated events revealed 5 cases of confirmed pancreatitis in patients exposed to TRULICITY (1.4 cases per 1000 patient years) versus 1 case in non-incretin comparators (0.88 cases per 1000 patient years).

Based on an analysis of adjudicated events in a clinical trial evaluating Trulicity 1.5 mg, 3 mg, or 4.5 mg once weekly, pancreatitis occurred in 1 patient exposed to TRULICITY 1.5 mg (0.2%), in 2 patients exposed to TRULICITY 3 mg (0.3%), and 3 patients exposed to TRULICITY 4.5 mg (0.5%).

After initiation of TRULICITY, observe patients carefully for signs and symptoms of pancreatitis, including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting. If pancreatitis is suspected, promptly discontinue TRULICITY and initiate appropriate management. If pancreatitis is confirmed, TRULICITY should not be restarted. TRULICITY has not been evaluated in patients with a prior history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.

5.3 Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

Patients receiving TRULICITY 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) and Drug Interactions (7)]*.

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

There have been postmarketing reports of serious hypersensitivity reactions including anaphylactic reactions and angioedema in patients treated with TRULICITY *[see Adverse Reactions (6.2)]*. If a hypersensitivity reaction occurs, discontinue TRULICITY; treat promptly per standard of care, and monitor until signs and symptoms resolve. TRULICITY is contraindicated in patients with a previous serious hypersensitivity reaction to dulaglutide or to any of the components of TRULICITY.

Anaphylaxis and angioedema have been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema or anaphylaxis with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to anaphylaxis with TRULICITY.

5.5 Acute Kidney Injury

In patients treated with GLP-1 receptor agonists, including TRULICITY, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events were reported in patients without known underlying renal disease. A majority of reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Because these reactions may worsen renal function, use caution when initiating or escalating doses of TRULICITY in patients with renal impairment. Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions *[see Use in Specific Populations (8.6)]*.

5.6 Severe Gastrointestinal Disease

Use of TRULICITY may be associated with gastrointestinal adverse reactions, sometimes severe *[see Adverse Reactions (6.1)]*. TRULICITY 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

In a cardiovascular outcomes trial with a median follow up of 5.4 years involving patients with type 2 diabetes with established cardiovascular disease or multiple cardiovascular risk factors, diabetic retinopathy complications occurred in patients treated with TRULICITY 1.5 mg (1.9%) and placebo (1.5%). These events were prospectively ascertained as a secondary composite endpoint. The proportion of patients with diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline (TRULICITY 8.5%, placebo 6.2%) than among patients without a known history of diabetic retinopathy (TRULICITY 1%, placebo 1%).

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. 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 a cardiovascular outcomes trial with a median follow up of 5.4 years, cholelithiasis occurred at a rate of 0.62/100 patient-years in TRULICITY-treated patients and 0.56/100 patient-years in placebo-treated patients after adjusting for prior cholecystectomy. Serious events of acute cholecystitis were reported in 0.5% and 0.3% of patients on TRULICITY and placebo respectively. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

6 ADVERSE REACTIONS

The following serious 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 in Patients with a History of Diabetic Retinopathy *[see Warnings and Precautions (5.7)]*
- Acute Gallbladder Disease *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

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

Adverse Reactions in the Clinical Trials in Adults with Type 2 Diabetes Mellitus

Pool of Adult Placebo-Controlled Trials for TRULICITY 0.75 mg and 1.5 mg Doses

The data in Table 1 are derived from a pool of placebo-controlled trials and include 1,670 adult patients with type 2 diabetes mellitus exposed to TRULICITY with a mean duration of exposure of 23.8 weeks *[see Clinical Studies (14)]*. The mean age of patients was 56 years, 1% were 75 years or older and 53% were male. The population was 69% White, 7% Black or African American, 13% Asian; 30% were of Hispanic or Latino ethnicity. At baseline, the population had diabetes for an average of 8 years, a mean HbA1c of 8.0%, and 2.5% of the population reported retinopathy. Baseline estimated renal function was normal or mildly impaired (eGFR ≥60 mL/min/1.73 m^2) in 96%.

Table 1 shows adverse reactions, excluding hypoglycemia, occurring in ≥5% of TRULICITY treated adult patients and more commonly than placebo in a pool of placebo-controlled trials.

Table 1: Adverse Reactions in Pool of Placebo-Controlled Trials That Occurred in ≥5% of TRULICITY-Treated Adult Patients with Type 2 Diabetes Mellitus

Adverse Reaction	Placebo (N=568) %	TRULICITY 0.75 mg (N=836) %	TRULICITY 1.5 mg (N=834) %
Nausea	5.3	12.4	21.1
Diarrhea[a]	6.7	8.9	12.6
Vomiting[b]	2.3	6.0	12.7
Abdominal Pain[c]	4.9	6.5	9.4
Decreased Appetite	1.6	4.9	8.6
Dyspepsia	2.3	4.1	5.8
Fatigue[d]	2.6	4.2	5.6

[a] Includes diarrhea, fecal volume increased, frequent bowel movements.
[b] Includes retching, vomiting, vomiting projectile.
[c] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, gastrointestinal pain.
[d] Includes fatigue, asthenia, malaise.
Note: Percentages reflect the number of patients that reported at least 1 treatment-emergent occurrence of the adverse reaction.

Gastrointestinal Adverse Reactions

In the pool of placebo-controlled trials, gastrointestinal (GI) adverse reactions occurred more frequently among patients who received TRULICITY compared to patients who received placebo (placebo 21%, 0.75 mg 32%, 1.5 mg 41%). A higher percentage of patients who received TRULICITY 0.75 mg (1.3%) and TRULICITY 1.5 mg (3.5%) discontinued treatment due to GI adverse reactions than patients who received placebo (0.2%). Investigators graded the severity of GI adverse reactions that occurred in those treated with 0.75 mg and 1.5 mg of TRULICITY as "mild" in 58% and 48% of cases, respectively, "moderate" in 35% and 42% of cases, respectively, or "severe" in 7% and 11% of cases, respectively.

The following GI adverse reactions were reported more frequently in TRULICITY-treated patients than placebo - treated patients (frequencies listed, respectively, as: placebo; 0.75 mg; 1.5 mg): constipation (0.7%, 3.9%, 3.7%), flatulence (1.4%, 1.4%, 3.4%), abdominal distension (0.7%, 2.9%, 2.3%), gastroesophageal reflux disease (0.5%, 1.7%, 2.0%), and eructation (0.2%, 0.6%, 1.6%).

Adult Dose Ranging Trial for TRULICITY 3 mg and 4.5 mg Doses

Table 2 shows adverse reactions occurring ≥5% in any of the treatment groups through 36 weeks in a clinical trial with 1842 adult patients with type 2 diabetes mellitus treated with TRULICITY 1.5 mg, 3 mg, or 4.5 mg subcutaneously once weekly as an add-on to metformin *[see Clinical Studies (14.3)]*. The adverse reaction profile is consistent with previous clinical trials in adults.

Table 2: Adverse Reactions That Occurred in ≥5% of TRULICITY-treated Adult Patients with Type 2 Diabetes Mellitus in a Clinical Trial through 36 Weeks[a]

Adverse Reaction	TRULICITY 1.5 mg (N=612) %	TRULICITY 3 mg (N=616) %	TRULICITY 4.5 mg (N=614) %
Nausea	13.4	15.6	16.4
Diarrhea	7.0	11.4	10.7
Vomiting	5.6	8.3	9.3
Dyspepsia	2.8	5.0	2.6

[a] Percentages reflect the number of patients that reported at least 1 treatment-emergent occurrence of the adverse reaction.

Other Adverse Reactions in Adults

Hypoglycemia

Table 3 summarizes the incidence of hypoglycemia in the placebo-controlled clinical studies in adult patients with type 2 diabetes mellitus: episodes with a glucose level <54 mg/dL with or without symptoms, and severe hypoglycemia, defined as an episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Table 3: Incidence (%) of Hypoglycemia in Adult Patients with Type 2 Diabetes Mellitus in Placebo-Controlled Trials

	Placebo	TRULICITY 0.75 mg	TRULICITY 1.5 mg
Add-on to Metformin			
(26 weeks)	**N=177**	**N=302**	**N=304**
Hypoglycemia with a glucose level <54 mg/dL	0	0.3	0.7
Severe hypoglycemia	0	0	0
Add-on to Metformin + Pioglitazone			
(26 weeks)	**N=141**	**N=280**	**N=279**
Hypoglycemia with a glucose level <54 mg/dL	1.4	2.1	0
Severe hypoglycemia	0	0	0
Add-on to Glimepiride			
(24 weeks)	**N=60**	-	**N=239**
Hypoglycemia with a glucose level <54 mg/dL	0	-	3.3
Severe hypoglycemia	0	-	0
In Combination with Insulin Glargine ± Metformin			
(28 weeks)	**N=150**	-	**N=150**
Hypoglycemia with a glucose level <54 mg/dL	9.3	-	14.7
Severe hypoglycemia	0	-	0.7
Add-on to SGLT2i ± Metformin			
(24 weeks)	**N=140**	**N=141**	**N=142**
Hypoglycemia with a glucose level <54 mg/dL	0.7	0.7	0.7
Severe hypoglycemia	0	0.7	0

Hypoglycemia was more frequent when TRULICITY was used in combination with a sulfonylurea or insulin than when used with non-secretagogues. In a 78-week adult clinical trial, hypoglycemia (glucose level <54 mg/dL) occurred in 20% and 21% of patients when TRULICITY 0.75 mg and 1.5 mg, respectively, were co-administered with a sulfonylurea. Severe hypoglycemia occurred in 0% and 0.7% of patients when TRULICITY 0.75 mg and 1.5 mg, respectively, were co-administered with a sulfonylurea. In a 52-week adult clinical trial, hypoglycemia (glucose level <54 mg/dL) occurred in 77% and 69% of patients when TRULICITY 0.75 mg and 1.5 mg, respectively, were co-administered with prandial insulin. Severe hypoglycemia occurred in 2.7% and 3.4% of patients when TRULICITY 0.75 mg and 1.5 mg, respectively, were co-administered with prandial insulin. Refer to Table 3 for the incidence of hypoglycemia in patients treated in combination with basal insulin glargine.

In the clinical trial with adult patients on TRULICITY 1.5 mg, TRULICITY 3 mg, or TRULICITY 4.5 mg once weekly, as add-on to metformin, incidences of hypoglycemia (glucose level <54 mg/dL) through 36 weeks were 1.1%, 0.3%, and 1.1%, respectively, and incidences of severe hypoglycemia were 0.2%, 0%, and 0.2%, respectively.

Cholelithiasis and Cholecystitis

In a cardiovascular outcomes trial in adult patients with type 2 diabetes mellitus and established cardiovascular (CV) disease or multiple cardiovascular risk factors with a median follow up of 5.4 years *[see Clinical Studies 14.5]*, cholelithiasis occurred at a rate of 0.62/100 patient-years in TRULICITY-treated patients and 0.56/100 patient-years in placebo-treated patients after adjusting for prior cholecystectomy. Serious events of acute cholecystitis were reported in 0.5% and 0.3% of patients on TRULICITY and placebo respectively.

Heart Rate Increase and Tachycardia-Related Adverse Reactions

In adult patients, TRULICITY 0.75 mg and 1.5 mg resulted in a mean increase in heart rate (HR) of 2-4 beats per minute (bpm).

Adverse reactions of sinus tachycardia were reported more frequently in patients exposed to TRULICITY. Sinus tachycardia was reported in 3.0%, 2.8%, and 5.6% of patients treated with placebo, TRULICITY 0.75 mg and TRULICITY 1.5 mg, respectively. Persistence of sinus tachycardia (reported at more than 2 visits) was reported in 0.2%, 0.4% and 1.6% of patients treated with placebo, TRULICITY 0.75 mg and TRULICITY 1.5 mg, respectively. Episodes of sinus tachycardia, associated with a concomitant increase from baseline in heart rate of ≥15 beats per minute, were reported in 0.7%, 1.3% and 2.2% of patients treated with placebo, TRULICITY 0.75 mg and TRULICITY 1.5 mg, respectively.

Hypersensitivity

Systemic hypersensitivity adverse reactions, sometimes severe (e.g., severe urticaria, systemic rash, facial edema, lip swelling), occurred in 0.5% of adult patients on TRULICITY in clinical studies.

Injection-site Reactions

In the placebo-controlled studies in adults, injection-site reactions (e.g., injection-site rash, erythema) were reported in 0.5% of TRULICITY-treated patients and in 0.0% of placebo-treated patients.

PR Interval Prolongation and Adverse Reactions of First-Degree Atrioventricular (AV) Block

A mean increase from baseline in PR interval of 2-3 milliseconds was observed in TRULICITY-treated adult patients in contrast to a mean decrease of 0.9 milliseconds in placebo-treated patients. The adverse reaction of first-degree AV block occurred more frequently in patients treated with TRULICITY than placebo (0.9%, 1.7% and 2.3% for placebo, TRULICITY 0.75 mg and TRULICITY 1.5 mg, respectively). On electrocardiograms, a PR interval increase to at least 220 milliseconds was observed in 0.7%, 2.5% and 3.2% of patients treated with placebo, TRULICITY 0.75 mg and TRULICITY 1.5 mg, respectively.

Amylase and Lipase Increase

Adult patients exposed to TRULICITY had mean increases from baseline in lipase and/or pancreatic amylase of 14% to 20%, while placebo-treated patients had mean increases of up to 3%.

Adverse Reactions in the Clinical Trial of Pediatric Patients 10 Years of Age and Older with Type 2 Diabetes Mellitus

TRULICITY was administered to 150 pediatric patients 10 years of age and older with type 2 diabetes mellitus for a mean duration of 41.3 weeks [*see Clinical Studies (14.6)*]. The mean age was 14.5 years and 71% of patients were female. Overall, 55% were White, 15% were Black or African American, 12% were Asian, 10% were American Indian or Alaska Native, 5% were other races, and 3% had unknown race. Additionally, 55% were Hispanic or Latino, 42% were not Hispanic or Latino, and 3% had unknown ethnicity. At baseline, the mean duration of type 2 diabetes mellitus was 2 years, mean HbA1c was 8.1%, mean weight was 90.5 kg and mean BMI was 34.1 kg/m^2.

The safety profile in pediatric patients treated with TRULICITY 0.75 mg and 1.5 mg subcutaneously once-weekly was consistent with that described above for adult patients with type 2 diabetes mellitus with the exception of injection site reactions. In pediatric patients, the incidence of injection site reactions was 3.9% (2 patients) in the TRULICITY 0.75 mg group, 3.8% (2 patients) in the TRULICITY 1.5 mg group, and 2.0% (1 patient) in the placebo group.

6.2 Postmarketing Experience

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

- *Gastrointestinal:* ileus
- *Hepatobiliary:* cholecystitis, cholelithiasis requiring cholecystectomy, cholestasis, elevation of liver enzymes, hepatitis
- *Hypersensitivity:* anaphylactic reactions, angioedema
- *Renal:* acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis

7 DRUG INTERACTIONS

7.1 Oral Medications

TRULICITY delays gastric emptying and thus has the potential to reduce the rate of absorption of concomitantly administered oral medications. The delay in gastric emptying is dose-dependent but is attenuated with the recommended dose escalation to higher doses of TRULICITY *[see Dosage and Administration (2.1)]*. The delay is largest after the first

dose and diminishes with subsequent doses. In clinical pharmacology studies, TRULICITY 1.5 mg did not affect the absorption of the tested orally administered medications to a clinically relevant degree *[see Clinical Pharmacology (12.3)]*. There is limited experience with the use of concomitant medications in clinical trials with TRULICITY doses of 3 mg and 4.5 mg.

Monitor drug levels of oral medications with a narrow therapeutic index (e.g., warfarin) when concomitantly administered with TRULICITY.

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

When initiating TRULICITY, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data with TRULICITY in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. There are clinical considerations regarding the risks of poorly controlled diabetes in pregnancy *[see Clinical Considerations]*. Based on animal reproduction studies, there may be risks to the fetus from exposure to dulaglutide during pregnancy. TRULICITY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant rats administered dulaglutide during organogenesis, early embryonic deaths, fetal growth reductions, and fetal abnormalities occurred at systemic exposures at least 6-times human exposure at the maximum recommended human dose (MRHD) of 4.5 mg/week. In pregnant rabbits administered dulaglutide during organogenesis, major fetal abnormalities occurred at 5-times human exposure at the MRHD. Adverse embryo/fetal effects in animals occurred in association with decreased maternal weight and food consumption attributed to the pharmacology of dulaglutide *[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

Pregnant rats given subcutaneous doses of 0.49, 1.63, or 4.89 mg/kg dulaglutide every 3 days during organogenesis had systemic exposures 2-, 6-, and 18-times human exposure at the maximum recommended human dose (MRHD) of 4.5 mg/week, respectively, based on plasma area under the time-concentration curve (AUC) comparison. Reduced fetal weights associated with decreased maternal food intake and decreased weight gain attributed to the pharmacology of dulaglutide were observed at ≥1.63 mg/kg. Irregular skeletal ossifications and increases in post-implantation loss also were observed at 4.89 mg/kg.

In pregnant rabbits given subcutaneous doses of 0.04, 0.12, or 0.41 mg/kg dulaglutide every 3 days during organogenesis, systemic exposures in pregnant rabbits were 0.5-, 2-, and 5-times human exposure at the MRHD, based on plasma AUC comparison. Fetal visceral malformation of lung lobular agenesis and skeletal malformations of the vertebrae and/or ribs were observed in conjunction with decreased maternal food intake and decreased weight gain attributed to the pharmacology of dulaglutide at 0.41 mg/kg.

In a prenatal-postnatal study in F_0 maternal rats given subcutaneous doses of 0.2, 0.49, or 1.63 mg/kg every third day from implantation through lactation, systemic exposures in pregnant rats were 1-, 2-, and 7-times human exposure at the MRHD, based on plasma AUC comparison. F_1 pups from F_0 maternal rats given 1.63 mg/kg dulaglutide had statistically significantly lower mean body weight from birth through postnatal day 63 for males and postnatal day 84 for females. F_1 offspring from F_0 maternal rats receiving 1.63 mg/kg dulaglutide had decreased forelimb and hindlimb grip strength and males had delayed balano-preputial separation. Females had decreased startle response. These physical findings may relate to the decreased size of the offspring relative to controls as they appeared at early postnatal

assessments but were not observed at a later assessment. F_1 female offspring of the F_0 maternal rats given 1.63 mg/kg of dulaglutide had a longer mean escape time and a higher mean number of errors relative to concurrent control during 1 of 2 trials in the memory evaluation portion of the Biel water maze. These findings occurred in conjunction with decreased F_0 maternal food intake and decreased weight gain attributed to the pharmacologic activity at 1.63 mg/kg. The human relevance of these memory deficits in the F_1 female rats is not known.

8.2 Lactation

Risk Summary

There are no data on the presence of dulaglutide in human milk, the effects on the breastfed infant, or the effects on milk production. The presence of dulaglutide in milk of treated lactating animals was not determined. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRULICITY and any potential adverse effects on the breastfed infant from TRULICITY or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of TRULICITY as an adjunct to diet and exercise to improve glycemic control in pediatric patients 10 years of age and older with type 2 diabetes mellitus have been established. Use of TRULICITY for this indication is supported by a 26-week, multicenter, randomized, double-blind, parallel arm, placebo-controlled trial in 154 pediatric patients 10 years of age and older with type 2 diabetes mellitus *[see Clinical Studies (14.6)]*.

TRULICITY-treated pediatric patients reported a higher incidence of injection site-related reactions compared to TRULICITY-treated adults *[see Adverse Reactions (6.1)]*.

The safety and effectiveness of TRULICITY have not been established in pediatric patients less than 10 years of age.

8.5 Geriatric Use

In the adult glycemic control trials *[see Clinical Studies (14.2, 14.3)]*, 620 (19%) of TRULICITY-treated patients were 65 years of age or older and 65 (2%) of TRULICITY-treated patients were 75 years of age or older at baseline. In the TRULICITY 1.5 mg treatment arm of the REWIND trial (cardiovascular outcomes trial in adults with type 2 diabetes mellitus and cardiovascular disease or multiple cardiovascular risk factors) *[see Clinical Studies (14.5)]*, 2,619 (53%) patients were 65 years of age or older, and 484 (10%) patients were 75 years of age or older at baseline.

No overall differences in safety or effectiveness for TRULICITY have been observed between patients 65 years of age and older and younger adult patients.

8.6 Renal Impairment

TRULICITY has been studied in patients with varying degrees of renal function, including a dedicated clinical trial in patients with moderate to severe chronic kidney disease. No overall differences in safety or effectiveness were observed in these studies according to renal function *[see Clinical Studies (14.2, 14.3, 14.4)]*.

In a clinical pharmacology study in patients with renal impairment, including end-stage renal disease (ESRD), no clinically relevant change in dulaglutide pharmacokinetics (PK) was observed. In the 52-week trial in patients with type 2 diabetes and moderate to severe renal impairment, the PK behavior of TRULICITY 0.75 mg and 1.5 mg once weekly was similar to that demonstrated in previous clinical studies *[see Clinical Pharmacology (12.3)]*.

No dose adjustment is recommended in patients with renal impairment including end-stage renal disease (ESRD). Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. Use TRULICITY with caution in patients with ESRD *[see Warning and Precautions (5.5), Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

In a clinical pharmacology study in patients with varying degrees of hepatic impairment, no clinically relevant change in dulaglutide PK was observed *[see Clinical Pharmacology (12.3)]*. However, there is limited clinical experience in patients with mild, moderate, or severe hepatic impairment; therefore, use TRULICITY with caution in these patient populations.

8.8 Gastroparesis

Dulaglutide slows gastric emptying. TRULICITY has not been studied in patients with preexisting gastroparesis. Use TRULICITY with caution in patients with gastroparesis.

10 OVERDOSAGE

Overdoses have been reported in clinical studies. Effects associated with these overdoses were primarily mild or moderate gastrointestinal events (e.g., nausea, vomiting) and non-severe hypoglycemia. In the event of overdose, appropriate supportive care (including frequent plasma glucose monitoring) should be initiated according to the patient's clinical signs and symptoms.

11 DESCRIPTION

Dulaglutide is a human glucagon-like peptide-1 (GLP-1) receptor agonist. The molecule is a fusion protein that consists of 2 identical, disulfide-linked chains, each containing an N-terminal GLP-1 analog sequence covalently linked to the Fc portion of a modified human immunoglobulin G4 (IgG4) heavy chain by a small peptide linker and is produced using mammalian cell (Chinese hamster ovary) culture. The GLP-1 analog portion of dulaglutide is 90% homologous to native human GLP-1 (7-37). Structural modifications were introduced in the GLP-1 part of the molecule responsible for interaction with the enzyme dipeptidyl-peptidase-IV (DPP-4). Additional modifications were made in an area with a potential T-cell epitope and in the areas of the IgG4 Fc part of the molecule responsible for binding the high-affinity Fc receptors and half-antibody formation. The overall molecular weight of dulaglutide is approximately 63 kilodaltons.

