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 ----------

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions (5.4) 08/2017

---------- 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.

Limitations of Use:

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise (1.1, 5.1).
- Has not been studied in patients with a history of pancreatitis. Consider another antidiabetic therapy (1, 5.2).
- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Not for patients with pre-existing severe gastrointestinal disease.

----------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 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)
- Injection: 0.75 mg/0.5 mL solution in a single-dose prefilled syringe (3)
- Injection: 1.5 mg/0.5 mL solution in a single-dose prefilled syringe (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).
- *Macrovascular outcomes:* There have been no studies establishing conclusive evidence of macrovascular risk reduction with TRULICITY (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 ----------

Dulaglutide 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: 06/2018

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.

1.1 Limitations of Use

- TRULICITY is not recommended as a first-line therapy for patients who have inadequate glycemic control on diet and exercise because of the uncertain relevance of rodent C-cell tumor findings to humans. Prescribe TRULICITY only to patients for whom the potential benefits outweigh the potential risk *[see Warnings and Precautions (5.1)]*.
- 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
- Injection: 0.75 mg/0.5 mL solution in a single-dose prefilled syringe
- Injection: 1.5 mg/0.5 mL solution in a single-dose prefilled syringe

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 (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. This patient had pretreatment calcitonin levels approximately 8 times the upper limit of normal (ULN). 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 value 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. 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 (6.2)]*. 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 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with TRULICITY.

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)]*

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 the 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 ≥60mL/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 the 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 documented symptomatic (≤70 mg/dL glucose threshold) and severe hypoglycemia in the placebo-controlled clinical studies.

Table 2: Incidence (%) of Documented Symptomatic and Severe Hypoglycemia Adverse Reactions 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**
Documented symptomatic	1.1%	2.6%	5.6%
Severe	0	0	0
Add-on to Metformin + Pioglitazone			
(26 weeks)	**N=141**	**N=280**	**N=279**
Documented symptomatic	1.4%	4.6%	5.0%
Severe	0	0	0
Add-on to Glimepiride			
(24 weeks)	**N=60**	-	**N=239**
Documented symptomatic	1.7%	-	11.3%
Severe	0	-	0
In Combination with Insulin Glargine ± Metformin			
(28 weeks)	**N=150**	-	**N=150**
Documented symptomatic	30.0%	-	35.3%

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