PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

WARNING: RISK OF THYROID C-CELL TUMOURS

- **In males and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumours (adenomas and carcinomas) after lifetime exposure. It is unknown whether TRULICITY causes thyroid C-cell tumours, including medullary thyroid carcinoma (MTC), in humans as human relevance of dulaglutide-induced rodent thyroid C-cell tumours has not been determined (see section 4.4).**

- **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 tumours (e.g. mass in the neck, dysphagia, dyspnoea, 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 sections 4.3 and 4.4).**

1. NAME OF THE MEDICINE

TRULICITY®

1,5 mg/0,5 mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-use pen contains 1,5 mg of dulaglutide in 0,5 mL solution.

Dulaglutide is produced in CHO cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless, sterile solution for subcutaneous injection.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TRULICITY is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus:

- as monotherapy
- in combination with other glucose-lowering medicines

TRULICITY is indicated 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.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

General

TRULICITY should be administered once weekly. The dose can be administered at any time of the day, with or without meals, and can be injected subcutaneously in the

abdomen, thigh or upper arm. TRULICITY should not be administered intravenously or intramuscularly. TRULICITY is for single use in one patient only. Discard the pen once the injection is completed.

Use in Adults (≥ 18 years)

The recommended dose of TRULICITY is 1,5 mg per week. Administer TRULICITY once weekly, at any time of day, independently of meals.

Use in the Elderly (≥ 65 years)

No dose adjustment is required based on age.

Use in Children and adolescents

The safety and effectiveness of TRULICITY have not been established in children and adolescents under 18 years of age.

Use in Renal Impairment

No dose adjustment is required in patients with mild (creatinine clearance 60 to < 90 mL/min), moderate (creatinine clearance 30 to < 60 mL/min) or severe (creatinine clearance < 30 mL/min to ≥ 15 mL/min not requiring dialysis) renal impairment.

There is limited experience in patients with end-stage renal disease (creatinine clearance < 15 mL/min requiring dialysis treatment), therefore TRULICITY cannot be recommended in this population (see 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic Properties).

Use in Hepatic Impairment

No dose adjustment is required based on hepatic impairment.

Missed dose

If a dose is missed, it should be administered 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, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.

Changing Weekly Dosage Schedule

The day of weekly administration can be changed, if necessary, as long as the last dose was administered 3 or more days (72 hours or more) before.

4.3 CONTRAINDICATIONS

TRULICITY is contraindicated in patients with:

- hypersensitivity to dulaglutide or to any of the excipients in TRULICITY (see section 6.1)
- a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) *(see section 4.4)*
- pancreatitis
- Type 1 Diabetes Mellitus
- diabetic ketoacidosis
- severe gastrointestinal disease including severe gastroparesis

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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. Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin (see section 4.2 and 4.3).

Risk of Thyroid C-cell Tumours:

In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumours (adenomas and carcinomas) after lifetime exposure (see section 5.3 PRECLINICAL SAFETY DATA). 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 tumours, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of dulaglutide-induced rodent thyroid C-cell tumours has not been determined.

One case of MTC was reported in a patient treated with TRULICITY in the phase 3 clinical studies. 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 long-term cardiovascular outcomes study (REWIND). Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the post-marketing 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 tumours (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.

Dehydration:

Dehydration, sometimes leading to acute renal failure or worsening renal impairment, has been reported in patients treated with TRULICITY, especially at the initiation of treatment. Many of the reported adverse renal events occurred in patients who had experienced nausea, vomiting, diarrhoea, or dehydration. Patients treated with TRULICITY should be advised of the potential risk of dehydration, particularly in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Severe gastrointestinal disease:

TRULICITY has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients. Events related to impaired gastric emptying, including severe gastroparesis, have been reported. Monitor and consider dose modification or discontinuation in patients who develop severe gastrointestinal symptoms while on treatment.

Aspiration in association with general anaesthesia or deep sedation:

Cases of pulmonary aspiration have been reported in patients receiving GLP-1 receptor agonists undergoing general anaesthesia or deep sedation. Therefore, the increased risk of residual gastric content due to delayed gastric emptying (see section 4.8) should be considered prior to performing procedures with general anaesthesia or deep sedation.

Acute pancreatitis:

Increased incidence of pancreatitis has been reported with use of TRULICITY. Patients should be informed of the characteristic symptoms of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, TRULICITY and other potentially suspect medicines should be discontinued until evaluation is complete.

If the diagnosis of pancreatitis is confirmed, TRULICITY should be permanently discontinued. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis (see section 4.8).