TRULICITY (dulaglutide) injection is a clear, colorless, sterile, preservative-free solution for subcutaneous use. Each single-dose pen contains a 0.5 mL solution of 0.75 mg, 1.5 mg, 3 mg, or 4.5 mg of dulaglutide and the following excipients: citric acid anhydrous (0.07 mg), mannitol (23.2 mg), polysorbate 80 (0.10 mg for 0.75 mg and 1.5 mg; 0.125 mg for 3 mg and 4.5 mg), and trisodium citrate dihydrate (1.37 mg), in water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TRULICITY contains dulaglutide, which is a human GLP-1 receptor agonist with 90% amino acid sequence homology to endogenous human GLP-1 (7-37). Dulaglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase in pancreatic beta cells. Dulaglutide increases intracellular cyclic AMP (cAMP) in beta cells leading to glucose-dependent insulin release. Dulaglutide also decreases glucagon secretion and slows gastric emptying.

12.2 Pharmacodynamics

TRULICITY lowers fasting glucose and reduces postprandial glucose (PPG) concentrations in patients with type 2 diabetes mellitus. The reduction in fasting and postprandial glucose can be observed after a single dose.

Fasting and Postprandial Glucose

In a clinical pharmacology study in patients with type 2 diabetes mellitus, treatment with once weekly TRULICITY resulted in a reduction of fasting and 2-hour PPG concentrations, and postprandial serum glucose incremental AUC, when compared to placebo (-25.6 mg/dL, -59.5 mg/dL, and -197 mg*h/dL, respectively); these effects were sustained after 6 weeks of dosing with the 1.5 mg dose.

First- and Second-Phase Insulin Secretion

Both first- and second-phase insulin secretion were increased in patients with type 2 diabetes treated with TRULICITY compared with placebo.

Insulin and Glucagon Secretion

TRULICITY stimulates glucose-dependent insulin secretion and reduces glucagon secretion. Treatment with TRULICITY 0.75 mg and 1.5 mg once weekly increased fasting insulin from baseline at Week 26 by 35.38 and 17.50 pmol/L, respectively, and C-peptide concentration by 0.09 and 0.07 nmol/L, respectively, in a monotherapy trial. In the same trial, fasting glucagon concentration was reduced by 1.71 and 2.05 pmol/L from baseline with TRULICITY 0.75 mg and 1.5 mg, respectively.

Gastric Motility

Dulaglutide causes a delay of gastric emptying. The delay in gastric emptying is dose-dependent but is attenuated with adequate dose escalation to higher doses of TRULICITY. The delay is largest after the first dose and diminishes with subsequent doses.

Cardiac Electrophysiology (QTc)

The effect of dulaglutide on cardiac repolarization was tested in a thorough QTc study. Dulaglutide did not produce QTc prolongation at doses of 4 and 7 mg. The maximum recommended dose is 4.5 mg once weekly.

12.3 Pharmacokinetics

The pharmacokinetics of dulaglutide is similar between healthy subjects and patients with type 2 diabetes mellitus. Following subcutaneous administration, the time to maximum plasma concentration of dulaglutide at steady state ranges from 24 to 72 hours, with a median of 48 hours. After reaching steady state, the accumulation ratio was approximately 1.56. Steady-state plasma dulaglutide concentrations were achieved between 2 and 4 weeks following once weekly administration. Site of subcutaneous administration (abdomen, upper arm, and thigh) had no statistically significant effect on the exposure to dulaglutide.

Absorption – The mean absolute bioavailability of dulaglutide following subcutaneous administration of single 0.75 mg and 1.5 mg doses was 65% and 47%, respectively. Absolute subcutaneous bioavailability for 3 mg and 4.5 mg doses were estimated to be similar to 1.5 mg although this has not been specifically studied. Dulaglutide concentrations increased approximately proportional to dose from 0.75 mg to 4.5 mg.

Distribution – Apparent population mean central volume of distribution was 3.09 L and the apparent population mean peripheral volume of distribution was 5.98 L.

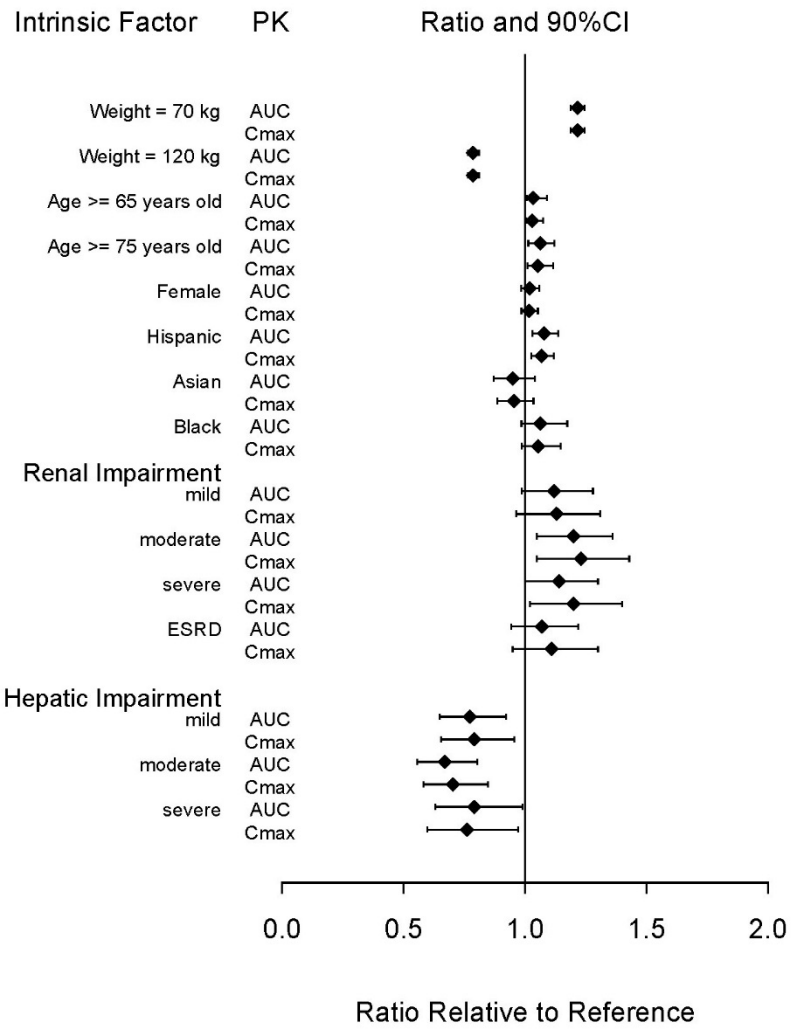
Elimination

The apparent population mean clearance of dulaglutide was 0.142 L/h. The elimination half-life of dulaglutide was approximately 5 days.

Metabolism – Dulaglutide is presumed to be degraded into its component amino acids by general protein catabolism pathways.

Specific Populations

The intrinsic factors of age (≥ 65 years), sex, race, ethnicity, body weight, or renal or hepatic impairment did not have a clinically relevant effect on the PK of dulaglutide as shown in Figure 1.



Abbreviations: AUC = area under the time-concentration curve; CI = confidence interval; C_{max} = maximum concentration; ESRD = end-stage renal disease; PK = pharmacokinetics.

Note: Reference values for weight, age, gender, and race comparisons are 93 kg, 56 years old, male, and white, respectively; reference groups for renal and hepatic impairment data are subjects with normal renal and hepatic function from the respective clinical pharmacology studies. The weight values shown in the plot (70 and 120 kg) are the 10^{th} and 90^{th} percentiles of weight in the PK population.

Figure 1: Impact of intrinsic factors on dulaglutide pharmacokinetics.

Pediatric Patients

A population pharmacokinetic analysis was conducted for dulaglutide 0.75 mg and 1.5 mg using data from 128 pediatric patients 10 years of age and older with type 2 diabetes mellitus. The AUC in pediatric patients was approximately 37% lower than that in adult patients. However, this difference was not determined to be clinically meaningful.

Patients with Renal Impairment

Dulaglutide systemic exposure was increased by 20, 28, 14 and 12% for mild, moderate, severe, and ESRD renal impairment sub-groups, respectively, compared to subjects with normal renal function. The corresponding values for increase in C_{max} were 13, 23, 20 and 11%, respectively (Figure 1). Additionally, in a 52 week clinical trial in patients with type 2 diabetes mellitus and moderate to severe renal impairment, the PK behavior of TRULICITY 0.75 mg and 1.5 mg once weekly was similar to that demonstrated in previous clinical studies *[see Warning and Precautions (5.5), Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

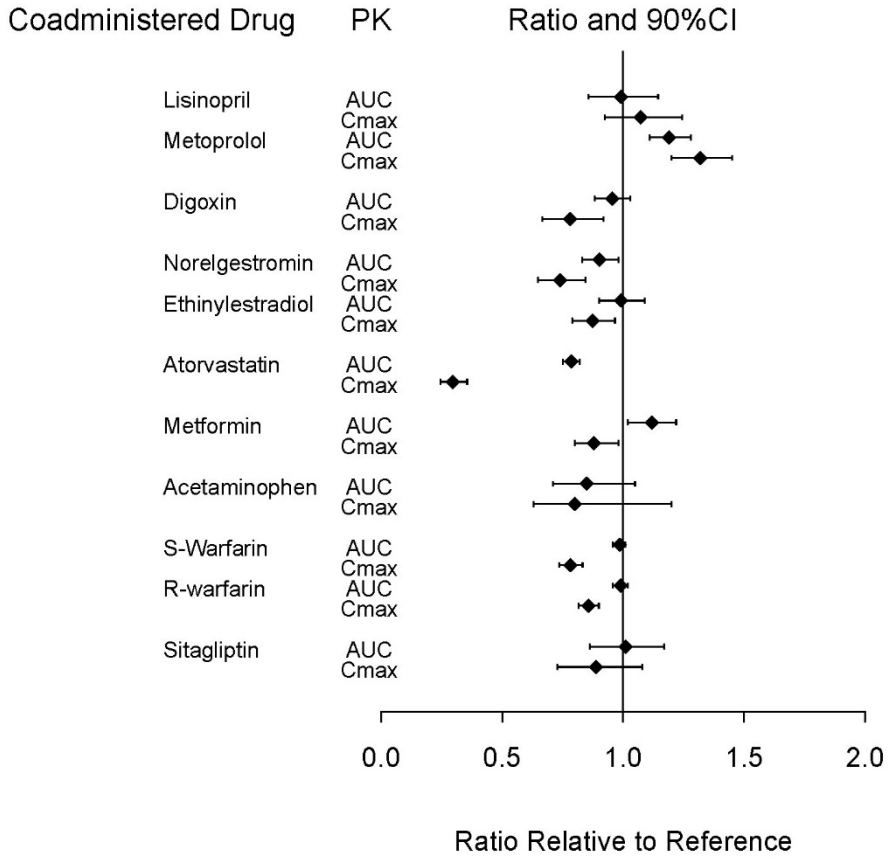
Dulaglutide systemic exposure decreased by 23, 33 and 21% for mild, moderate and severe hepatic impairment groups, respectively, compared to subjects with normal hepatic function, and C_{max} was decreased by a similar magnitude (Figure 1) *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies

The potential effect of co-administered medications on the PK of dulaglutide 1.5 mg and vice versa was studied in several single- and multiple-dose studies in healthy subjects, patients with type 2 diabetes mellitus, and patients with hypertension.

Potential for Dulaglutide to Influence the Pharmacokinetics of Other Drugs

Dulaglutide slows gastric emptying and, as a result, may reduce the extent and rate of absorption of orally co-administered medications. In clinical pharmacology studies, dulaglutide at a dose of 1.5 mg did not affect the absorption of the tested orally administered medications to any clinically relevant degree. The delay in gastric emptying is dose-dependent but is attenuated with the recommended dose escalation to higher doses of TRULICITY *[see Dosage and Administration (2.1), Drug Interactions (7.1)]*. The delay is largest after the first dose and diminishes with subsequent doses. PK measures indicating the magnitude of these interactions are presented in Figure 2.



Abbreviations: AUC = area under the time-concentration curve; CI = confidence interval; C_{max} = maximum concentration; PK = pharmacokinetics.
Note: Reference group is co-administered medication given alone.

Figure 2: Impact of dulaglutide 1.5 mg on the pharmacokinetics of co-administered medications.

Potential for Co-administered Drugs to Influence the Pharmacokinetics of Dulaglutide

In a clinical pharmacology study, the co-administration of a single dose of 1.5 mg dulaglutide with steady-state dose of 100 mg sitagliptin caused an increase in dulaglutide AUC and C_{max} of approximately 38% and 27%, which is not considered clinically relevant.

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 studies described below with the incidence of anti-drug antibodies in other studies.

In glycemic control trials in adults with type 2 diabetes mellitus (monotherapy and combination therapy) *[see Clinical Studies (14.2, 14.3)]*, during a treatment period ranging from 24 to 104 weeks, 64/3,907 (1.6%) of TRULICITY-treated

patients developed anti-dulaglutide antibodies (referred to as anti-drug-antibodies (ADA)). Of the 64 TRULICITY-treated patients that developed ADA, 34 patients (0.9% of the overall population) developed dulaglutide-neutralizing antibodies, and 36 patients (0.9% of the overall population) developed antibodies against native GLP-1. There was no identified clinically significant effect of ADA on pharmacokinetics, pharmacodynamics, safety, or effectiveness of TRULICITY over the 24 to 104 week treatment duration in the trials in adults with type 2 diabetes mellitus.

During the 26-week controlled period of the glycemic control trial in pediatric patients 10 years of age or older with type 2 diabetes mellitus *[see Clinical Studies (14.6)]*, 4/101 (4%) of TRULICITY-treated pediatric patients developed ADA. Of the 4 pediatric patients that developed ADA, 1 patient (1% of the overall population) developed dulaglutide-neutralizing antibodies and 3 patients (3% of the overall population) developed antibodies against native GLP-1. During the 52-week postbaseline period of the same trial (through safety follow-up), 6/103 (6%) of TRULICITY-treated patients developed ADA. Of the 6 patients that developed ADA, 1 patient (1% of the overall population) developed dulaglutide-neutralizing antibodies and 4 patients (4% of the overall population) developed antibodies against native GLP-1. Because of the low occurrence of ADA, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of TRULICITY is unknown in pediatric patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

A 2-year carcinogenicity study was conducted with dulaglutide in male and female rats at doses of 0.05, 0.5, 1.5, and 5 mg/kg (0.2-, 3-, 8-, and 24-fold the MRHD of 4.5 mg once weekly based on AUC) administered by subcutaneous injection twice weekly. In rats, dulaglutide caused a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and/or carcinomas) compared to controls, at ≥3-fold the MRHD based on AUC. A statistically significant increase in C-cell adenomas was observed in rats receiving dulaglutide at ≥0.5 mg/kg. Numerical increases in thyroid C-cell carcinomas occurred at 5 mg/kg (24 times the MRHD based on AUC) and were considered to be treatment-related despite the absence of statistical significance.

A 6-month carcinogenicity study was conducted with dulaglutide in rasH2 transgenic mice at doses of 0.3, 1, and 3 mg/kg administered by subcutaneous injection twice weekly. Dulaglutide did not produce increased incidences of thyroid C-cell hyperplasia or neoplasia at any dose.

Dulaglutide is a recombinant protein; no genotoxicity studies have been conducted.

Human relevance of thyroid C-cell tumors in rats is unknown and could not be determined by clinical studies or nonclinical studies *[see Boxed Warning and Warnings and Precautions (5.1)]*.

In fertility and early embryonic development studies in male and female rats, no adverse effects of dulaglutide on sperm morphology, mating, fertility, conception, and embryonic survival were observed at up to 16.3 mg/kg (55-fold the MRHD based on AUC). In female rats, an increase in the number of females with prolonged diestrus and a dose-related decrease in the mean number of corpora lutea, implantation sites, and viable embryos were observed at ≥4.9 mg/kg (≥13-fold the MRHD based on AUC), which occurred in the presence of decreased maternal food consumption and body weight gain.

13.2 Animal Toxicology and/or Pharmacology

Zucker diabetic fatty (ZDF) rats were given 0.5, 1.5, or 5 mg/kg/twice weekly of dulaglutide (1-, 3-, and 13-fold the MRHD based on AUC) for 3 months. Increases of 12% to 33% in total and pancreatic amylase, but not lipase, were observed at all doses without microscopic pancreatic inflammatory correlates in individual animals. Other changes in the dulaglutide-treated animals included increased interlobular ductal epithelium without active ductal cell proliferation (≥0.5 mg/kg), increased acinar atrophy with/without inflammation (≥1.5 mg/kg), and increased neutrophilic inflammation of the acinar pancreas (5 mg/kg).

Treatment of monkeys for 12 months with 8.15 mg/kg/twice weekly of dulaglutide (nearly 200-fold the MRHD based on AUC) demonstrated no evidence of pancreatic inflammation or pancreatic intraepithelial neoplasia. In 4 of 19 monkeys on dulaglutide treatment, there was an increase in goblet cells within the pancreatic ducts, but no differences from the control group in total amylase or lipase at study termination. There were no proliferative changes in the thyroid C-cells.

14 CLINICAL STUDIES

14.1 Overview of Clinical Trials

TRULICITY has been studied in adults as monotherapy and in combination with metformin, sulfonylurea, metformin and sulfonylurea, metformin and thiazolidinedione, sodium-glucose co-transporter-2 inhibitors (SGLT2i) with or without metformin, basal insulin with or without metformin, and prandial insulin with or without metformin. TRULICITY has also been studied in patients with type 2 diabetes mellitus and moderate to severe renal impairment.

Dose escalation was performed in one trial in adults with TRULICITY doses up to 4.5 mg added to metformin. All other clinical studies in adults evaluated TRULICITY 0.75 mg and 1.5 mg without dose escalation; patients were initiated and maintained on either 0.75 mg or 1.5 mg for the duration of the trials *[see Clinical Studies (14.2, 14.3, 14.4)]*.

TRULICITY 0.75 mg and 1.5 mg was studied in pediatric patients 10 years of age and older with type 2 diabetes in combination with or without metformin and/or basal insulin treatment *[see Clinical Studies (14.6)]*.

In patients with type 2 diabetes mellitus, TRULICITY produced reductions from baseline in HbA1c compared to placebo. No overall differences in glycemic effectiveness were observed across demographic subgroups (age, gender, race/ethnicity, duration of diabetes).

A cardiovascular outcomes trial was conducted in adult patients with type 2 diabetes mellitus and established cardiovascular (CV) disease or multiple cardiovascular risk factors. Patients were randomized to TRULICITY 1.5 mg or placebo both added to standard of care. TRULICITY significantly reduced the risk of first occurrence of primary composite endpoint of CV death, non-fatal MI, or non-fatal stroke *[see Clinical Studies (14.5)]*.

14.2 Glycemic Control Monotherapy Trials in Adults with Type 2 Diabetes Mellitus

In a double-blind trial with primary endpoint at 26 weeks, 807 adult patients inadequately treated with diet and exercise, or with diet and exercise and one antidiabetic agent used at submaximal dose, were randomized to TRULICITY 0.75 mg once weekly, TRULICITY 1.5 mg once weekly, or metformin 1500 to 2000 mg/day following a two-week washout. Seventy-five percent (75%) of the randomized population were treated with one antidiabetic agent at the screening visit. Most patients previously treated with an antidiabetic agent were receiving metformin (~90%) at a median dose of 1000 mg daily and approximately 10% were receiving a sulfonylurea.

Patients had a mean age of 56 years and a mean duration of type 2 diabetes of 3 years. Forty-four percent were male. The White, Black and Asian race accounted for 74%, 7% and 8% of the population, respectively. Twenty-nine percent of the trial population were from the US.

Treatment with TRULICITY 0.75 mg and 1.5 mg once weekly resulted in reduction in HbA1c from baseline at 26-weeks (Table 4). The difference in observed effect size between TRULICITY 0.75 mg and 1.5 mg, respectively, and metformin excluded the pre-specified non-inferiority margin of 0.4%.

Table 4: Results at Week 26 in a Trial of TRULICITY as Monotherapy in Adult Patients with Type 2 Diabetes Mellitus[a]

	26-Week Primary Time Point		
	TRULICITY 0.75 mg	**TRULICITY 1.5 mg**	**Metformin 1500-2000 mg**
Intent-to-Treat (ITT) Population (N)‡	270	269	268
HbA1c (%) (Mean)			
Baseline	7.6	7.6	7.6
Change from baseline[b]	-0.7	-0.8	-0.6
Fasting Serum Glucose (mg/dL) (Mean)			
Baseline	161	164	161
Change from baseline[b]	-26	-29	-24
Body Weight (kg) (Mean)			
Baseline	91.8	92.7	92.4
Change from baseline[b]	-1.4	-2.3	-2.2

Abbreviation: HbA1c = hemoglobin A1c.

[a] Intent-to-treat population. Last observation carried forward (LOCF) was used to impute missing data. Data post-onset of rescue therapy are treated as missing. At Week 26, primary efficacy was missing for 10%, 12% and 14% of individuals randomized to TRULICITY 0.75 mg, TRULICITY 1.5 mg and metformin, respectively.

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

‡ Patients included in the analysis are a subset of the ITT population that had at least one post-baseline assessment. The primary analysis included 265 individuals in each of the treatment arms.

14.3 Glycemic Control Combination Therapy Trials in Adults with Type 2 Diabetes Mellitus

Sitagliptin-Controlled Trial (Add-on to Metformin)

In this placebo-controlled, double-blind trial with primary endpoint at 52 weeks, 972 adult patients were randomized to placebo, TRULICITY 0.75 mg once weekly, TRULICITY 1.5 mg once weekly, or sitagliptin 100 mg/day (after 26 weeks, patients in the placebo treatment group received blinded sitagliptin 100 mg/day for the remainder of the trial), all as add-on to metformin. Randomization occurred after an 11-week lead-in period to allow for a metformin titration period, followed by a 6-week glycemic stabilization period. Patients had a mean age of 54 years; mean duration of type 2 diabetes of 7 years; 48% were male; race: White, Black and Asian were 53%, 4% and 27%, respectively; and 24% of the trial population were in the US.

