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)	2/2020
Warnings and Precautions, Diabetic Retinopathy (5.7)	2/2020

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

TRULICITY® is a 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.
- 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 another antidiabetic therapy (1.1, 5.2).
- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis (1.1).
- Not for patients with pre-existing severe gastrointestinal disease (1.1, 5.6).

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

- Administer once weekly at any time of day (2.1).
- Inject subcutaneously in the abdomen, thigh, or upper arm (2.1).
- Initiate at 0.75 mg subcutaneously once weekly. Dose can be increased to 1.5 mg once weekly for additional glycemic control (2.1).
- 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 (2.1).

----------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)

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

- TRULICITY is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4, 5.1).
- TRULICITY is contraindicated in patients with a prior serious hypersensitivity reaction to TRULICITY 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. Consider other antidiabetic therapies in patients with history of pancreatitis (5.2).
- *Hypoglycemia:* When TRULICITY is used with an insulin secretagogue (e.g., a sulfonylurea) or insulin, consider lowering the dose of the sulfonylurea or insulin to reduce the risk of hypoglycemia (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).

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

The most common adverse reactions, reported in ≥5% of patients treated with TRULICITY 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 ----------

TRULICITY slows gastric emptying and may impact absorption of concomitantly administered oral medications (7.1, 12.3).

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

- Pregnancy: TRULICITY should be used during pregnancy only if the potential benefit justifies the potential risk to fetus (8.1).
- Renal Impairment: No dosage adjustment recommended. Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions (5.5, 8.7).

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

Revised: 02/2020

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 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.

1.1 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.
- TRULICITY should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. TRULICITY is not a substitute for insulin.
- TRULICITY has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis. The use of TRULICITY is not recommended in patients with pre-existing severe gastrointestinal disease *[see Warnings and Precautions (5.6)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

The recommended initiating dose of TRULICITY is 0.75 mg once weekly. The dose may be increased to 1.5 mg once weekly for additional glycemic control. The maximum recommended dose is 1.5 mg once weekly.

Administer TRULICITY once weekly, any time of day, with or without food. TRULICITY should be injected subcutaneously in the abdomen, thigh, or upper arm.

If a dose is missed, instruct patients to administer 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.

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

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

2.3 Important Administration Instructions

Prior to initiation of TRULICITY, patients should be trained by their healthcare professional on proper injection technique. Training reduces the risk of administration errors such as improper injection site, needle sticks, and incomplete

dosing. Refer to the accompanying Instructions for Use for complete administration instructions with illustrations. The instructions can also be found at www.trulicity.com.

When using TRULICITY with insulin, instruct patients to administer as separate injections and to never mix the products. It is acceptable to inject TRULICITY and insulin in the same body region but the injections should not be adjacent to each other.

When injecting in the same body region, advise patients to use a different injection site each week. TRULICITY must not be administered intravenously or intramuscularly.

TRULICITY solution should be visually inspected for particulate matter and discoloration prior to administration.

3 DOSAGE FORMS AND STRENGTHS

- Injection: 0.75 mg/0.5 mL solution in a single-dose pen
- Injection: 1.5 mg/0.5 mL solution in a single-dose pen

4 CONTRAINDICATIONS

- **Medullary Thyroid Carcinoma**

TRULICITY 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)]*.

- **Hypersensitivity**

TRULICITY is contraindicated in patients with a prior 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 the phase 3 clinical program. 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 Phase 2 and Phase 3 clinical 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).

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. 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

The risk of hypoglycemia is increased when TRULICITY is used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin. Patients may require a lower dose of sulfonylurea or insulin to reduce the risk of hypoglycemia in this setting *[see Dosage and Administration (2.2), Adverse Reactions (6.1)]*.

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 (6.3)]*. If a hypersensitivity reaction occurs, discontinue TRULICITY; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity reaction to TRULICITY *[see Contraindications (4)]*.

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 (8.7)]*.

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 1.0%, placebo 1.0%).

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.

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)]*

6.1 Clinical Studies 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.

Pool of Placebo-controlled Trials

The data in Table 1 are derived from placebo-controlled trials *[see Clinical Studies (14)]*.

These data reflect exposure of 1670 patients to TRULICITY and a mean duration of exposure to TRULICITY of 23.8 weeks. Across the treatment arms, the mean age of patients was 56 years, 1% were 75 years or older and 53% were male. The population in these studies 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 8.0 years and had a mean HbA1c of 8.0%. At baseline, 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 96.0% of the pooled study populations.