At the 26-week placebo-controlled time point, the HbA1c change was 0.1%, -1.0%, -1.2%, and -0.6% for placebo, TRULICITY 0.75 mg, TRULICITY 1.5 mg, and sitagliptin, respectively. The percentage of patients who achieved HbA1c <7.0% was 22%, 56%, 62% and 39% for placebo, TRULICITY 0.75 mg, TRULICITY 1.5 mg, and sitagliptin, respectively. At 26 weeks, there was a mean weight reduction of 1.4 kg, 2.7 kg, 3.0 kg, and 1.4 kg for placebo, TRULICITY 0.75 mg, TRULICITY 1.5 mg, and sitagliptin, respectively. There was a mean reduction of fasting glucose of 9 mg/dL, 35 mg/dL, 41 mg/dL, and 18 mg/dL for placebo, TRULICITY 0.75 mg, TRULICITY 1.5 mg, and sitagliptin, respectively.

Treatment with TRULICITY 0.75 mg and 1.5 mg once weekly resulted in a statistically significant reduction in HbA1c compared to placebo (at 26 weeks) and compared to sitagliptin (at 26 and 52 weeks), all in combination with metformin (Table 5 and Figure 3).

Table 5: Results at Week 52 of TRULICITY Compared to Sitagliptin used as Add-On to Metformin in Adult Patients with Type 2 Diabetes Mellitus[a]

	52-Week Primary Time Point		
	TRULICITY 0.75 mg	**TRULICITY 1.5 mg**	**Sitagliptin 100 mg**
Intent-to-Treat (ITT) Population (N)[‡]	281	279	273
HbA1c (%) (Mean)			
Baseline	8.2	8.1	8.0
Change from baseline[b]	-0.9	-1.1	-0.4
Difference from sitagliptin[b] (95% CI)	-0.5 (-0.7, -0.3)[††]	-0.7 (-0.9, -0.5)[††]	-
Percentage of patients HbA1c <7.0%	49[##]	59[##]	33
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	174	173	171
Change from baseline[b]	-30	-41	-14
Difference from sitagliptin[b] (95% CI)	-15 (-22, -9)	-27 (-33, -20)	-
Body Weight (kg) (Mean)			
Baseline	85.5	86.5	85.8
Change from baseline[b]	-2.7	-3.1	-1.5
Difference from sitagliptin[b] (95% CI)	-1.2 (-1.8, -0.6)	-1.5 (-2.1, -0.9)	-

Abbreviations: HbA1c = hemoglobin A1c.

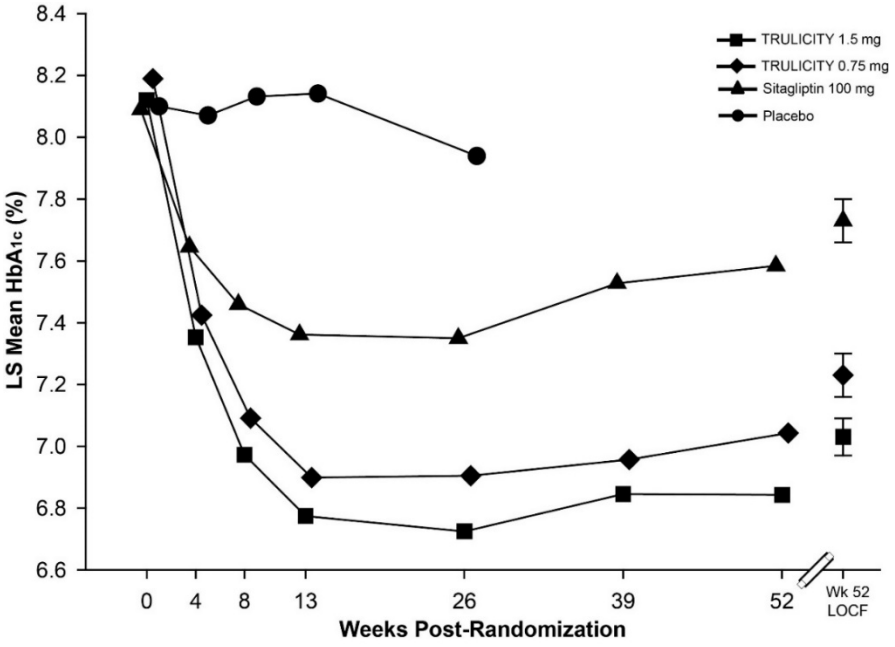
[a] All ITT patients randomized after the dose-finding portion of the trial. Last observation carried forward (LOCF) was used to impute missing data. At Week 52 primary efficacy was missing for 15%, 19%, and 20% of individuals randomized to TRULICITY 0.75 mg, TRULICITY 1.5 mg and sitagliptin, respectively.

[b] Least-squares (LS) mean adjusted for baseline value and other stratification factors.

[‡] Patients included in the analysis are a subset of the ITT population that had at least one post-baseline assessment. The primary analysis included 276, 277, and 270 individuals randomized to TRULICITY 0.75 mg, TRULICITY 1.5 mg and sitagliptin, respectively.

[††] Multiplicity adjusted 1-sided p-value <0.001, for superiority of TRULICITY compared to sitagliptin, assessed only for HbA1c.

[##] p<0.001 TRULICITY compared to sitagliptin, assessed only for HbA1c <7.0%.



Number of patients with observed data			
Placebo	139	108	
TRULICITY 0.75 mg	281	258	238
TRULICITY 1.5 mg	279	249	225
Sitagliptin	273	241	219

Mean HbA1c adjusted for baseline HbA1c and country.

Figure 3: Adjusted Mean HbA1c at each Time Point (ITT, MMRM) and at Week 52 (ITT, LOCF) in Adult Patients with Type 2 Diabetes Mellitus

Dosage Ranging Trial of TRULICITY 1.5, 3 mg, and 4.5 mg (Add-on to Metformin)

In this parallel-arm, double-blind trial with primary endpoint at 36 weeks, a total of 1842 adult patients were randomized 1:1:1 to TRULICITY 1.5 mg, TRULICITY 3 mg, or TRULICITY 4.5 mg once weekly, all as add-on to metformin (NCT03495102).

Following randomization, all patients received TRULICITY 0.75 mg once weekly. The dose was increased every 4 weeks to the next higher dose until the patients reached their assigned dose (1.5 mg, 3 mg, or 4.5 mg). Patients were to remain on the assigned study dose for the duration of the trial.

Patients had a mean age of 57.1 years; a mean duration of type 2 diabetes of 7.6 years; 51.2% were male; race: White, Black, and Asian were 85.8%, 4.5%, and 2.4%, respectively; and 27.6% of the trial population was in the US.

At 36 weeks, treatment with TRULICITY 4.5 mg resulted in a statistically significant reduction in HbA1c and in body weight compared to TRULICITY 1.5 mg (Table 6 and Figure 4).

Table 6. Results at Week 36 of TRULICITY 1.5 mg Compared to 3 mg and 4.5 mg as Add-On to Metformin in Adult Patients with Type 2 Diabetes Mellitus[a]

	36-Week Primary Time Point		
	TRULICITY 1.5 mg	**TRULICITY 3 mg**	**TRULICITY 4.5 mg**
Intent-to-Treat (ITT) Population (N)	612	616	614
HbA1c (%) (Mean)			
Baseline	8.6	8.6	8.6
Change from baseline[b]	-1.5	-1.6	-1.8
Difference from 1.5 mg[b] (95% CI)		-0.1 (-0.2, 0.0)	-0.2 (-0.4, -0.1) ^
Percentage of patients HbA1c <7.0%[c]	50	56	62
Fasting Serum Glucose (mg/dL) (Mean)			
Baseline	185	184	183
Change from baseline[b]	-45	-46	-51
Difference from 1.5 mg[b] (95% CI)		- 2 (-7, 3)	-6 (-11, -2)
Body Weight (kg) (Mean)			
Baseline	95.5	96.3	95.4
Change from baseline[b]	-3.0	-3.8	-4.6
Difference from 1.5 mg[b] (95% CI)		-0.9 (-1.4, -0.4)	-1.6 (-2.2, -1.1) ^^

Abbreviations: HbA1c = hemoglobin A1c

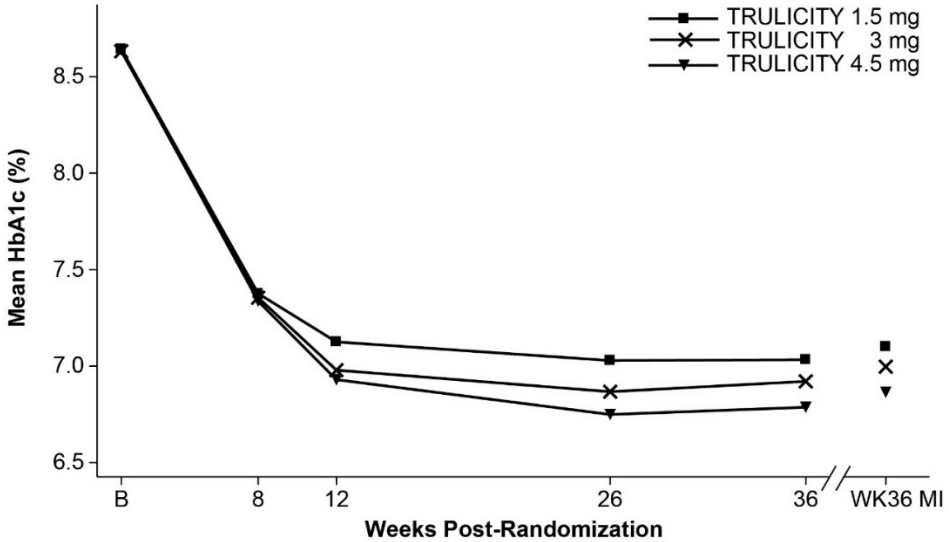
[a] Intent-to-treat population. At Week 36, primary efficacy was missing for 7%, 7%, and 6% of individuals treated with TRULICITY 1.5 mg, TRULICITY 3 mg, and TRULICITY 4.5 mg, respectively.

[b] Least-squares mean adjusted for baseline value and other stratification factors. Missing data were imputed using multiple imputation.

[c] Patients with missing HbA1c data at Week 36 were considered as not achieving HbA1c target.

^ p=0.0001 for superiority compared to TRULICITY 1.5 mg, overall type I error controlled.

^^ p<0.0001 for superiority compared to TRULICITY 1.5 mg, overall type I error controlled.



Number of patients with observed data

TRULICITY 1.5 mg	612	567
TRULICITY 3 mg	616	572
TRULICITY 4.5 mg	614	575

Observed mean HbA1c at scheduled visits and retrieved dropout multiple imputation (MI) based estimate at week 36.

Figure 4: Mean HbA1c at each Time Point (ITT) and at Week 36 (ITT, MI)

Placebo-Controlled Trial (Add-on to Sulfonylurea)

In this 24-week placebo-controlled, double-blind trial, 299 adult patients were randomized to and received placebo or once weekly TRULICITY 1.5 mg, both as add-on to glimepiride. Patients had a mean age of 58 years; mean duration of type 2 diabetes of 8 years; 44% were male; race: White, Black, and Asian were 83%, 4%, and 2%, respectively; and 24% of the trial population were in the US.

At 24 weeks, treatment with once weekly TRULICITY 1.5 mg resulted in a statistically significant reduction in HbA1c compared to placebo (Table 7).

Table 7: Results at Week 24 of TRULICITY Compared to Placebo as Add-On to Glimepiride in Adult Patients with Type 2 Diabetes Mellitus[a]

	24-Week Primary Time Point	
	Placebo	**TRULICITY 1.5 mg**
Intent-to-Treat (ITT) Population (N)	60	239
HbA1c (%) (Mean)		
Baseline	8.4	8.4
Change from baseline[b]	-0.3	-1.3
Difference from placebo[b] (95% CI)		-1.1 (-1.4, -0.7)††
Percentage of patients HbA1c <7.0%[c]	17	50††
Fasting Serum Glucose (mg/dL) (Mean)		
Baseline	175	178
Change from baseline[b]	2	-28
Difference from placebo[b] (95% CI)		-30 (-44, -15)††
Body Weight (kg) (Mean)		
Baseline	89.5	84.5
Change from baseline[b]	-0.2	-0.5
Difference from placebo[b] (95% CI)		-0.4 (-1.2, 0.5)

Abbreviations: HbA1c = hemoglobin A1c.

[a] Intent-to-treat population. Data post-onset of rescue therapy are treated as missing. At Week 24 primary efficacy was missing for 10% and 12% of individuals randomized to TRULICITY 1.5 mg and placebo, respectively.

[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors. Placebo multiple imputation, with respect to the baseline values, was used to model a wash-out of the treatment effect for patients having missing Week 24 data.

[c] Patients with missing HbA1c data at Week 24 were considered as non-responders.

†† p<0.001 for superiority of TRULICITY 1.5 mg compared to placebo, overall type I error controlled.

Placebo- and Exenatide-Controlled Trial (Add-on to Metformin and Thiazolidinedione)

In this placebo-controlled trial with primary endpoint at 26 weeks, 976 adult patients were randomized to and received placebo, TRULICITY 0.75 mg once weekly, TRULICITY 1.5 mg once weekly, or exenatide 10 mcg BID, all as add-on to maximally tolerated doses of metformin (≥1500 mg per day) and pioglitazone (up to 45 mg per day). Exenatide treatment group assignment was open-label while the treatment assignments to placebo, TRULICITY 0.75 mg, and TRULICITY 1.5 mg were blinded. After 26 weeks, patients in the placebo treatment group were randomized to either TRULICITY 0.75 mg once weekly or TRULICITY 1.5 mg once weekly to maintain blinding. Randomization occurred after a 12-week lead-in period; during the initial 4 weeks of the lead-in period, patients were titrated to maximally tolerated doses of metformin and pioglitazone; this was followed by an 8-week glycemic stabilization period prior to randomization. Patients randomized to exenatide started at a dose of 5 mcg BID for 4 weeks and then were escalated to 10 mcg BID. Patients had a mean age of 56 years; mean duration of type 2 diabetes of 9 years; 58% were male; race: White, Black and Asian were 74%, 8% and 3%, respectively; and 81% of the trial population were in the US.

Treatment with TRULICITY 0.75 mg and 1.5 mg once weekly resulted in a statistically significant reduction in HbA1c compared to placebo (at 26 weeks) and compared to exenatide at 26 weeks (Table 8 and Figure 5). Over the 52-week trial period, the percentage of patients who required glycemic rescue was 8.9% in the TRULICITY 0.75 mg once weekly +

metformin and pioglitazone treatment group, 3.2% in the TRULICITY 1.5 mg once weekly + metformin and pioglitazone treatment group, and 8.7% in the exenatide BID + metformin and pioglitazone treatment group.

Table 8: Results at Week 26 of TRULICITY Compared to Placebo and Exenatide, All as Add-On to Metformin and Thiazolidinedione in Adult Patients with Type 2 Diabetes Mellitus[a]

	26-Week Primary Time Point			
	Placebo	**TRULICITY 0.75 mg**	**TRULICITY 1.5 mg**	**Exenatide 10 mcg BID**
Intent-to-Treat (ITT) Population (N)‡	141	280	279	276
HbA1c (%) (Mean)				
Baseline	8.1	8.1	8.1	8.1
Change from baseline[b]	-0.5	-1.3	-1.5	-1.0
Difference from placebo[b] (95% CI)	-	-0.8 (-1.0, -0.7)‡‡	-1.1 (-1.2, -0.9)‡‡	-
Difference from exenatide[b] (95% CI)	-	-0.3 (-0.4, -0.2)††	-0.5 (-0.7, -0.4)††	-
Percentage of patients HbA1c <7.0%	43	66**, ##	78**, ##	52
Fasting Serum Glucose (mg/dL) (Mean)				
Baseline	166	159	162	164
Change from baseline[b]	-5	-34	-42	-24
Difference from placebo[b] (95% CI)	-	-30 (-36, -23)	-38 (-45, -31)	-
Difference from exenatide[b] (95% CI)	-	-10 (-15, -5)	-18 (-24, -13)	-
Body Weight (kg) (Mean)				
Baseline	94.1	95.5	96.2	97.4
Change from baseline[b]	1.2	0.2	-1.3	-1.1
Difference from placebo[b] (95% CI)	-	-1.0 (-1.8, -0.3)	-2.5 (-3.3, -1.8)	-
Difference from exenatide[b] (95% CI)	-	1.3 (0.6, 1.9)	-0.2 (-0.9, 0.4)	-

Abbreviations: BID = twice daily; HbA1c = hemoglobin A1c.

[a] Intent-to-treat population. Last observation carried forward (LOCF) was used to impute missing data. Data post-onset of rescue therapy are treated as missing. At Week 26, primary efficacy was missing for 23%, 10%, 7% and 12% of individuals randomized to placebo, TRULICITY 0.75 mg, TRULICITY 1.5 mg, and exenatide, respectively.

[b] Least-squares (LS) mean adjusted for baseline value and other stratification factors.

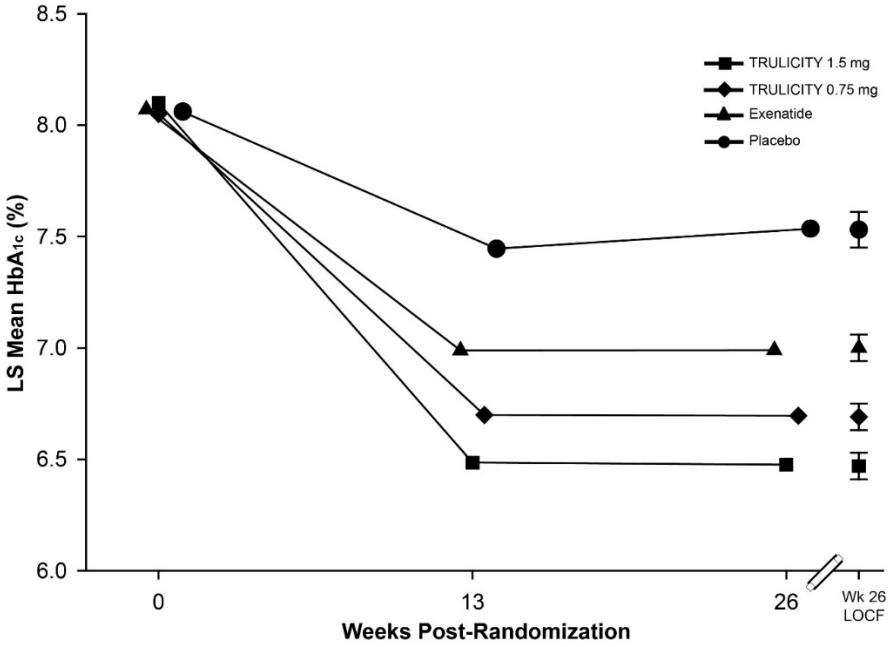
‡ Patients included in the analysis are a subset of the ITT population that had at least one post-baseline assessment. The primary analysis included 119, 269, 271 and 266 individuals randomized to placebo, TRULICITY 0.75 mg, TRULICITY 1.5 mg, and exenatide, respectively.

‡‡ Multiplicity adjusted 1-sided p-value <0.001, for superiority of TRULICITY compared to placebo, assessed only for HbA1c.

†† Multiplicity adjusted 1-sided p-value <0.001, for superiority of TRULICITY compared to exenatide, assessed only for HbA1c.

** p<0.001 TRULICITY compared to placebo, assessed only for HbA1c <7.0%.

p<0.001 TRULICITY compared to exenatide, assessed only for HbA1c <7.0%.



Number of patients with observed data		
Placebo	141	108
TRULICITY 0.75 mg	280	251
TRULICITY 1.5 mg	279	259
Exenatide	276	242

Mean HbA1c adjusted for baseline HbA1c and country.

Figure 5: Adjusted Mean HbA1c at Each Time Point (ITT, MMRM) and at Week 26 (ITT, LOCF)

Placebo-Controlled Trial (Add-on to SGLT2i, with or without Metformin)

In this 24-week placebo-controlled, double-blind trial, 423 adult patients were randomized to and received TRULICITY 0.75 mg, TRULICITY 1.5 mg, or placebo, as add-on to sodium-glucose co-transporter 2 inhibitor (SGLT2i) therapy (96% with and 4% without metformin). Trulicity was administered once weekly, and SGLT2i was administered according to the local country label. Patients had a mean age of 57 years; mean duration of type 2 diabetes of 9.4 years; 50% were male; race: White, Black, and Asian were 89%, 3%, and 0.2%, respectively; and 21% of the trial population was in the US.

At 24 weeks, treatment with once weekly TRULICITY 0.75 mg and 1.5 mg resulted in a statistically significant reduction from baseline in HbA1c compared to placebo (Table 9).

The mean baseline body weight was 90.5, 91.1, and 92.9 kg in the placebo, TRULICITY 0.75 mg, and TRULICITY 1.5 mg groups, respectively. The mean changes from baseline in body weight at Week 24 were -2.0, -2.5, and -2.9 kg for placebo, TRULICITY 0.75 mg, and TRULICITY 1.5 mg, respectively. The difference from placebo (95% CI) was -0.9 kg (-1.7, -0.1) for TRULICITY 1.5 mg.

Table 9: Results at Week 24 of TRULICITY as Add-on to SGLT2i in Adult Patients with Type 2 Diabetes Mellitus[a]

	24-Week Primary Time Point		
	Placebo	**TRULICITY 0.75 mg**	**TRULICITY 1.5 mg**
Intent-to-Treat (ITT) Population (N)	140	141	142
HbA1c (%) (Mean)			
Baseline	8.1	8.1	8.0
Change from baseline[b]	-0.6	-1.2	-1.3
Difference from placebo[b] (95% CI)	-	-0.7 (-0.8, -0.5)††	-0.8 (-0.9, -0.6)††
Percentage of patients HbA1c <7.0%[c]	31	59††	67††
Fasting Serum Glucose (mg/dL) (Mean)			
Baseline	153	162	161
Change from baseline[b]	-6	-25	-30
Difference from placebo[b] (95% CI)	-	-19 (-25, -13)	-24 (-30, -18)††

Abbreviations: HbA1c = hemoglobin A1c; SGLT2i = sodium-glucose co-transporter-2 inhibitors.

[a] Intent-to-treat population. At Week 24, primary efficacy was missing for 3%, 4%, and 6% of individuals treated with placebo, TRULICITY 0.75 mg, and TRULICITY 1.5 mg, respectively.

[b] Least-squares mean adjusted for baseline value and other stratification factors. Placebo multiple imputation, using baseline and 24-week values from the placebo arm, was applied to model a washout of the treatment effect for patients missing 24-week values (HbA1c, fasting serum glucose, and body weight).

[c] Patients with missing HbA1c data at Week 24 were considered as non-responders.

†† p<0.001 for superiority of TRULICITY compared to placebo, overall type I error controlled.