Table 1 shows common adverse reactions, excluding hypoglycemia, associated with the use of TRULICITY in a pool of placebo-controlled trials. These adverse reactions were not present at baseline, occurred more commonly on TRULICITY than on placebo, and occurred in at least 5% of patients treated with TRULICITY.

Table 1: Adverse Reactions in Placebo-Controlled Trials Reported in ≥5% of TRULICITY-Treated Patients

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 adverse reactions occurred more frequently among patients receiving TRULICITY than placebo (placebo 21.3%, 0.75 mg 31.6%, 1.5 mg 41.0%). More patients receiving TRULICITY 0.75 mg (1.3%) and TRULICITY 1.5 mg (3.5%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.2%). Investigators graded the severity of gastrointestinal adverse reactions occurring on 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.

In addition to the reactions in Table 1, the following adverse reactions were reported more frequently in TRULICITY-treated patients than placebo (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%).

Pool of Placebo- and Active-Controlled Trials

The occurrence of adverse reactions was also evaluated in a larger pool of patients with type 2 diabetes participating in 6 placebo- and active-controlled trials evaluating the use of TRULICITY as monotherapy and add-on therapy to oral medications or insulin *[see Clinical Studies (14)]*. In this pool, a total of 3342 patients with type 2 diabetes were treated with TRULICITY for a mean duration of 52 weeks. The mean age of patients was 56 years, 2% were 75 years or older and 51% were male. The population in these studies was 71% White, 7% Black or African American, 11% Asian; 32% were of Hispanic or Latino ethnicity. At baseline, the population had diabetes for an average of 8.2 years and had a mean HbA1c of 7.6-8.5%. At baseline, 5.2% of the population reported retinopathy. Baseline estimated renal function was normal or mildly impaired (eGFR ≥60 mL/min/1.73 m^2) in 95.7% of the TRULICITY population.

In the pool of placebo- and active-controlled trials, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed in Table 1.

Other Adverse Reactions

Hypoglycemia

Table 2 summarizes the incidence of hypoglycemia in the placebo-controlled clinical studies: 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 2: Incidence (%) of Hypoglycemia 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 *[see Warnings and Precautions (5.3)]*. In a 78-week 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 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 2 for the incidence of hypoglycemia in patients treated in combination with basal insulin glargine.

Cholelithiasis and Cholecystitis

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.

Heart Rate Increase and Tachycardia-Related Adverse Reactions

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 patients on TRULICITY in the four Phase 2 and five Phase 3 studies.

Injection-site Reactions

In the placebo-controlled studies, 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 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

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%.

6.2 Immunogenicity

Across four Phase 2 and five Phase 3 clinical studies, 64 (1.6%) TRULICITY-treated patients developed anti-drug antibodies (ADAs) to the active ingredient in TRULICITY (i.e., dulaglutide).

Of the 64 dulaglutide-treated patients that developed dulaglutide ADAs, 34 patients (0.9% of the overall population) had dulaglutide-neutralizing antibodies, and 36 patients (0.9% of the overall population) developed antibodies against native GLP-1.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to dulaglutide cannot be directly compared with the incidence of antibodies of other products.

6.3 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.

- Anaphylactic reactions, angioedema *[see Contraindications (4), Warnings and Precautions (5.4), Patient Counseling Information (17)]*.
- Acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis *[see Warnings and Precautions (5.5) and Patient Counseling Information (17)]*.

7 DRUG INTERACTIONS

7.1 Oral Medications

TRULICITY slows gastric emptying and thus has the potential to reduce the rate of absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with TRULICITY. Drug levels of oral medications with a narrow therapeutic index should be adequately monitored when concomitantly administered with TRULICITY. In clinical pharmacology studies, TRULICITY did not affect the absorption of the tested, orally administered medications to a clinically relevant degree *[see Clinical Pharmacology (12.3)]*.

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 14-times human exposure at the maximum recommended human dose (MRHD) of 1.5 mg/week. In pregnant rabbits administered dulaglutide during organogenesis, major fetal abnormalities occurred at 13-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, stillbirth 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 4-, 14-, and 44-times human exposure at the maximum recommended human dose (MRHD) of 1.5 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 1-, 4-, and 13-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 2-, 4-, and 16-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

Safety and effectiveness of TRULICITY have not been established in pediatric patients. TRULICITY is not recommended for use in pediatric patients younger than 18 years.

8.5 Geriatric Use

In the glycemic control trials *[see Adverse Reactions (6.1)]*, 620 (18.6%) TRULICITY-treated patients were 65 years of age or older and 65 (1.9%) TRULICITY-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.

In the TRULICITY 1.5 mg treatment arm of the REWIND trial *[see Clinical Studies (14.2)]*, a total of 2619 (52.9%) patients were 65 years of age or older, and 484 (9.8%) patients were 75 years of age or older at baseline. No overall differences in safety or efficacy were observed based on age.

8.6 Hepatic Impairment

There is limited clinical experience in patients with mild, moderate, or severe hepatic impairment. Therefore, TRULICITY should be used with caution in these patient populations.

In a clinical pharmacology study in subjects with varying degrees of hepatic impairment, no clinically relevant change in dulaglutide pharmacokinetics (PK) was observed *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

In four Phase 2 and five Phase 3 randomized clinical studies, at baseline, 50 (1.2%) TRULICITY-treated patients had mild renal impairment (eGFR ≥60 but <90 mL/min/1.73 m^2), 171 (4.3%) TRULICITY-treated patients had moderate renal impairment (eGFR ≥30 but <60 mL/min/1.73 m^2), and no TRULICITY-treated patients had severe renal impairment (eGFR <30 mL/min/1.73 m^2). In a 52-week clinical trial, 270 (71%) TRULICITY-treated patients had moderate renal impairment (eGFR ≥ 30 but <60 mL/min/1.73 m^2) and 112 (29%) TRULICITY-treated patients had severe renal impairment (eGFR ≥ 15 but <30 mL/min/1.73 m^2) *[see Clinical Studies (14.1)]*. No overall differences in safety or effectiveness were observed in this study.

In the TRULICITY 1.5 mg arm of the REWIND trial *[see Clinical Studies (14.2)]*, 2435 (50.2%) patients had mild renal impairment, 1031 (21.2%) patients had moderate renal impairment, and 50 (1.0%) patients had severe renal impairment at baseline. No overall differences in safety or efficacy were observed between patients with moderate to severe renal impairment (eGFR <60 mL/min/1.73 m^2) and patients with mild or no renal impairment (eGFR ≥60 mL/min/1.73 m^2).

In a clinical pharmacology study in subjects with renal impairment, including end-stage renal disease (ESRD), no clinically relevant change in dulaglutide PK was observed. In the 52-week Phase 3 study 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. There is limited clinical experience in patients with ESRD. TRULICITY should be used with caution in patients with ESRD *[see Warning and Precautions (5.5), Clinical Pharmacology (12.3)]*.

8.8 Gastroparesis

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

TRULICITY contains dulaglutide, a human 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 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 is a clear, colorless, sterile solution. Each 0.5 mL of TRULICITY solution contains 0.75 mg or 1.5 mg of dulaglutide. Each single-dose pen contains 0.5 mL of solution and the following excipients: citric acid anhydrous (0.07 mg), mannitol (23.2 mg), polysorbate 80 (0.10 mg), 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 adults 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 Phase 3 monotherapy study. In the same study, 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 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 supratherapeutic doses of 4 and 7 mg.

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 multiple-dose administration of 1.5 mg to steady state, the mean peak plasma concentration (C_{max}) and total systemic exposure (AUC) of dulaglutide were 114 ng/mL (range 56 to 231 ng/mL) and 14,000 ng*h/mL (range 6940 to 26,000 ng*h/mL), respectively; 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.

Distribution – The mean volumes of distribution after subcutaneous administration of TRULICITY 0.75 mg and 1.5 mg to steady state were approximately 19.2 L (range 14.3 to 26.4 L) and 17.4 L (range 9.3 to 33 L), respectively.

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

Elimination – The mean apparent clearance at steady state of dulaglutide is approximately 0.111 L/h for the 0.75 mg dose, and 0.107 L/h for the 1.5 mg dose. The elimination half-life of dulaglutide for both doses is approximately 5 days.

Specific Populations

No dose adjustment of dulaglutide is needed based on age, gender, race, ethnicity, body weight, or renal or hepatic impairment. The effects of intrinsic factors on the PK of dulaglutide are shown in Figure 1.

- Inform patients that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and HbA1c levels, with a goal of decreasing these levels towards the normal range. HbA1c is especially useful for evaluating long-term glycemic control.

Eli Lilly and Company, Indianapolis, IN 46285, USA

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