Insulin Glargine Controlled Trial (Add-on to Metformin and Sulfonylurea)

In this open-label comparator trial (double-blind with respect to TRULICITY dose assignment) with primary endpoint at 52 weeks, 807 adult patients were randomized to and received TRULICITY 0.75 mg once weekly, TRULICITY 1.5 mg once weekly, or insulin glargine once daily, all as add-on to maximally tolerated doses of metformin and glimepiride. Randomization occurred after a 10-week lead-in period; during the initial 2 weeks of the lead-in period, patients were titrated to maximally tolerated doses of metformin and glimepiride. This was followed by a 6- to 8-week glycemic stabilization period prior to randomization.

Patients randomized to insulin glargine were started on a dose of 10 units once daily. Insulin glargine dose adjustments occurred twice weekly for the first 4 weeks of treatment based on self-measured fasting plasma glucose (FPG), followed by once weekly titration through Week 8 of treatment, utilizing an algorithm that targeted a fasting plasma glucose of <100 mg/dL. Only 24% of patients were titrated to goal at the 52-week primary endpoint. The dose of glimepiride could be reduced or discontinued after randomization (at the discretion of the investigator) in the event of persistent hypoglycemia. The dose of glimepiride was reduced or discontinued in 28%, 32%, and 29% of patients randomized to TRULICITY 0.75 mg, TRULICITY 1.5 mg, and glargine.

Patients had a mean age of 57 years; mean duration of type 2 diabetes of 9 years; 51% were male; race: White, Black and Asian were 71%, 1% and 17%, respectively; and 0% of the trial population were in the US.

Treatment with TRULICITY once weekly resulted in a reduction in HbA1c from baseline at 52 weeks when used in combination with metformin and sulfonylurea (Table 10). The difference in observed effect size between TRULICITY 0.75 mg and 1.5 mg, respectively, and glargine in this trial excluded the pre-specified non-inferiority margin of 0.4%.

Table 10: Results at Week 52 of TRULICITY Compared to Insulin Glargine, Both as Add-on to Metformin and Sulfonylurea in Adult Patients with Type 2 Diabetes Mellitus[a]

	52-Week Primary Time Point		
	TRULICITY 0.75 mg	**TRULICITY 1.5 mg**	**Insulin Glargine**
Intent-to-Treat (ITT) Population (N)‡	272	273	262
HbA1c (%) (Mean)			
Baseline	8.1	8.2	8.1
Change from baseline[b]	-0.8	-1.1	-0.6
Fasting Serum Glucose (mg/dL) (Mean)			
Baseline	161	165	163
Change from baseline[b]	-16	-27	-32
Difference from insulin glargine[b] (95% CI)	16 (9, 23)	5 (-2, 12)	-
Body Weight (kg) (Mean)			
Baseline	86.4	85.2	87.6
Change from baseline[b]	-1.3	-1.9	1.4
Difference from insulin[b] (95% CI)	-2.8 (-3.4, -2.2)	-3.3 (-3.9, -2.7)	-

Abbreviations: HbA1c = hemoglobin A1c.

[a] Intent-to-treat population. Last observation carried forward (LOCF) was used to impute missing data. Data post-onset of rescue therapy are treated as missing. At Week 52, primary efficacy was missing for 17%, 13% and 12% of individuals randomized to TRULICITY 0.75 mg, TRULICITY 1.5 mg and glargine, respectively.

[b] Least-squares (LS) mean adjusted for baseline value and other stratification factors.

‡ Patients included in the analysis are a subset of the ITT population that had at least one post-baseline assessment. The primary analysis included 267, 263 and 259 individuals randomized to TRULICITY 0.75 mg, TRULICITY 1.5 mg, and glargine, respectively.

Placebo-Controlled Trial (Add-on to Basal Insulin, with or without Metformin)

In this 28-week placebo-controlled, double-blind trial, 300 adult patients were randomized to placebo or once weekly TRULICITY 1.5 mg, as add-on to titrated basal insulin glargine (with or without metformin). Patients had a mean age of 60 years; mean duration of type 2 diabetes of 13 years; 58% were male; race: White, Black, and Asian were 94%, 4%, and 0.3%, respectively; and 20% of the trial population was in the US.

The mean starting dose of insulin glargine was 37 units/day for patients receiving placebo and 41 units/day for patients receiving TRULICITY 1.5 mg. At randomization, the initial insulin glargine dose in patients with HbA1c <8.0% was reduced by 20%.

At 28 weeks, treatment with once weekly TRULICITY 1.5 mg resulted in a statistically significant reduction in HbA1c compared to placebo (Table 11).

Table 11: Results at Week 28 of TRULICITY Compared to Placebo as Add-On to Basal Insulin in Adult Patients with Type 2 Diabetes Mellitus[a]

	28-Week Primary Time Point	
	Placebo	**TRULICITY 1.5 mg**
Intent-to-Treat (ITT) Population (N)	150	150
HbA1c (%) (Mean)		
Baseline	8.3	8.4
Change from baseline[b]	-0.7	-1.4
Difference from placebo[b] (95% CI)		-0.7 (-0.9, -0.5)††
Percentage of patients HbA1c <7.0%[c]	33	67††
Fasting Serum Glucose (mg/dL) (Mean)		
Baseline	156	157
Change from baseline[b]	-30	-44
Difference from placebo[b] (95% CI)		-14 (-23, -4)†
Body Weight (kg) (Mean)		
Baseline	92.6	93.3
Change from baseline[b]	0.8	-1.3
Difference from placebo[b] (95% CI)		-2.1 (-2.9, -1.4)††

Abbreviations: HbA1c = hemoglobin A1c.

[a] Intent-to-treat population. At Week 28, primary efficacy was missing for 12% and 8% of individuals randomized to placebo and TRULICITY 1.5 mg, respectively.

[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors. Placebo multiple imputation, with respect to baseline values, was used to model a wash-out of the treatment effect for patients having missing Week 28 data.

[c] Patients with missing HbA1c data at Week 28 were considered as non-responders.

†† $p<0.001$ for superiority of TRULICITY 1.5 mg compared to placebo, overall type I error controlled.

† $p\leq0.005$ for superiority of TRULICITY 1.5 mg compared to placebo, overall type I error controlled.

Insulin Glargine-Controlled Trial (Combination with Prandial Insulin, with or without Metformin)

In this open-label comparator trial (double-blind with respect to TRULICITY dose assignment) with primary endpoint at 26 weeks, 884 adult patients on 1 or 2 insulin injections per day were enrolled. Randomization occurred after a 9-week lead-in period; during the initial 2 weeks of the lead-in period, patients continued their pre-trial insulin regimen but could be initiated and/or up-titrated on metformin, based on investigator discretion; this was followed by a 7-week glycemic stabilization period prior to randomization.

At randomization, patients discontinued their pre-trial insulin regimen and were randomized to TRULICITY 0.75 mg once weekly, TRULICITY 1.5 mg once weekly, or insulin glargine once daily, all in combination with prandial insulin lispro 3 times daily, with or without metformin. Insulin lispro was titrated in each arm based on preprandial and bedtime glucose, and insulin glargine was titrated to a fasting plasma glucose goal of <100 mg/dL. Only 36% of patients randomized to glargine were titrated to the fasting glucose goal at the 26-week primary timepoint.

Patients had a mean age of 59 years; mean duration of type 2 diabetes of 13 years; 54% were male; race: White, Black and Asian were 79%, 10% and 4%, respectively; and 33% of the trial population were in the US.

Treatment with TRULICITY 0.75 mg and 1.5 mg once weekly resulted in a reduction in HbA1c from baseline. The difference in observed effect size between TRULICITY 0.75 mg and 1.5 mg, respectively, and glargine in this trial excluded the pre-specified non-inferiority margin of 0.4% (Table 12).

Table 12: Results at Week 26 of TRULICITY Compared to Insulin Glargine, Both in Combination with Insulin Lispro in Adult Patients with Type 2 Diabetes Mellitus[a]

	26-Week Primary Time Point		
	TRULICITY 0.75 mg	**TRULICITY 1.5 mg**	**Insulin Glargine**
Intent-to-Treat (ITT) Population (N)[‡]	293	295	296
HbA1c (%) (Mean)			
Baseline	8.4	8.5	8.5
Change from baseline[b]	-1.6	-1.6	-1.4
Fasting Serum Glucose (mg/dL) (Mean)			
Baseline	150	157	154
Change from baseline[b]	4	-5	-28
Difference from insulin glargine[b] (95% CI)	32 (24, 41)	24 (15, 32)	-
Body Weight (kg) (Mean)			
Baseline	91.7	91.0	90.8
Change from baseline[b]	0.2	-0.9	2.3
Difference from insulin glargine[b] (95% CI)	-2.2 (-2.8, -1.5)	-3.2 (-3.8, -2.6)	-

Abbreviation: HbA1c = hemoglobin A1c

[a] Intent-to-treat population. Last observation carried forward (LOCF) was used to impute missing data. Data post-onset of rescue therapy are treated as missing. At Week 26, primary efficacy was missing for 14%, 15%, and 14% of individuals randomized to TRULICITY 0.75 mg, TRULICITY 1.5 mg and glargine, respectively.

[b] Least-squares (LS) mean adjusted for baseline value and other stratification factors.

[‡] Patients included in the analysis are a subset of the ITT population that had at least one post-baseline assessment. The primary analysis included 275, 273 and 276 individuals randomized to TRULICITY 0.75 mg, TRULICITY 1.5 mg, and glargine, respectively.

14.4 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus and Moderate to Severe Chronic Kidney Disease

In this open-label comparator trial (double-blind with respect to TRULICITY dose assignment) with primary endpoint at 26 weeks, a total of 576 adult patients with type 2 diabetes were randomized and treated to compare TRULICITY 0.75 mg and 1.5 mg with insulin glargine (NCT01621178).

Patients on insulin and other antidiabetic therapy (e.g., oral antidiabetic drugs, pramlintide) had non-insulin therapies discontinued and had their insulin dose adjusted for 12 weeks prior to randomization. Patients on insulin therapy alone maintained a stable insulin dose for 3 weeks prior to randomization. At randomization, patients discontinued their pre-trial insulin regimen and patients were randomized to TRULICITY 0.75 mg once weekly, TRULICITY 1.5 mg once weekly, or insulin glargine once daily, all in combination with prandial insulin lispro. For patients randomized to insulin glargine, the initial insulin glargine dose was based on the basal insulin dose prior to randomization. Insulin glargine was allowed to be titrated with a fasting plasma glucose goal of ≤150 mg/dL. Insulin lispro was allowed to be titrated with a preprandial and bedtime glucose goal of ≤180 mg/dL.

Patients had a mean age of 65 years; a mean duration of type 2 diabetes of 18 years; 52% were male; race: White, Black, and Asian were 69%, 16%, and 3%, respectively; and 32% of the trial population were in the US. At baseline, overall mean eGFR was 38 mL/min/1.73 m^2, 30% of patients had eGFR <30 mL/min/1.73 m^2, and 45% of patients had macroalbuminuria. Patients on over 70 units/day of basal insulin were excluded from the trial.

Treatment with TRULICITY 0.75 mg and 1.5 mg once weekly resulted in a reduction in HbA1c at 26-weeks from baseline. The difference in observed effect size between TRULICITY 0.75 mg and 1.5 mg, respectively, and glargine in this trial excluded the pre-specified non-inferiority margin of 0.4%. Mean fasting plasma glucose increased in the TRULICITY arms (Table 13).

Mean baseline body weight was 90.9 kg, 88.1 kg, and 88.2 kg in the TRULICITY 0.75 mg, TRULICITY 1.5 mg, and insulin glargine arms, respectively. The mean changes from baseline at Week 26 were -1.1, -2, and 1.9 kg in the TRULICITY 0.75 mg, TRULICITY 1.5 mg, and insulin glargine arms, respectively.

Table 13: Results at Week 26 of TRULICITY Compared to Insulin Glargine, Both in Combination with Insulin Lispro, in Patients with Moderate to Severe Chronic Kidney Disease in Adult Patients with Type 2 Diabetes Mellitus[a]

	26-Week Primary Time Point		
	TRULICITY 0.75 mg	**TRULICITY 1.5 mg**	**Insulin Glargine**
Intent-to-Treat Population (N)	190	192	194
HbA1c (%) (Mean)			
Baseline	8.6	8.6	8.6
Change from baseline[b]	-0.9	-1.0	-1.0
Difference from insulin glargine[b] (95% CI)	0.0 (-0.2, 0.3)	-0.1 (-0.3, 0.2)	
Percentage of patients HbA1c <8.0%	73	75	74
Fasting Serum Glucose (mg/dL) (Mean)			
Baseline	167	161	170
Change from baseline[b]	6	14	-23
Difference from insulin glargine[b] (95% CI)	30 (16, 43)	37 (24, 50)	

Abbreviation: HbA1c = hemoglobin A1c

[a] Intent-to-treat population (all randomized and treated patients) was used in the analysis regardless of discontinuation of study drug or initiation of rescue therapy. At Week 26, primary efficacy was missing for 12%, 15%, and 9% of individuals randomized to and treated with TRULICITY 0.75 mg, TRULICITY 1.5 mg, and insulin glargine, respectively. Missing data were imputed using multiple imputation within treatment group.

[b] Least-squares (LS) mean from ANCOVA pattern mixture model adjusted for baseline value and other stratification factors.

14.5 Cardiovascular Outcomes Trial in Adults with Type 2 Diabetes Mellitus and Cardiovascular Disease or Multiple Cardiovascular Risk Factors

The REWIND trial (NCT01394952) was a multi-national, multi-center, randomized, placebo-controlled, double-blind trial. In this trial, 9901 adult patients with type 2 diabetes mellitus and established cardiovascular (CV) disease or multiple cardiovascular risk factors were randomized to TRULICITY 1.5 mg or placebo both added to standard of care. The median follow-up duration was 5.4 years. The primary endpoint was the time to the first occurrence of a composite 3-component Major Adverse Cardiovascular Events (MACE) outcome, which included CV death, non-fatal myocardial infarction (MI), and non-fatal stroke.

Patients eligible to enter the trial were 50 years of age or older who had type 2 diabetes mellitus, had an HbA1c value ≤9.5% with no lower limit at screening, and had either established CV disease, or did not have established CV disease but had multiple CV risk factors. Patients who were confirmed to have established CV disease (31.5% of randomized patients) had a history of at least one of the following: MI (16.2%); myocardial ischemia by a stress test or with cardiac imaging (9.3%); ischemic stroke (5.3%); coronary, carotid, or peripheral artery revascularization (18.0%); unstable angina (5.9%); or hospitalization for unstable angina with at least one of the following: ECG changes, myocardial ischemia on imaging, or a need for percutaneous coronary intervention (12.0%). Patients confirmed to be without established CV disease, but with multiple CV risk factors, comprised 62.8% of the randomized trial population.

At baseline, demographic and disease characteristics were balanced between treatment groups. Patients had a mean age of 66 years; 46% were female; race: White, Black, and Asian were 76%, 7%, and 4%, respectively.

The median baseline HbA1c was 7.2%. The mean duration of type 2 diabetes was 10.5 years and the mean BMI was 32.3 kg/m^2.

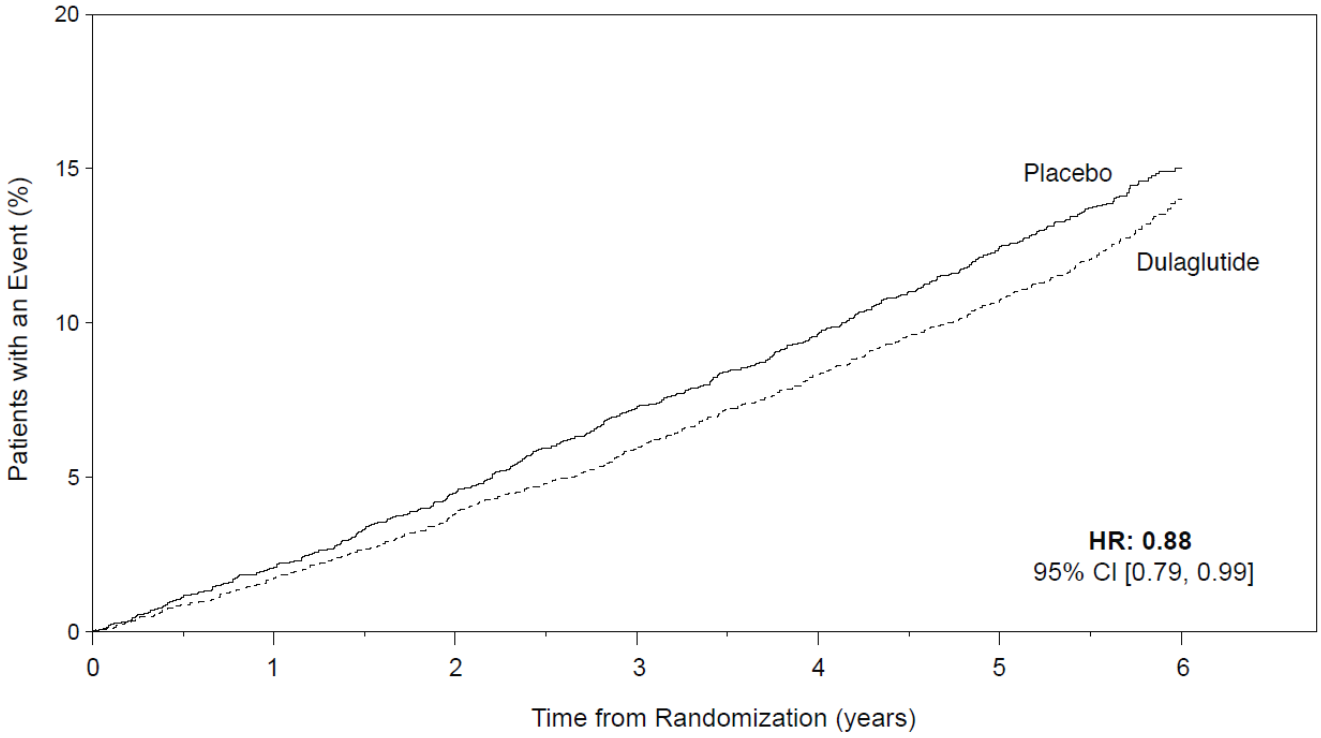
At baseline, 50.5% of patients had mild renal impairment (eGFR ≥60 but <90 mL/min/1.73m^2), 21.6% had moderate renal impairment (eGFR ≥30 but <60 mL/min/1.73m^2), and 1.1% of patients had severe renal impairment (eGFR <30 mL/min/1.73m^2) out of 9713 patients whose eGFR were available.

At baseline, 94.7% of patients were taking antidiabetic medication, with 10.5% of patients taking three or more antidiabetic drugs. The most common background antidiabetic drugs used at baseline were metformin (81.2%), sulfonylurea (46.0%), and insulin (23.9%). At baseline, CV disease and risk factors were managed with ACE inhibitors or angiotensin receptor blockers (81.5%), beta blockers (45.6%), calcium channel blockers (34.4%), diuretics (46.5%), statin therapy (66.1%), antithrombotic agents (58.7%), and aspirin (51.7%). During the trial, investigators were to modify anti-diabetic and cardiovascular medications to achieve local standard of care treatment targets with respect to blood glucose,

lipids, and blood pressure, and manage patients recovering from an acute coronary syndrome or stroke event per local treatment guidelines.

For the primary analysis, a Cox proportional hazards model was used to test for superiority. Type I error was controlled across multiple tests. TRULICITY significantly reduced the risk of first occurrence of primary composite endpoint of CV death, non-fatal MI, or non-fatal stroke (HR: 0.88, 95% CI 0.79, 0.99). Refer to Figure 6 and Table 14.

Vital status was available for 99.7% of patients in the trial. A total of 1128 deaths were recorded during the REWIND trial. A majority of the deaths in the trial were adjudicated as CV deaths, and non-CV deaths were comparable between the treatment groups (4.4% in patients treated with TRULICITY and 5.0% in patients treated with placebo). There were 536 all-cause deaths (10.8%) in the dulaglutide group compared to 592 deaths (12.0%) in the placebo group.



Number of patients at risk

Placebo	4952	4791	4625	4437	4275	3575	742
Dulaglutide	4949	4815	4670	4521	4369	3686	741

Figure 6. KAPLAN MEIER CURVE: Time to First Occurrence of MACE in the REWIND Trial

Table 14: Treatment Effect for MACE and the Individual Components in the REWIND Trial, Median Trial Observation Time of 5.4 years in Adult Patients with Type 2 Diabetes Mellitus[a]

Time to First Occurrence of:	TRULICITY N=4949	Placebo N=4952	Hazard Ratio (95% CI)[b]
Composite of non-fatal myocardial infarction, non-fatal stroke, cardiovascular death (MACE)[d]	594 (12.0%)	663 (13.4%)	0.88 (0.79, 0.99)[c]
Cardiovascular death[d,e]	317 (6.4%)	346 (7.0%)	0.91 (0.78, 1.06)
Non-fatal myocardial infarction[d,e]	205 (4.1%)	212 (4.3%)	0.96 (0.79, 1.16)
Non-fatal stroke[d,e]	135 (2.7%)	175 (3.5%)	0.76 (0.61, 0.95)
Fatal or non-fatal myocardial infarction[d,e]	223 (4.5%)	231 (4.7%)	0.96 (0.79, 1.15)
Fatal or non-fatal stroke[d,e]	158 (3.2%)	205 (4.1%)	0.76 (0.62, 0.94)

[a] All randomized patients.
[b] Cox-proportional hazards model with treatment as a factor. Type I error was controlled for the primary and secondary endpoints.
[c] p=0.026 for superiority (2-sided).
[d] Number and percentage of patients with events.
[e] Results for components of MACE, fatal and non-fatal stroke, and fatal and non-fatal MI are listed descriptively for supportive purposes. No statistical significance should be inferred since these CIs are not adjusted for multiplicity.

14.6 Glycemic Control Trial in Pediatric Patients 10 Years of Age and Older with Type 2 Diabetes Mellitus

In this 26-week randomized, double-blind, placebo-controlled, parallel-arm, multicenter trial with an open-label extension for an additional 26 weeks,154 pediatric patients 10 years of age and older with type 2 diabetes mellitus, who had inadequate glycemic control despite diet and exercise, were randomized to subcutaneous TRULICITY once weekly (0.75 mg and 1.5 mg) or subcutaneous placebo once weekly in combination with or without metformin and/or basal insulin treatment (NCT02963766).

Overall, in this trial demographic and baseline disease characteristics were comparable across the treatment groups. At baseline, 71% of patients were female, and the mean age was 14.5 years (ranging from 10 to 17 years). Overall, 55% were White, 15% were Black or African American, 12% were Asian, 10% were American Indian or Alaska Native, 5% were other races, and 3% had unknown race. Additionally, 55% were Hispanic or Latino, 42% were not Hispanic or Latino, and 3% had unknown ethnicity. At baseline, the mean duration of type 2 diabetes mellitus was 2 years, mean HbA1c was 8.1%, mean weight was 90.5 kg and mean BMI was 34.1 kg/m^2.

In this trial, once weekly TRULICITY (0.75 mg and 1.5 mg, pooled) (with or without metformin and/or basal insulin) was superior to placebo ($p<0.001$) in the change from baseline at Week 26 in HbA1c in pediatric patients 10 years of age and older with type 2 diabetes mellitus (see Table 15).

Table 15: Glycemic Results at Week 26 in Pediatric Patients 10 Years of Age and Older with Type 2 Diabetes Mellitus with Inadequate Glycemic Control Despite Diet and Exercise (With or Without Metformin and/or Basal Insulin)

	Placebo	TRULICITY 0.75 mg once weekly	TRULICITY 1.5 mg once weekly	TRULICITY once weekly Pooled[a]
Intent-to-Treat Population (N)	51	51	52	103
HbA1c (%) (Mean)[c]				
Baseline Change from baseline at Week 26[b] Difference from placebo (95% CI)[b]	8.1 0.6 -	7.9 -0.6 -1.2 (-1.8, -0.6)	8.2 -0.9 -1.5 (-2.1, -0.9)	8.0 -0.8 -1.4 (-1.9, -0.8)
Percentage of Patients with HbA1c <7.0% at Week 26[d]	14%	55%	48%	52%
Fasting Blood Glucose (mg/dL) (Mean)[c]				
Baseline Change from baseline at Week 26[b] Difference from placebo (95% CI)[b]	159 17.1 -	149 -12.8 -29.9 (-50.7, -9.1)	163 -24.9 -42.0 (-63.0, -20.9)	156 -18.9 -35.9 (-54.2, -17.6)

Abbreviations: HbA1c = hemoglobin A1c.

[a] Combined results for TRULICITY 0.75 mg and 1.5 mg. The comparison of the two dosages together and individually with placebo was prespecified with overall type I error controlled.

[b] The change from baseline and difference from placebo were analyzed using analysis of covariance with effects for treatment, the baseline value as a covariate, and stratification factors which were HbA1c at screening (< 8% vs >= 8%), insulin use at baseline (yes/no), metformin use at baseline (yes/no).

[c] For HbA1c and Fasting Blood Glucose, multiple imputation was performed for missing data guided by washout method. At Week 26 primary efficacy (HbA1c) was missing for 8%, 6%, and 10% of patients on placebo, TRULICITY 0.75 mg and TRULICITY 1.5 mg respectively.

[d] For percentage of patients HbA1c < 7%, missing data was imputed as not achieving the target.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TRULICITY (dulaglutide) injection is a clear and colorless solution supplied in single-dose pens. TRULICITY is packaged in a cardboard outer carton containing 4 single-dose TRULICITY pens and is supplied as follows:

Total Strength per Total Volume	NDC
0.75 mg/0.5 mL	NDC 0002-1433-80
1.5 mg/0.5 mL	NDC 0002-1434-80
3 mg/0.5 mL	NDC 0002-2236-80
4.5 mg/0.5 mL	NDC 0002-3182-80

16.2 Storage and Handling

- Store TRULICITY in the refrigerator at 36°F to 46°F (2°C to 8°C).
- If needed, each single-dose pen can be kept at room temperature, not to exceed 86°F (30°C) for a total of 14 days.
- Do not freeze TRULICITY. Do not use TRULICITY if it has been frozen.
- Protect TRULICITY from light. Storage of TRULICITY in the original carton is recommended until time of administration.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling *(Medication Guide and Instructions for Use).*

- Inform patients that TRULICITY causes benign and malignant 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 physician *[see Boxed Warning and Warnings and Precautions (5.1)]*.

- Inform patients that persistent severe abdominal pain, that may radiate to the back and which may (or may not) be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue TRULICITY promptly, and to contact their physician, if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.2)]*.
- Inform patients that the risk of hypoglycemia may be increased when TRULICITY is used in combination 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)]*.
- Advise patients of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Inform patients treated with TRULICITY 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)]*.
- Inform patients that serious hypersensitivity reactions have been reported with use of TRULICITY. Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking TRULICITY and seek medical advice promptly if such symptoms occur *[see Warnings and Precautions (5.4)]*.
- Inform patients to contact their physician if changes in vision are experienced during treatment with TRULICITY *[see Warnings and Precautions (5.7)]*.
- Inform patients of the potential risk for cholelithiasis or cholecystitis. Instruct patients to contact their physician if cholelithiasis or cholecystitis is suspected for appropriate clinical follow-up *[see Warnings and Precautions (5.8)]*.
- Advise patients to inform their healthcare provider if they are pregnant or intend to become pregnant *[see Use in Specific Populations (8.1)]*.
- Inform patients if a dose is missed and there are at least 3 days (72 hours) until the next scheduled dose, they should administer it as soon as possible and then resume their usual once weekly dosing schedule. If a dose is missed and the next regularly scheduled dose is due in 1 or 2 days, inform the patient to not administer the missed dose and instead resume TRULICITY with the next regularly scheduled dose *[see Dosage and Administration (2.3)]*.
- Advise patients treated with TRULICITY of the potential risk of gastrointestinal side effects *[see Adverse Reactions (6.1)]*.

Eli Lilly and Company, Indianapolis, IN 46285, USA

US License Number 1891

B5.0-TRU-0016-USPI-2022MMDD

Medication Guide

TRULICITY® (TRU-li-si-tee)

(dulaglutide)

injection, for subcutaneous use

Read this Medication Guide before you start using TRULICITY 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 your treatment.

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

TRULICITY 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 or mice, TRULICITY and medicines that work like TRULICITY caused thyroid tumors, including thyroid cancer. It is not known if TRULICITY will cause thyroid tumors or a type of thyroid cancer called medullary thyroid carcinoma (MTC) in people.
- Do not use TRULICITY 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 TRULICITY?

- TRULICITY is an injectable prescription medicine that is used:
  - along with diet and exercise to improve blood sugar (glucose) in adults and children 10 years of age and older with type 2 diabetes mellitus.
  - to reduce the risk of major cardiovascular events such as death, heart attack, or stroke in adults with type 2 diabetes mellitus with known heart disease or multiple cardiovascular risk factors.
- It is not known if TRULICITY can be used in people who have had pancreatitis.
- TRULICITY is not for use in people with type 1 diabetes.
- TRULICITY is not recommended for use in people with severe stomach or intestinal problems.
- It is not known if TRULICITY is safe and effective in children under 10 years of age.

Do not use TRULICITY 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 dulaglutide or any of the ingredients in TRULICITY. See the end of this Medication Guide for a complete list of ingredients in TRULICITY. Symptoms of a serious allergic reaction include:
  - swelling of your face, lips, tongue or throat
  - problems breathing or swallowing
  - severe rash or itching
  - fainting or feeling dizzy
  - very rapid heartbeat

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

- have or have had problems with your pancreas, kidneys or liver.
- 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 TRULICITY will harm your unborn baby. Tell your healthcare provider if you become pregnant while using TRULICITY.
- are breastfeeding or plan to breastfeed. It is not known if TRULICITY passes into your breast milk. You and your healthcare provider should decide if you should breastfeed while taking TRULICITY.

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

Before using TRULICITY, 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 TRULICITY?

- Read the **Instructions for Use** that comes with TRULICITY.
- Use TRULICITY exactly as your healthcare provider tells you to.
- TRULICITY is injected under the skin (subcutaneously) of your stomach (abdomen), thigh, or upper arm.
- **Use TRULICITY 1 time each week on the same day each week at any time of the day.**
- You may change the day of the week as long as your last dose was given **3** or more days before.
- If you miss a dose of TRULICITY, take the missed dose as soon as possible if there are at least **3** days (72 hours) until your next scheduled dose. If there are less than **3** days remaining, skip the missed dose and take your next dose on the regularly scheduled day. **Do not** take **2** doses of TRULICITY within **3** days of each other.
- TRULICITY may be taken with or without food.
- **Do not** mix insulin and TRULICITY together in the same injection.
- You may give an injection of TRULICITY 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 TRULICITY, call your healthcare provider or go to the nearest emergency room right away.

What are the possible side effects of TRULICITY?

TRULICITY may cause serious side effects, including:

- See **"What is the most important information I should know about TRULICITY?"**
- **Inflammation of your pancreas (pancreatitis).** Stop using TRULICITY 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 TRULICITY 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 TRULICITY 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.
- **Severe stomach problems.** Other medicines like TRULICITY may cause severe stomach problems. It is not known if TRULICITY causes or worsens stomach problems.
- **Changes in vision.** Tell your healthcare provider if you have changes in vision during treatment with TRULICITY.
- **Gallbladder problems.** Gallbladder problems have happened in some people who take TRULICITY. 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 TRULICITY may include:

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

Tell 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 TRULICITY. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of TRULICITY.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TRULICITY for a condition for which it was not prescribed. Do not give TRULICITY to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about TRULICITY. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about TRULICITY that is written for health professionals.

What are the ingredients in TRULICITY?

Active ingredient: dulaglutide

Inactive ingredients: citric acid anhydrous, mannitol, polysorbate 80, trisodium citrate dihydrate, in water for injection

TRULICITY® is a registered trademark of Eli Lilly and Company.

Manufactured by: Eli Lilly and Company, Indianapolis, IN 46285, USA, US License Number 1891

www.TRULICITY.com.

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

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 11/2022

A4.0-TRU-0008-MG-YYYYMMDD

BREAK SEAL

BREAK SEAL

Instructions for Use

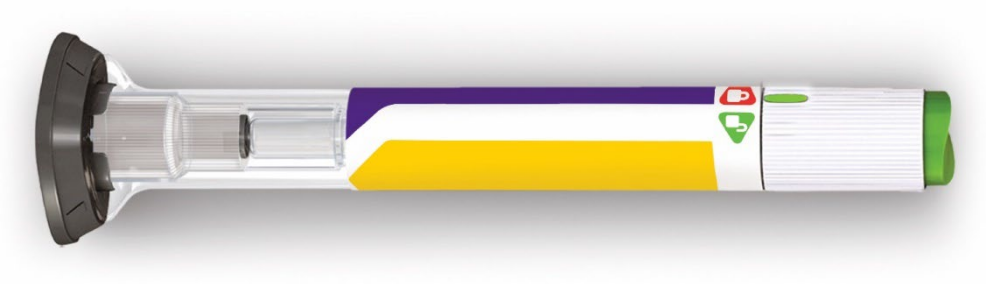
TRULICITY® (TRU-li-si-tee)

(dulaglutide)

injection, for subcutaneous use

0.75 mg/0.5 mL Single-Dose Pen

use 1 time each week (once weekly)



←Unfold and lay flat→

Read both sides for full instructions

Information About TRULICITY Single-Dose Pen

Please read this Instructions for Use and the Medication Guide carefully and completely before using your TRULICITY Single-Dose Pen. Talk to your healthcare provider about how to inject TRULICITY the right way.

- TRULICITY Single-Dose Pen (Pen) is a disposable, prefilled medicine delivery device. Each Pen contains 1 dose of TRULICITY (0.75 mg/0.5 mL). Each Pen should only be used 1 time.
- **TRULICITY is used 1 time each week.**
  You may want to mark your calendar to remind you when to take your next dose.

Before You Get Started

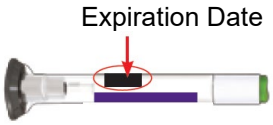
Remove

Remove the Pen from the refrigerator.

Leave the Base Cap on until you are ready to inject.

Check

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



Inspect

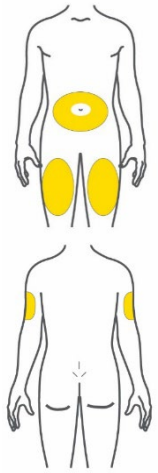
Check the Pen to make sure that it is not damaged and inspect the medicine to make sure it is not cloudy, discolored or has particles in it.

Prepare

Wash your hands.

Choose Your Injection Site

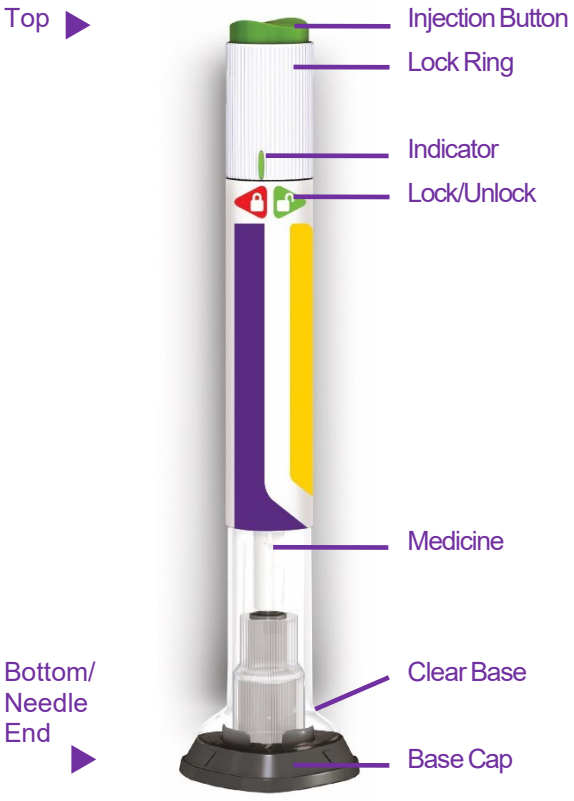
Your healthcare provider can help you choose the injection site that is best for you.



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.

You may inject the medicine into your stomach (abdomen) or thigh.

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


Top
Injection Button
Lock Ring
Indicator
Lock/Unlock
Medicine
Bottom/
Needle
End
Clear Base
Base Cap

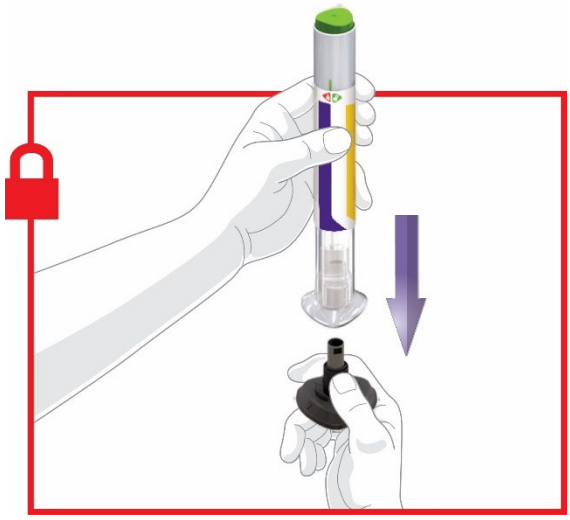
Step 1 Uncap the Pen

Make sure the Pen is **locked**.

- Pull the Base Cap straight off and throw it away in your household trash.

  Do not put the Base Cap back on — this could damage the needle.

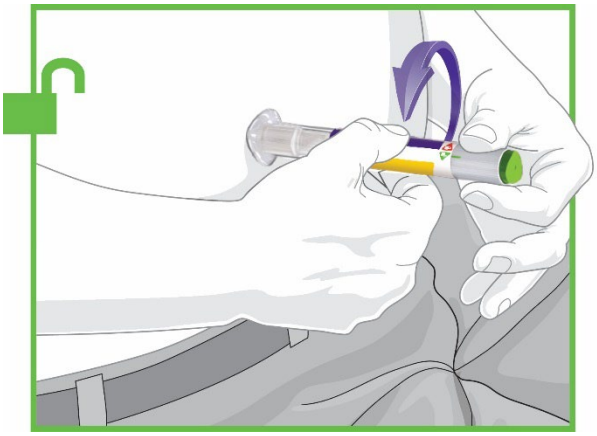
  Do not touch the needle.



Step 2 Place and Unlock

- Place the Clear Base flat and firmly against your skin at the injection site.

Unlock by turning the Lock Ring.

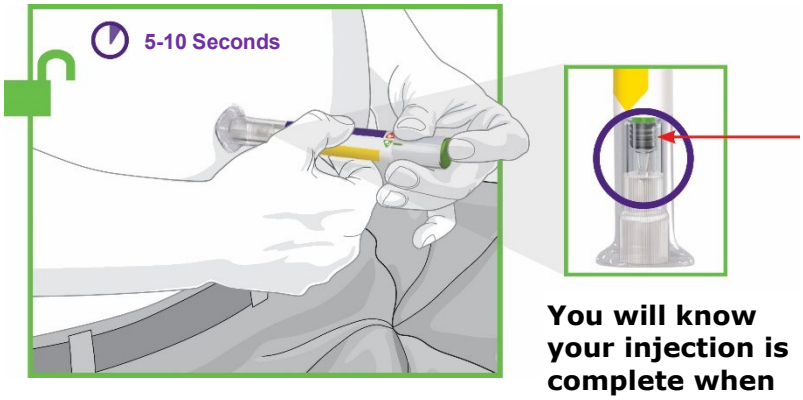


Step 3 Press and Hold

- Press and hold the green Injection Button. You will hear a loud click.

Continue holding the Clear Base firmly against your skin until you hear a second click. This happens when the needle starts retracting in about 5-10 seconds.

- Remove the Pen from your skin.



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

Important Information

Disposal of Pen

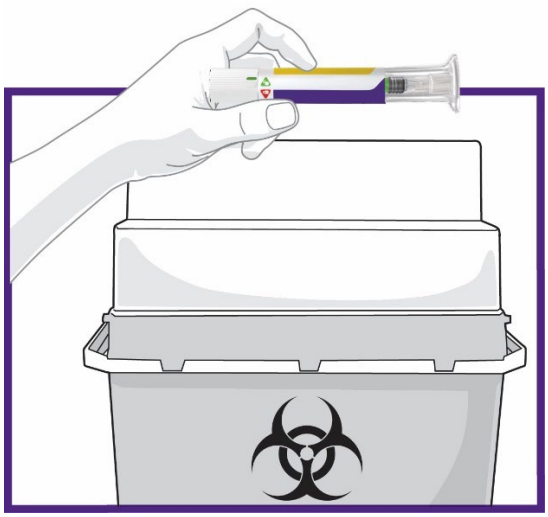
Storage and Handling

Commonly Asked Questions

Other Information

Where to Learn More

Disposing of Your Used Pens



- Put your used Pens in a 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 a 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.

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 below 86°F (30°C) for up to a total of 14 days.
- Do not freeze your Pen. If the Pen has been frozen, throw the Pen away and use a new Pen.
- Storage of your Pen in the original carton is recommended. Protect your Pen from direct heat and light.
- The Pen has glass parts. Handle it carefully. If you drop it on a hard surface, do not use it. Use a new Pen for your injection.
- Keep your TRULICITY Pen and all medicines out of the reach of children.

Commonly Asked Questions

What if I see air bubbles in my Pen?

Air bubbles are normal.

What if I unlock the Pen and press the green Injection Button before pulling off the Base Cap?

Do not remove the 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 Base Cap?

A drop of liquid on the tip of the needle is normal.

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 and firm against your skin.

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

Some patients 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 louder click.

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

This is normal.

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 *(see step 3)*. Also 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.

Other Information

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

Where to Learn More

- If you have any questions or problems with your TRULICITY Single-Dose Pen, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) or call your healthcare provider.
- For more information about TRULICITY Single-Dose Pen, visit our website at: www.trulicity.com.

SCAN THIS CODE TO LAUNCH
www.trulicity.com

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

Eli Lilly and Company
Indianapolis, IN 46285, USA
US License Number 1891

The TRULICITY Pen meets the current dose accuracy and functional requirements of ISO 11608-1:2012 and 11608-5:2012.

Revised: 11/2022

TRULOAI-0003-IFU-YYYYMMDD

BREAK SEAL

BREAK SEAL

Instructions for Use

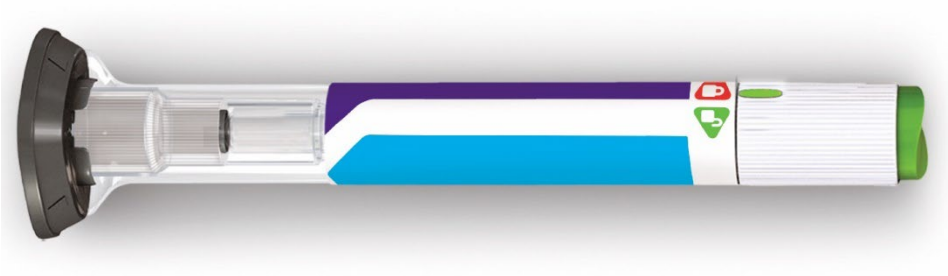
TRULICITY® (TRU-li-si-tee)

(dulaglutide)

injection, for subcutaneous use

1.5 mg/0.5 mL Single-Dose Pen

use 1 time each week (once weekly)



←Unfold and lay flat→

Read both sides for full instructions

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Before You Get Started

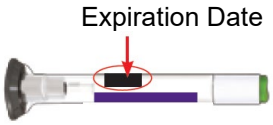
Remove

Remove the Pen from the refrigerator.

Leave the Base Cap on until you are ready to inject.

Check

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



Inspect

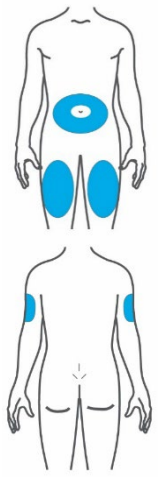
Check the Pen to make sure that it is not damaged and inspect the medicine to make sure it is not cloudy, discolored or has particles in it.

Prepare

Wash your hands.

Choose Your Injection Site

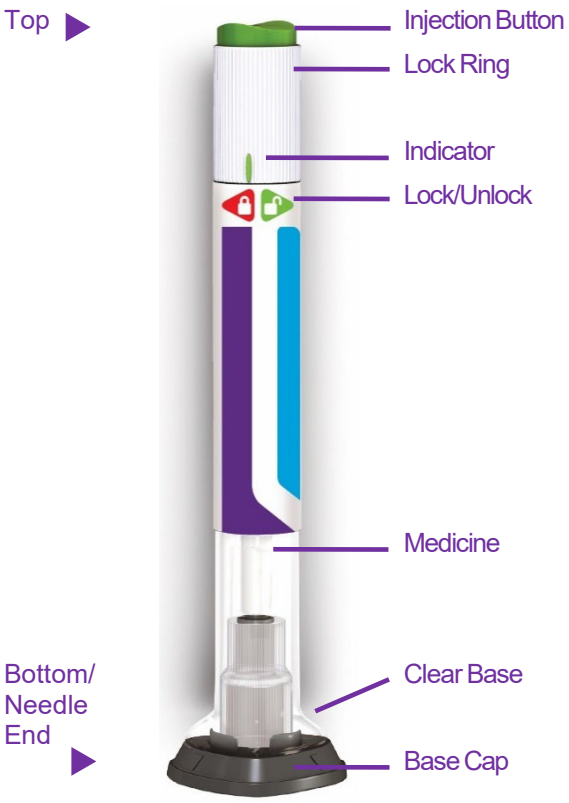
Your healthcare provider can help you choose the injection site that is best for you.



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.

You may inject the medicine into your stomach (abdomen) or thigh.

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


Top
Injection Button
Lock Ring
Indicator
Lock/Unlock
Medicine
Bottom/
Needle
End
Clear Base
Base Cap

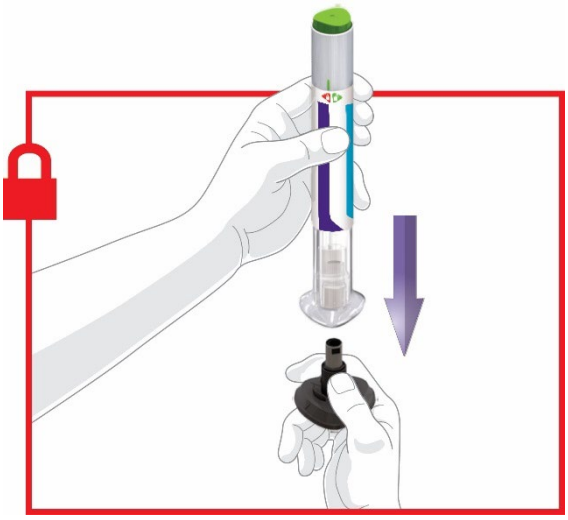
Step 1 Uncap the Pen

Make sure the Pen is **locked**.

- Pull the Base Cap straight off and throw it away in your household trash.

  Do not put the Base Cap back on — this could damage the needle.

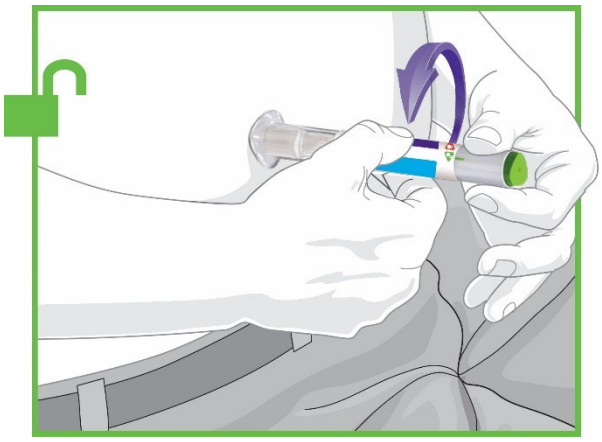
  Do not touch the needle.



Step 2 Place and Unlock

- Place the Clear Base flat and firmly against your skin at the injection site.

Unlock by turning the Lock Ring.

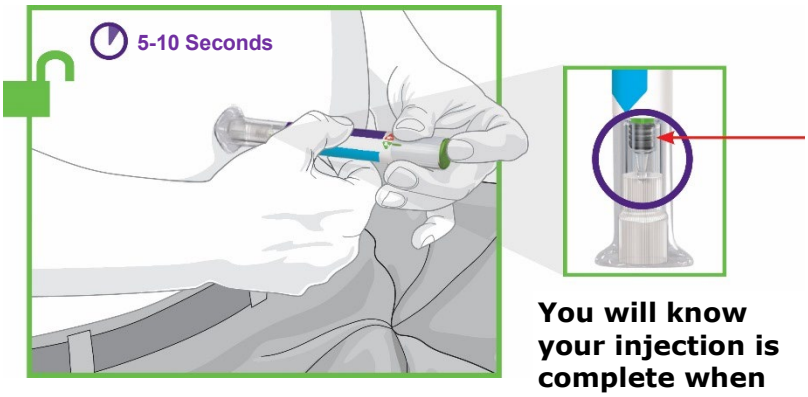


Step 3 Press and Hold

- Press and hold the green Injection Button. You will hear a loud click.

Continue holding the Clear Base firmly against your skin until you hear a second click. This happens when the needle starts retracting in about 5-10 seconds.

- Remove the Pen from your skin.



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

Important Information

Disposal of Pen

Storage and Handling

Commonly Asked Questions

Other Information

Where to Learn More

Disposing of Your Used Pens

- Put your used Pens in a 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 a 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.

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 below 86°F (30°C) for up to a total of 14 days.
- Do not freeze your Pen. If the Pen has been frozen, throw the Pen away and use a new Pen.
- Storage of your Pen in the original carton is recommended. Protect your Pen from direct heat and light.
- The Pen has glass parts. Handle it carefully. If you drop it on a hard surface, do not use it. Use a new Pen for your injection.
- Keep your TRULICITY Pen and all medicines out of the reach of children.

Commonly Asked Questions

What if I see air bubbles in my Pen?

Air bubbles are normal.

What if I unlock the Pen and press the green Injection Button before pulling off the Base Cap?

Do not remove the 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 Base Cap?

A drop of liquid on the tip of the needle is normal.

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 and firm against your skin.

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

Some patients 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 louder click.

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

This is normal.

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 *(see step 3)*. Also 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.

Other Information

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

Where to Learn More

- If you have any questions or problems with your TRULICITY Single-Dose Pen, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) or call your healthcare provider.
- For more information about TRULICITY Single-Dose Pen, visit our website at: www.trulicity.com.

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www.trulicity.com

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

Eli Lilly and Company
Indianapolis, IN 46285, USA
US License Number 1891

The TRULICITY Pen meets the current dose accuracy and functional requirements of ISO 11608-1:2012 and 11608-5:2012.

Revised: 11/2022

TRUHIAI-0003-IFU-YYYYMMDD

BREAK SEAL

BREAK SEAL

Instructions for Use

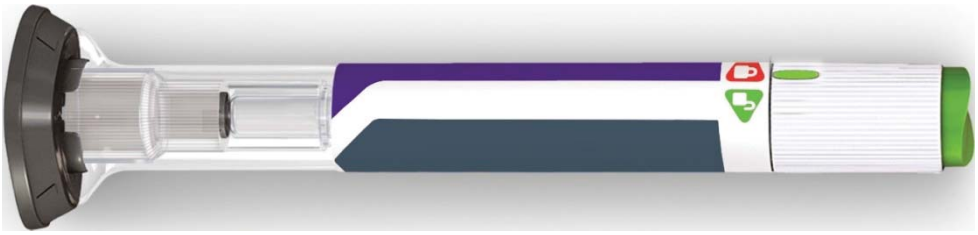
TRULICITY® (TRU-li-si-tee)

(dulaglutide)

injection, for subcutaneous use

3 mg/0.5 mL Single-Dose Pen

use 1 time each week (once weekly)



←Unfold and lay flat→

Read both sides for full instructions

Information About TRULICITY Single-Dose Pen

Please read this Instructions for Use and the Medication Guide carefully and completely before using your TRULICITY Single-Dose Pen. Talk to your healthcare provider about how to inject TRULICITY the right way.

- TRULICITY Single-Dose Pen (Pen) is a disposable, prefilled medicine delivery device. Each Pen contains 1 dose of TRULICITY (3 mg/0.5 mL). Each Pen should only be used 1 time.
- **TRULICITY is used 1 time each week.** You may want to mark your calendar to remind you when to take your next dose.

Before You Get Started

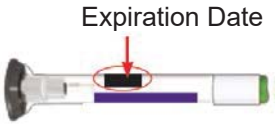
Remove

Remove the Pen from the refrigerator.

Leave the Base Cap on until you are ready to inject.

Check

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



Inspect

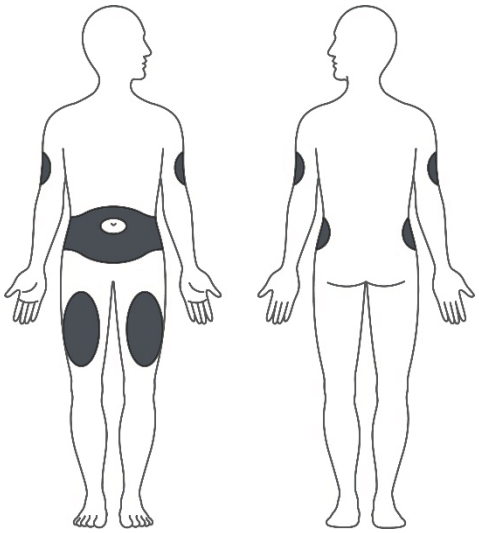
Check the Pen to make sure that it is not damaged and inspect the medicine to make sure it is not cloudy, discolored or has particles in it.

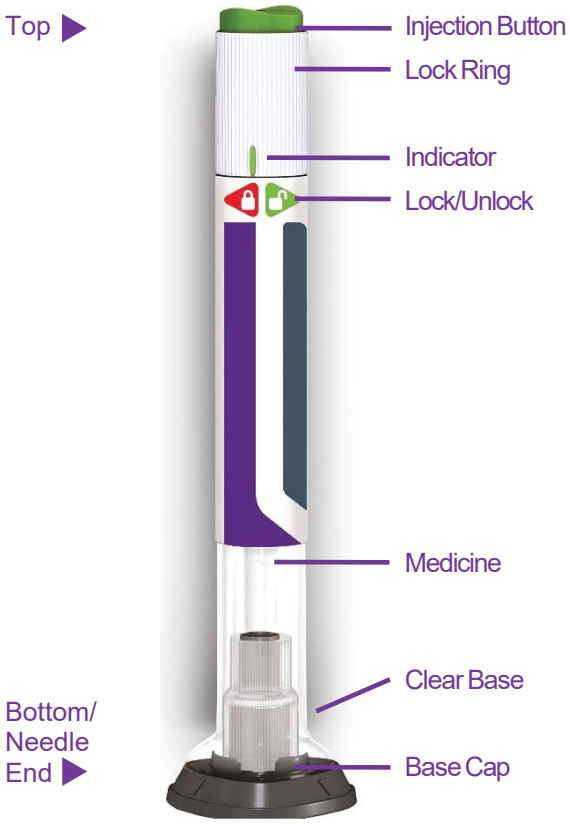
Prepare

Wash your hands.

Choose Your Injection Site

- Your healthcare provider can help you choose the injection site that is best for you.
- You may inject the medicine into your stomach (abdomen) or thigh.
- Another person may give you the injection in 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.




Top
Injection Button
Lock Ring
Indicator
Lock/Unlock
Medicine
Clear Base
Bottom/
Needle
End
Base Cap

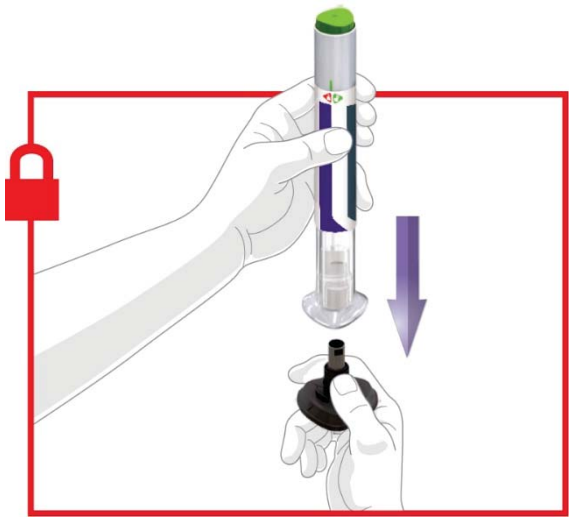
Step 1 Uncap the Pen

Make sure the Pen is **locked**.

- Pull the Base Cap straight off and throw it away in your household trash.

  Do not put the Base Cap back on — this could damage the needle.

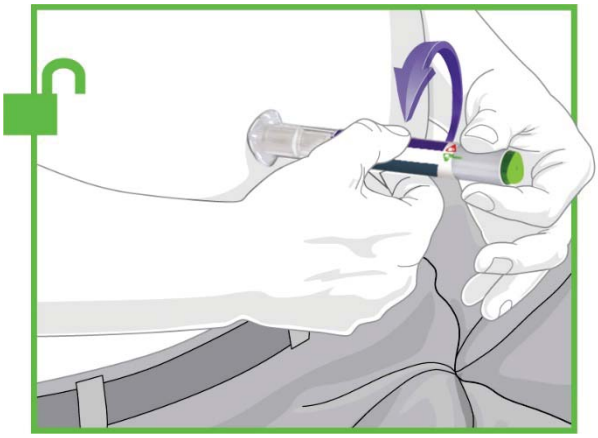
  Do not touch the needle.



Step 2 Place and Unlock

- Place the Clear Base flat and firmly against your skin at the injection site.

Unlock by turning the Lock Ring.

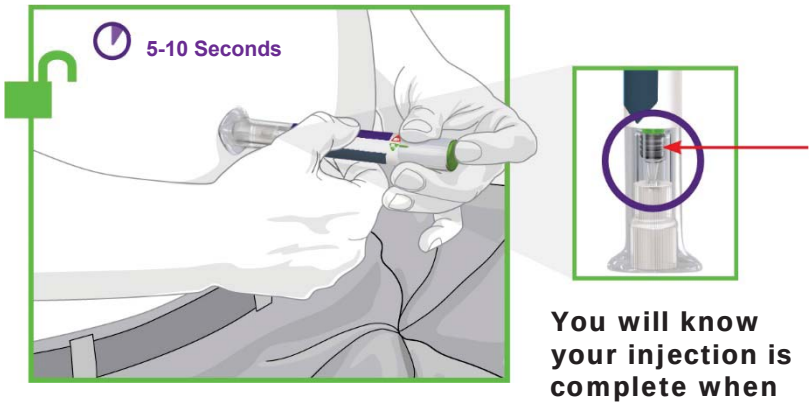


Step 3 Press and Hold

- Press and hold the green Injection Button. You will hear a loud click.

⚠ Continue holding the Clear Base firmly against your skin until you hear a second click. This happens when the needle starts retracting in about 5-10 seconds.

- Remove the Pen from your skin.



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

Important Information

Disposal of Pen

Storage and Handling

Commonly Asked Questions

Other Information

Where to Learn More

Disposing of Your Used Pens

- Put your used Pens in a 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 a 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.

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 below 86°F (30°C) for a total of 14 days.
- Do not freeze your Pen. If the Pen has been frozen, throw the Pen away and use a new Pen.
- Storage of your Pen in the original carton is recommended. Protect your Pen from direct heat and light.
- The Pen has glass parts. Handle it carefully. If you drop it on a hard surface, do not use it. Use a new Pen for your injection.
- Keep your TRULICITY Pen and all medicines out of the reach of children.

Commonly Asked Questions

What if I see air bubbles in my Pen?

Air bubbles are normal.

What if I unlock the Pen and press the green Injection Button before pulling off the Base Cap?

Do not remove the 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 Base Cap?

A drop of liquid on the tip of the needle is normal.

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 and firm against your skin.

I heard more than 2 clicks during my injection—2 louder 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 louder click.

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

This is normal.

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 *(see step 3)*. Also 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.

Other Information

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

Where to Learn More

- If you have any questions or problems with your TRULICITY Single-Dose Pen, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) or call your healthcare provider.
- For more information about TRULICITY Single-Dose Pen, visit our website at: www.trulicity.com.

Scan this code to launch
www.trulicity.com

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

Eli Lilly and Company
Indianapolis, IN 46285, USA
US License Number 1891
TRULICITY is a registered trademark of Eli Lilly and Company.

The TRULICITY Pen meets the current dose accuracy and functional requirements of ISO 11608-1:2012 and 11608-5:2012.

Approved: 09/2020

TRU3MG-0001-IFU-202009

BREAK SEAL

BREAK SEAL

Instructions for Use

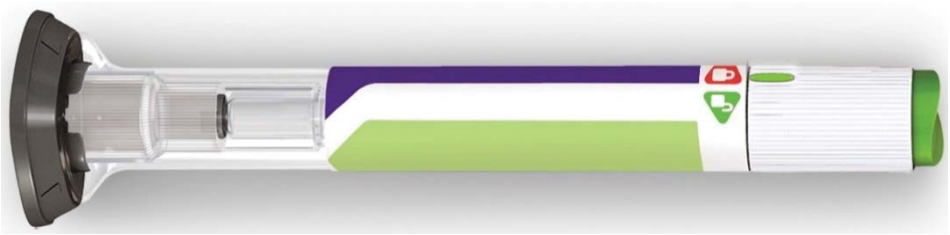
TRULICITY® (TRU-li-si-tee)

(dulaglutide)

injection, for subcutaneous use

4.5 mg/0.5 mL Single-Dose Pen

use 1 time each week (once weekly)



←Unfold and lay flat→

Read both sides for full instructions

Information About TRULICITY Single-Dose Pen

Please read this Instructions for Use and the Medication Guide carefully and completely before using your TRULICITY Single-Dose Pen. Talk to your healthcare provider about how to inject TRULICITY the right way.

- TRULICITY Single-Dose Pen (Pen) is a disposable, prefilled medicine delivery device. Each Pen contains 1 dose of TRULICITY (4.5 mg/0.5 mL). Each Pen should only be used 1 time.
- **TRULICITY is used 1 time each week.** You may want to mark your calendar to remind you when to take your next dose.

Before You Get Started

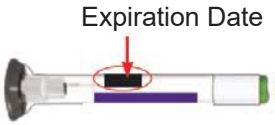
Remove

Remove the Pen from the refrigerator.

Leave the Base Cap on until you are ready to inject.

Check

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



Inspect

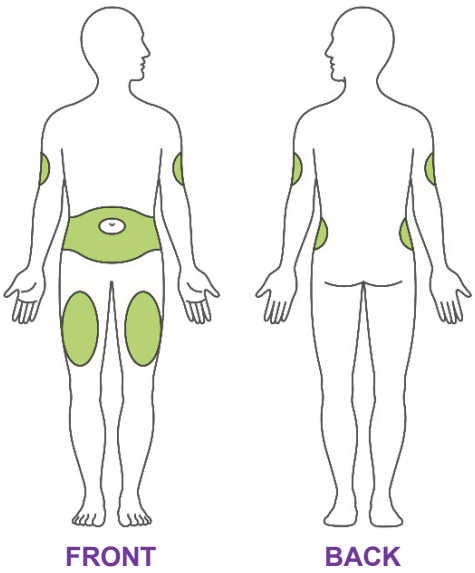
Check the Pen to make sure that it is not damaged and inspect the medicine to make sure it is not cloudy, discolored or has particles in it.

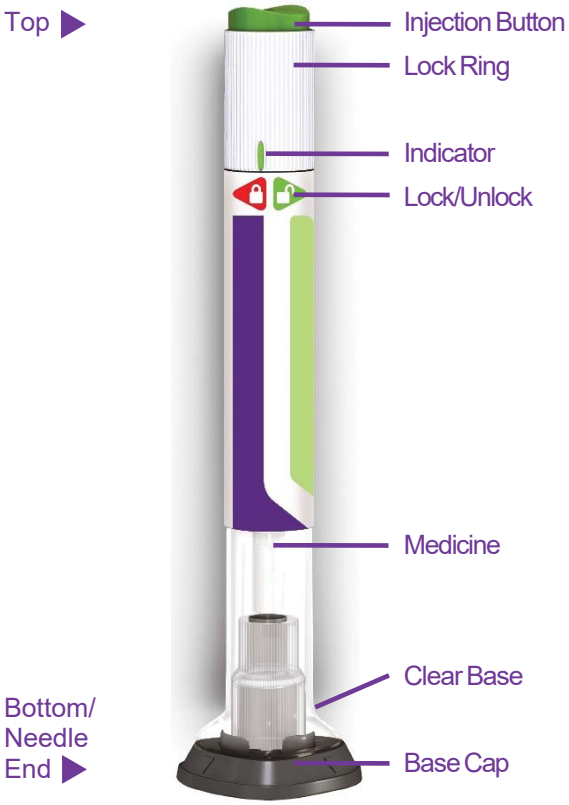
Prepare

Wash your hands.

Choose Your Injection Site

- Your healthcare provider can help you choose the injection site that is best for you.
- You may inject the medicine into your stomach (abdomen) or thigh.
- Another person may give you the injection in 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.




Top
Injection Button
Lock Ring
Indicator
Lock/Unlock
Medicine
Clear Base
Bottom/
Needle
End
Base Cap

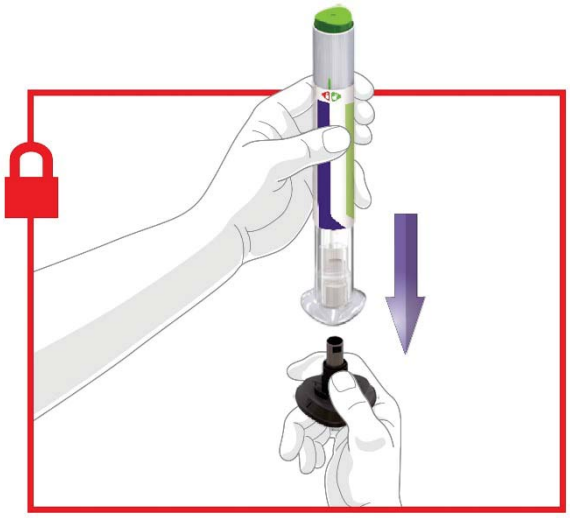
Step 1 Uncap the Pen

Make sure the Pen is **locked**.

- Pull the Base Cap straight off and throw it away in your household trash.

  Do not put the Base Cap back on — this could damage the needle.

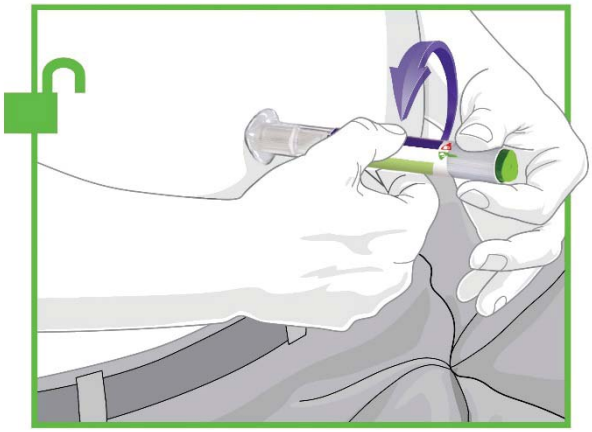
  Do not touch the needle.



Step 2 Place and Unlock

- Place the Clear Base flat and firmly against your skin at the injection site.

Unlock by turning the Lock Ring.

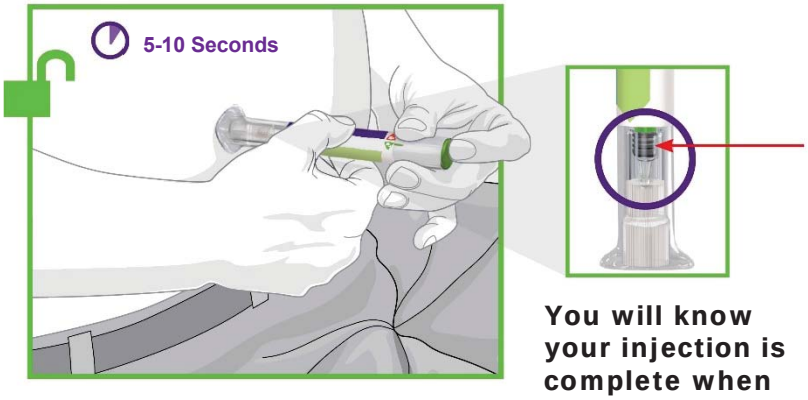


Step 3 Press and Hold

- Press and hold the green Injection Button. You will hear a loud click.

Continue holding the Clear Base firmly against your skin until you hear a second click. This happens when the needle starts retracting in about 5-10 seconds.

- Remove the Pen from your skin.



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

Important Information

Disposal of Pen

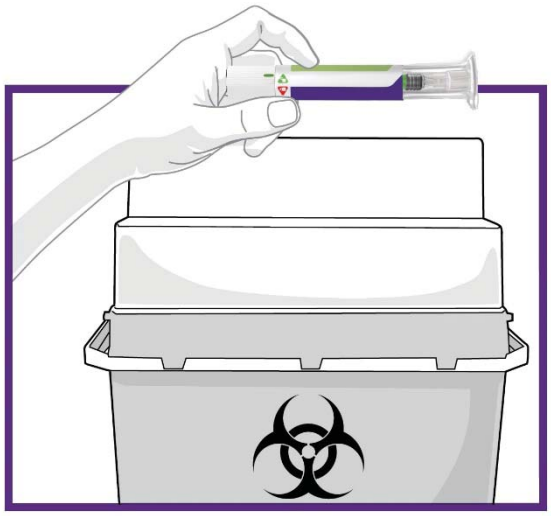
Storage and Handling

Commonly Asked Questions

Other Information

Where to Learn More

Disposing of Your Used Pens



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- If you do not have a 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,
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  - properly labeled to warn of hazardous waste inside the container.
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- **Do not** recycle your used sharps disposal container.

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 below 86°F (30°C) for a total of 14 days.
- Do not freeze your Pen. If the Pen has been frozen, throw the Pen away and use a new Pen.
- Storage of your Pen in the original carton is recommended. Protect your Pen from direct heat and light.
- The Pen has glass parts. Handle it carefully. If you drop it on a hard surface, do not use it. Use a new Pen for your injection.
- Keep your TRULICITY Pen and all medicines out of the reach of children.

Commonly Asked Questions

What if I see air bubbles in my Pen?

Air bubbles are normal.

What if I unlock the Pen and press the green Injection Button before pulling off the Base Cap?

Do not remove the 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 Base Cap?

A drop of liquid on the tip of the needle is normal.

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 and firm against your skin.

I heard more than 2 clicks during my injection—2 louder 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 louder click.

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

This is normal.

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 *(see step 3)*. Also 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.

Other Information

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

Where to Learn More

- If you have any questions or problems with your TRULICITY Single-Dose Pen, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) or call your healthcare provider.
- For more information about TRULICITY Single-Dose Pen, visit our website at: www.trulicity.com.

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Eli Lilly and Company
Indianapolis, IN 46285, USA
US License Number 1891
TRULICITY is a registered trademark of Eli Lilly and Company.

The TRULICITY Pen meets the current dose accuracy and functional requirements of ISO 11608-1:2012 and 11608-5:2012.

Approved: 09/2020

TRU4.5MG-0001-IFU-202009

Exhibit C

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 prescribing 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)]*.

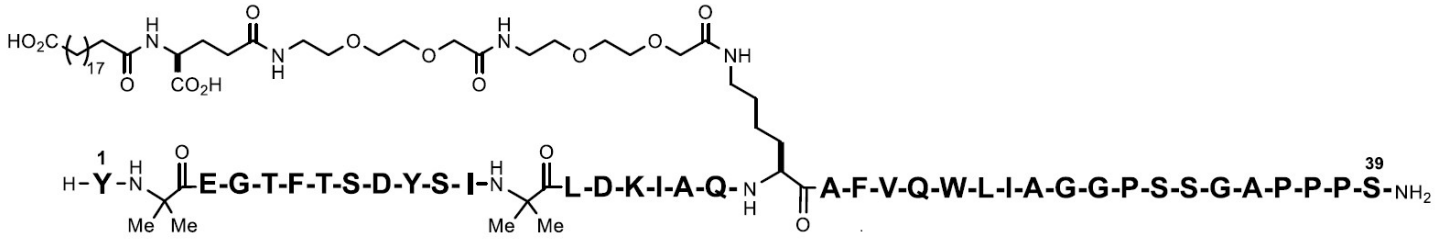
10 OVERDOSAGE

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.

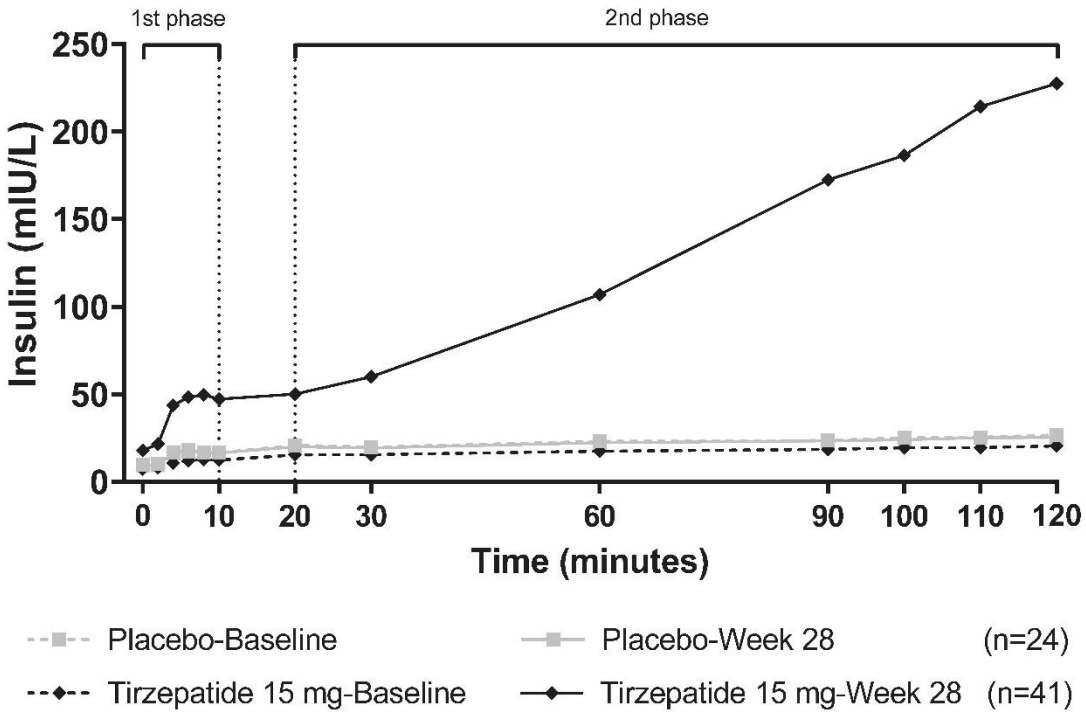
12.2 Pharmacodynamics

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 ($AUC_{0\text{-}24hr}$) 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.

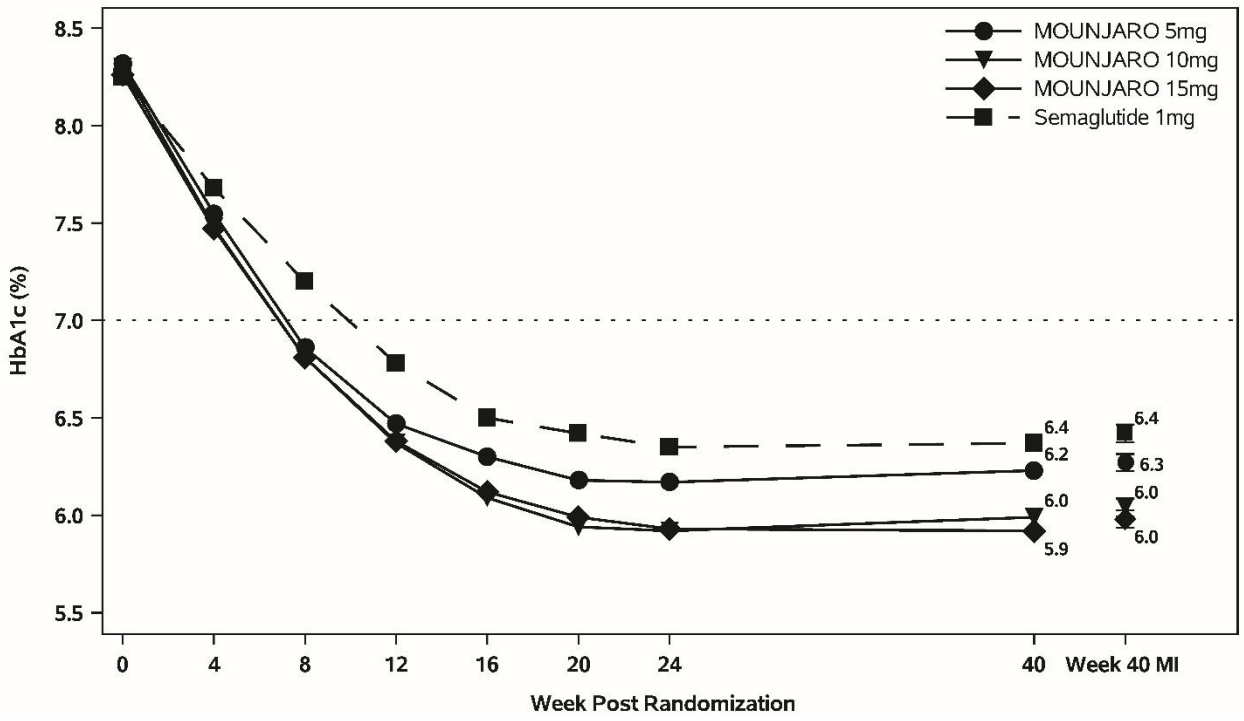
[c] p<0.05 (two-sided) for superiority vs. semaglutide, adjusted for multiplicity.

[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.

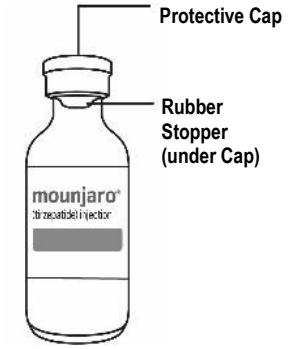
- MOUNJARO is a single-dose vial.
- MOUNJARO is used 1 time each week.
- Inject under the skin (subcutaneously) only.
- You or another person may inject into your stomach (abdomen) or thigh.
- Another person can inject into the back of your upper arm.

Gather supplies needed to give your injection

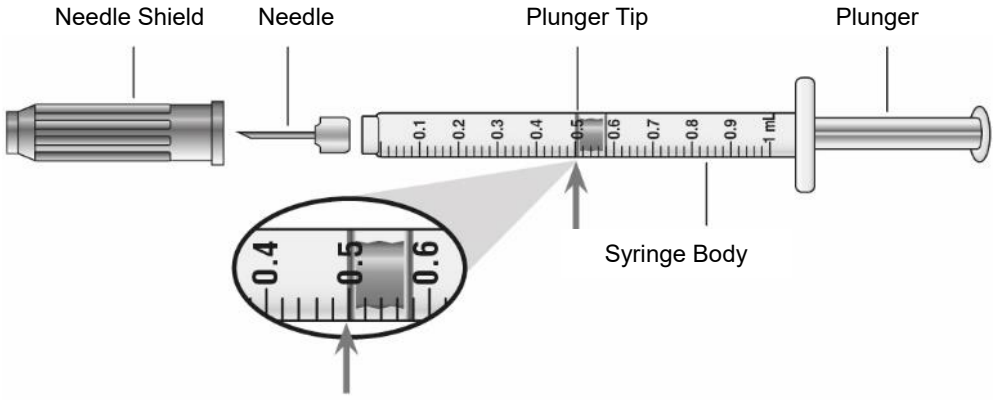
- 1 single-dose MOUNJARO vial
- 1 syringe and 1 needle, supplied separately (for example, use a 1 mL syringe and needle as recommended by your healthcare provider)
- 1 alcohol swab
- gauze
- 1 sharps container for throwing away used needles and syringes. **See** “Disposing of used needles and syringes”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

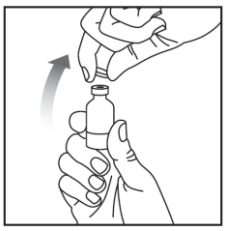
Check the vial label to make sure you have the right medicine and dose, and that it has not expired.

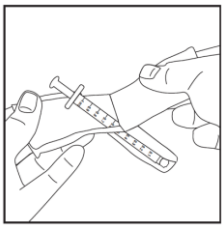
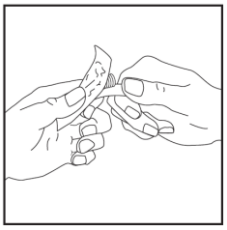
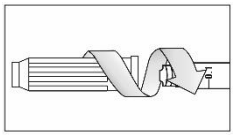
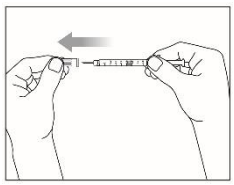
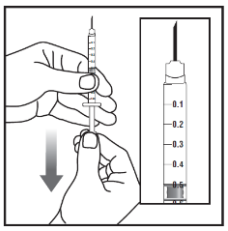
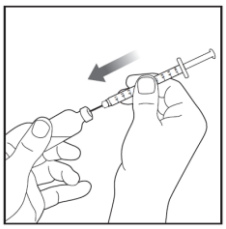
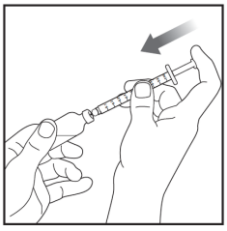
Make sure the medicine:

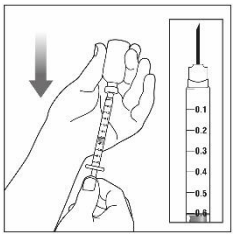
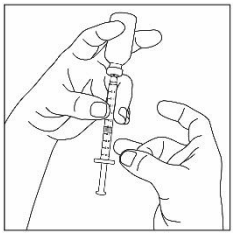
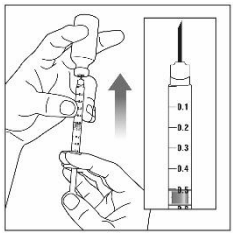
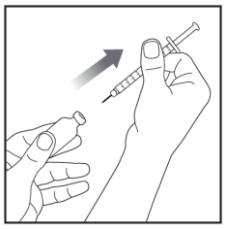
- is not frozen
- is colorless to slightly yellow
- is not cloudy
- does not have particles

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.

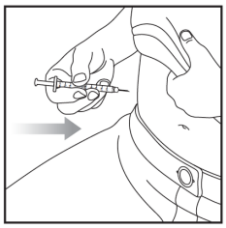
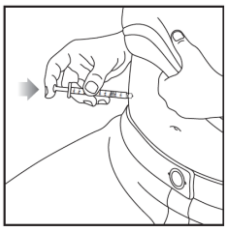
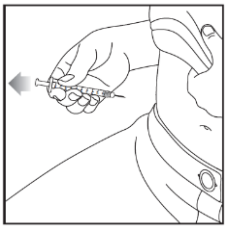
Step 1: Pull off the plastic protective cap. **Do not** remove the rubber stopper.	
Step 2: Wipe the rubber stopper with an alcohol swab.	

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.

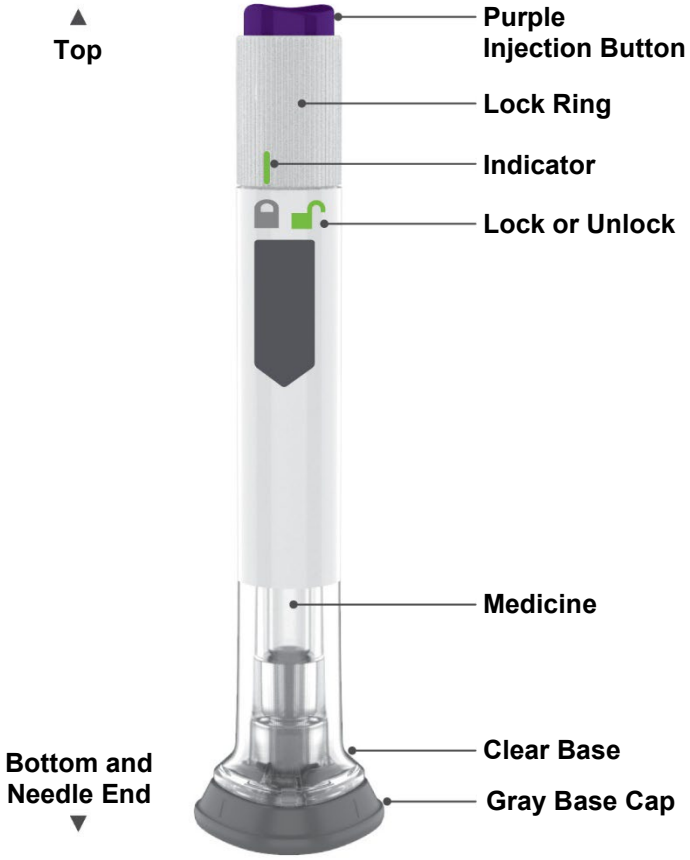
Talk to your healthcare provider about how to inject MOUNJARO the right way.

- 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



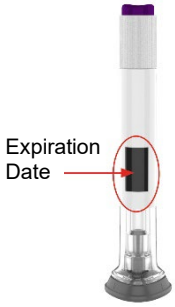
Preparing to inject MOUNJARO

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.



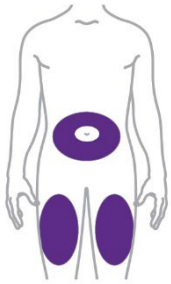
Make sure the medicine:

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

Wash your hands.

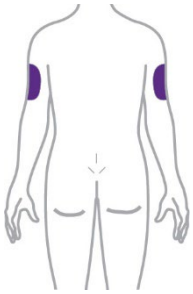
Step 1

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.



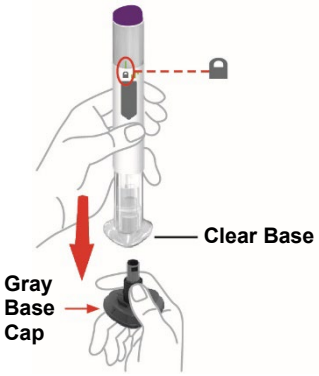
Another person should give you the injection in the back of your upper arm.

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.

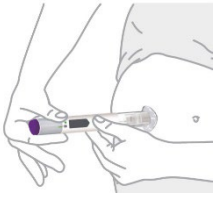
Pull the gray base cap straight off and throw it away in your household trash.

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

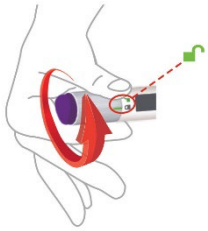
Do not touch the needle.

Step 3

Place clear base on skin, then unlock

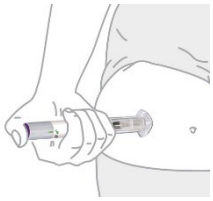


Place the clear base flat against your skin at the injection site.



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.

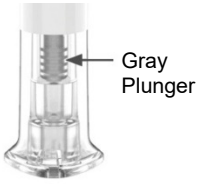
Do I need to hold the injection button down until the injection is complete?

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

MOUNJARO is a trademark of Eli Lilly and Company.

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

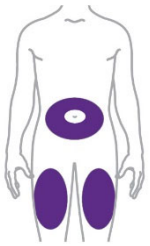
MOU-0001-IFU-YYYYMMDD

Quick Reference Guide

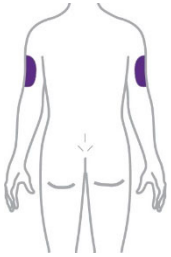
These are not complete instructions. Read the full INSTRUCTIONS FOR USE.

Step
1 Choose your injection site

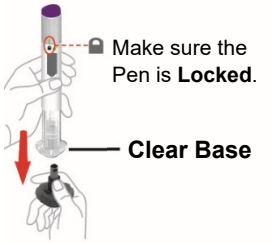
You or another person can inject the medicine in your stomach (abdomen) or thigh.



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



Step
2 Pull off the gray base cap

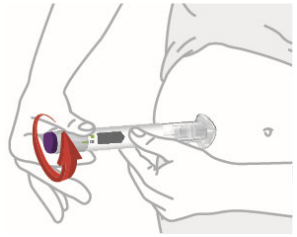


Pull the gray base cap straight off and throw it away in your household trash.

Do not put the gray base cap back on.

Do not touch the needle.

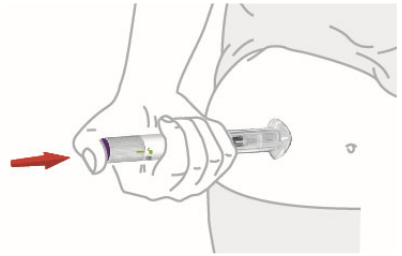
Step
3 Place clear base on skin, then unlock



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:

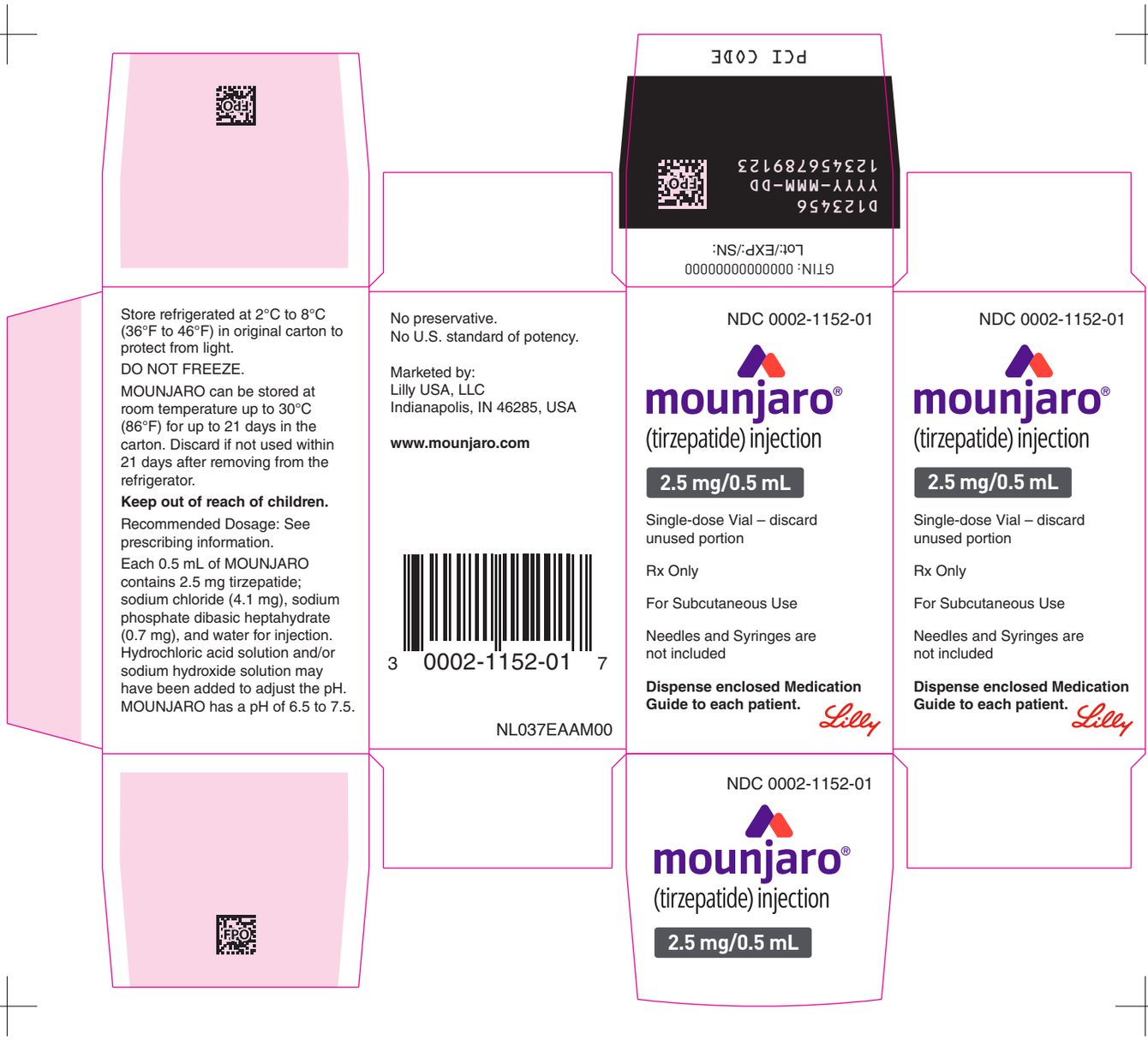
- First click = injection started
- Second click = injection completed

Injection is complete when you see the gray plunger.

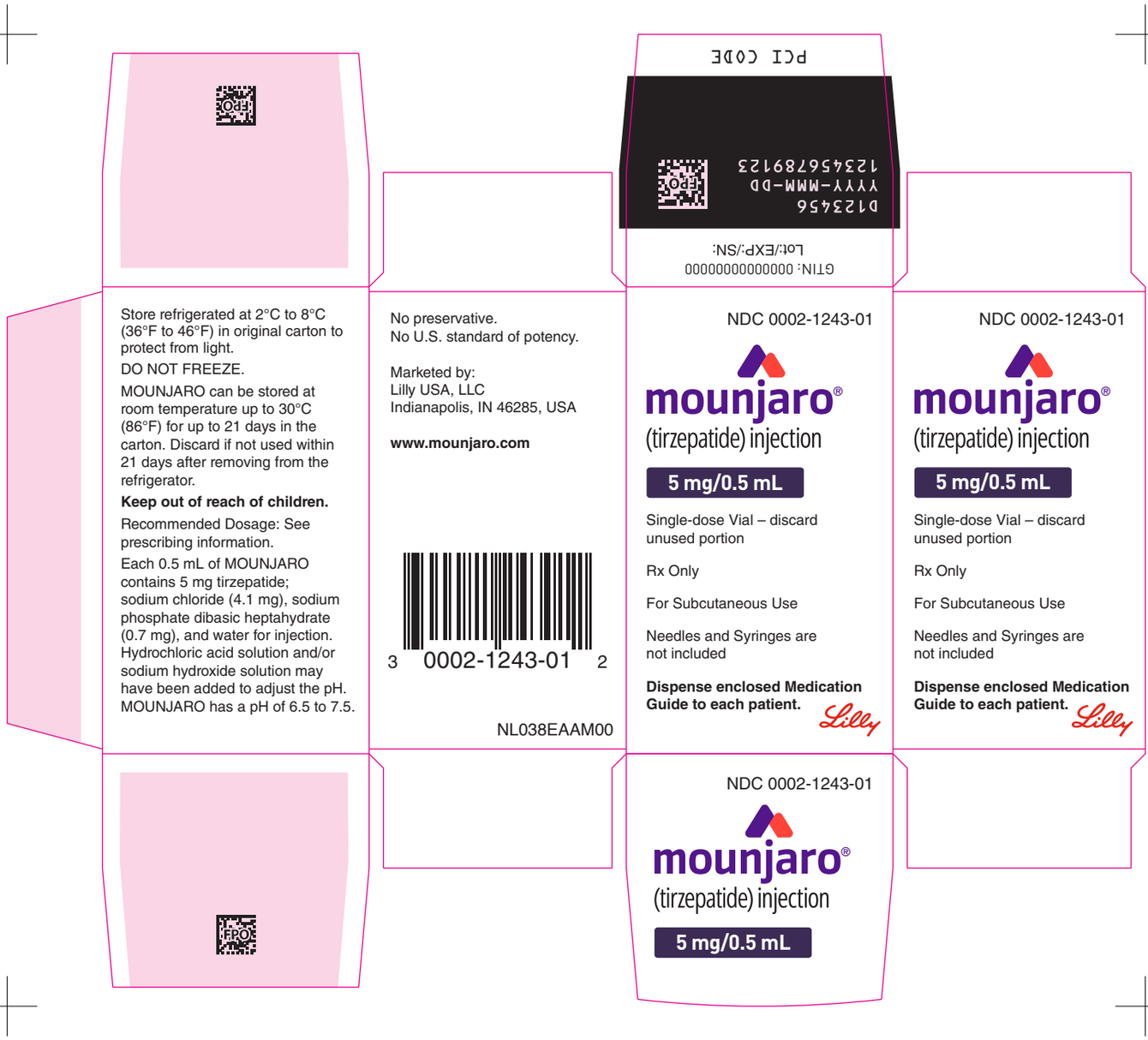
After your injection

Place the used Pen in a sharps container.

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



PPD Information Box		ALRP Information Box
Technical Information: Black, Cool Gray 11, Warm Red, 485, 2597 — DIE CUT, COATING FREE		**Translations of Variable Data** Lot: Lot: Exp Date: EXP: Mfg Date: N/A Price: N/A GTIN: N/A Serial Number : SN:
Previous Item Code *(to be destroyed)* N/A		**Serialization Information** Type: N/A Code: N/A
Lilly		



PPD Information Box			ALRP Information Box	
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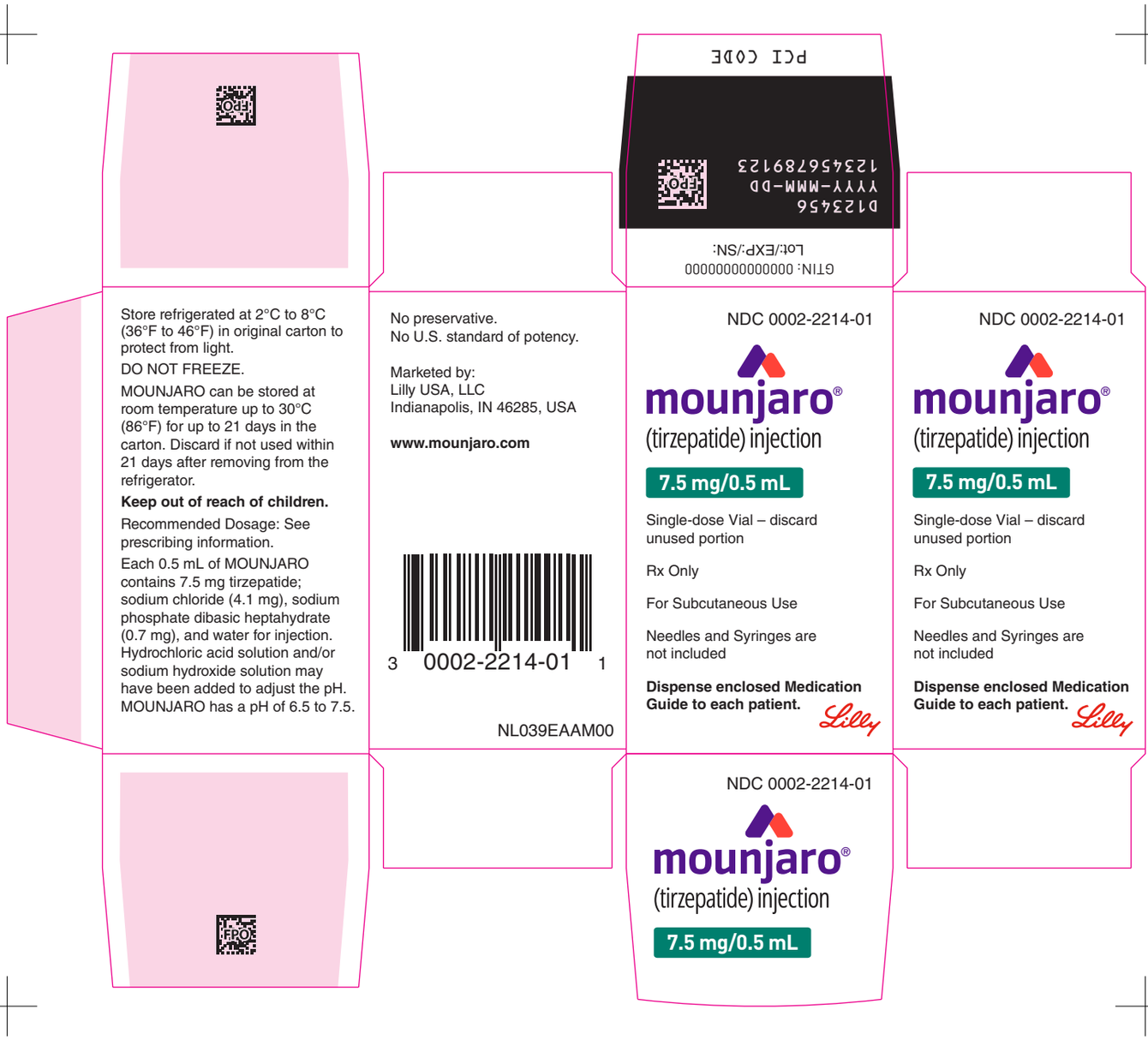
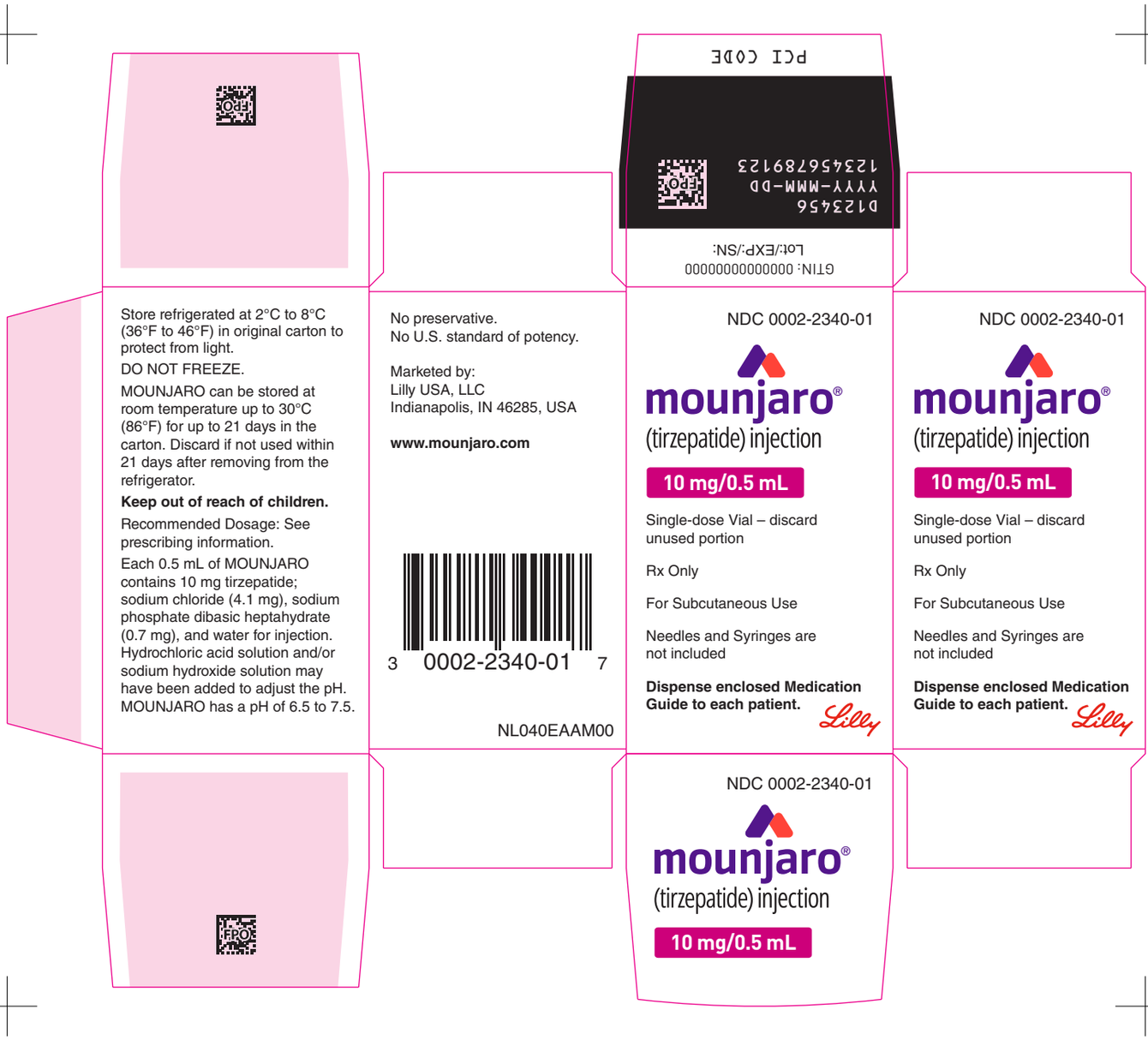
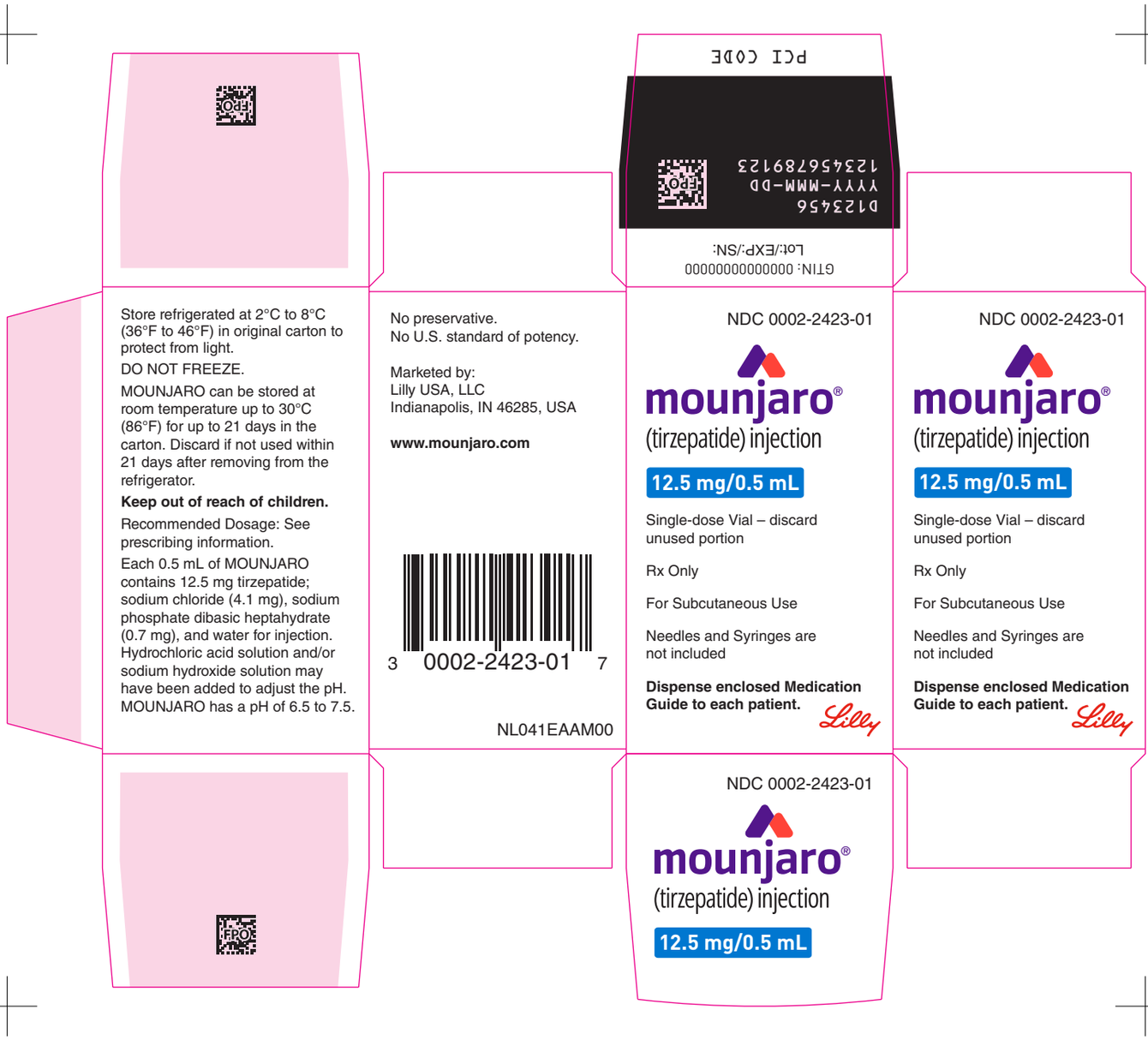
Previous Item Code *(to be destroyed)* N/A			**Serialization Information** Type: N/A Code: N/A	



PPD Information Box			ALRP Information Box	
Technical Information:	Black Warm Red 485 569 2597	DIE CUT COATING FREE	**Translations of Variable Data**	Lot: Lot: Exp Date: EXP: Mfg Date: N/A Price: N/A GTIN: N/A Serial Number : SN:
Previous Item Code *(to be destroyed)* N/A			**Serialization Information** Type: N/A Code: N/A	



PPD Information Box			ALRP Information Box	
Technical Information:	Black Warm Red 233 485 2597	DIE CUT COATING FREE	**Translations of Variable Data**	Lot: Exp Date: Mfg Date: Price: GTIN: Serial Number :
				Lot: EXP: N/A N/A N/A SN:
Previous Item Code *(to be destroyed)* N/A			**Serialization Information** Type: N/A Code: N/A	
Lilly				



PPD Information Box			ALRP Information Box
Technical Information:	Black Warm Red 485 2195 2597	DIE CUT COATING FREE	**Translations of Variable Data** Lot: Lot: Exp Date: EXP: Mfg Date: N/A Price: N/A GTIN: N/A Serial Number : SN:
Previous Item Code *(to be destroyed)* N/A			**Serialization Information** Type: N/A Code: N/A
Lilly			

PPD Information Box			ALRP Information Box
Technical Information:	Black Warm Red 485 2597	DIE CUT COATING FREE	**Translations of Variable Data** Lot: Lot: Exp Date: EXP: Mfg Date: N/A Price: N/A GTIN: N/A Serial Number : SN:
Previous Item Code *(to be destroyed)* N/A			**Serialization Information** Type: N/A Code: N/A
			Lilly

PPD Information Box		ALRP Information Box
Technical Information: Black; 485; Cool Gray 11; 2597; SCREEN WHITE; ☐ DIE CUT; COATING FREE		**Translations of Variable Data** Lot: Lot Exp Date: Exp Date Mfg Date: N/A Price: N/A GTIN: N/A Serial Number : N/A
Previous Item Code *(to be destroyed)* N/A		**Serialization Information** Type: N/A Code: N/A
Lilly		

PPD Information Box	ALRP Information Box
Technical Information: Black; 485; 669; 2597; SCREEN WHITE; ☐ DIE CUT; ☐ COATING FREE	**Translations of Variable Data** Lot: Lot Exp Date: Exp Date Mfg Date: N/A Price: N/A GTIN: N/A Serial Number : N/A
Previous Item Code *(to be destroyed)* N/A	**Serialization Information** Type: N/A Code: N/A
Lilly	

PPD Information Box			ALRP Information Box	
Technical Information:	Black 485 569 2597 SCREEN WHITE	DIE CUT COATING FREE	**Translations of Variable Data**	
			Lot:	Lot
			Exp Date:	Exp Date
			Mfg Date:	N/A
			Price:	N/A
			GTIN:	N/A
			Serial Number :	N/A
Previous Item Code *(to be destroyed)* N/A			**Serialization Information** Type: N/A Code: N/A	

PPD Information Box	ALRP Information Box
Technical Information: Black 485 233 2597 SCREEN WHITE DIE CUT COATING FREE	**Translations of Variable Data** Lot: Lot Exp Date: Exp Date Mfg Date: N/A Price: N/A GTIN: N/A Serial Number : N/A
Previous Item Code *(to be destroyed)* N/A	**Serialization Information** Type: N/A Code: N/A
Lilly	

PPD Information Box	ALRP Information Box
Technical Information: Black; 485; 2195; 2597; SCREEN WHITE; ☐ DIE CUT; COATING FREE	**Translations of Variable Data** Lot: Lot Exp Date: Exp Date Mfg Date: N/A Price: N/A GTIN: N/A Serial Number : N/A
Previous Item Code *(to be destroyed)* N/A	**Serialization Information** Type: N/A Code: N/A
Lilly	

PPD Information Box	ALRP Information Box
Technical Information: Black 485 Warm Red 2597 SCREEN WHITE DIE CUT COATING FREE	**Translations of Variable Data** Lot: Lot Exp Date: Exp Date Mfg Date: N/A Price: N/A GTIN: N/A Serial Number : N/A
Previous Item Code *(to be destroyed)* N/A	**Serialization Information** Type: N/A Code: N/A
Lilly	

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

CERTIFICATE OF SERVICE

I hereby certify that on April 9, 2024, a true and correct copy of the foregoing Position Statement of Defendants Novo Nordisk and Eli Lilly was electronically filed using the Court's CM/ECF System, which will send notification of such filing to all counsel of record.

/s/ Loren H. Brown
Loren H. Brown