Hypoglycaemia:

Hypoglycaemia occurred commonly with TRULICITY when used as monotherapy and in combination with metformin plus pioglitazone and very commonly when TRULICITY was taken in combination with other hypoglycaemic medicines.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

TRULICITY causes a delay in gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology studies, TRULICITY did not affect the absorption of the orally administered medications tested to any clinically relevant degree (e.g. warfarin, metformin, lisinopril, metoprolol,

digoxin, paracetamol, norelgestromin, ethinyloestradiol, sitagliptin, atorvastatin). No dosage adjustments of concomitant medications are required.

As elimination of TRULICITY is presumed to be by proteolytic degradation into its amino acid components and is not anticipated to be eliminated intact in the urine or metabolised by cytochrome P450 enzymes, pharmacokinetic interactions with medicines primarily renally eliminated or metabolised by cytochrome P450 enzymes are not expected.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy: There are no or limited amount of data from the use of TRULICITY in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Therefore, the use of TRULICITY is not recommended during pregnancy.

Breastfeeding: It is unknown whether TRULICITY is excreted in human milk. A risk to newborns/infants cannot be excluded. TRULICITY should not be used during breastfeeding

Fertility: The effect of TRULICITY on fertility in humans is unknown. In the rat, there was no direct effect on mating or fertility following treatment with TRULICITY (see section 5.3).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

TRULICITY has no or negligible influence on the ability to drive or use machines. When it is used in combination with a sulphonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines (see section 4.4).

4.8 UNDESIRABLE EFFECTS

Summary of safety profile: In the completed phase II and phase III initial registration studies, 4 006 patients were exposed to TRULICITY alone or in combination with other glucose lowering medicines. The most frequently reported adverse reactions in clinical trials were gastrointestinal, including nausea, vomiting and diarrhoea. In general, these reactions were mild or moderate in severity and transient in nature. Results from the long-term cardiovascular outcomes study with 4 949 patients randomised to TRULICITY and followed for a median of 5,4 years were consistent with these findings.

Tabulated list of adverse reactions: The following adverse reactions have been identified based on evaluation of the full duration of the phase II and phase III clinical studies, the long-term cardiovascular outcomes study and post-marketing reports. The adverse reactions are listed in Table 1 as MedDRA preferred term by system organ class and in order of decreasing incidence (very common: ≥ 1/10; common: ≥ 1/100 to < 1/10; uncommon: ≥ 1/1 000 to < 1/100; rare: ≥ 1/10 000 to < 1/1 000; very rare: < 1/10 000 and not known: cannot be estimated from available data). Within each incidence grouping, adverse reactions are presented in order of decreasing frequency. Frequencies for events have been calculated based on their incidence in the phase II and phase III registration studies.

Table 1: The frequency of adverse reactions of TRULICITY

System Organ Class	Very common	Common	Uncommon	Rare	Not known
Immune system disorders			Hypersensitivity	Anaphylactic reaction#	
Metabolism and nutrition disorders	Hypoglycaemia* (when used in combination with insulin, glimepiride, metformin or	Hypoglycaemia* (when used as monotherapy or in combination with metformin plus pioglitazone)	Dehydration		

	metformin plus glimepiride)				
Gastrointestinal disorders	Nausea, diarrhoea, vomiting, abdominal pain	Decreased appetite, dyspepsia, constipation, flatulence, abdominal distention, gastroesophageal reflux disease, eructation		Acute pancreatitis , delayed gastric emptying	Non-mechanical intestinal obstruction
Hepatobiliary disorders			Cholelithiasis, cholecystitis		
Skin and subcutaneous tissue disorders				Angioedema[#]	
General disorders and administration site conditions		Fatigue	Injection site reactions		
Investigations		Sinus tachycardia, first degree atrioventricular block (AVB)			

[#] From post-marketing reports.

* Documented, symptomatic hypoglycaemia with blood glucose ≤ 3,9 mmol/L

Description of selected adverse reactions

Hypoglycaemia:

When TRULICITY 0,75 mg and 1,5 mg were used as monotherapy or in combination with metformin alone or metformin and pioglitazone, the incidences of documented symptomatic hypoglycaemia were 5,9 % to 10,9 % and the rates were 0,14 to 0,62 events/patient/year, and no episodes of severe hypoglycaemia were reported.

The incidences of documented symptomatic hypoglycaemia when TRULICITY 0,75 mg and 1,5 mg, respectively, were used in combination with a sulphonylurea and metformin were 39,0 % and 40,3 % and the rates were 1,67 and 1,67 events/patient/year. The severe hypoglycaemia event incidences were 0 % and 0,7 %, and rates were 0,00 and 0,01 events/patient/year for each dose, respectively. The incidence of documented

symptomatic hypoglycaemia when TRULICITY 1,5 mg was used with sulphonylurea alone was 11,3 % and the rate was 0,90 events/patient/year, and there were no episodes of severe hypoglycaemia.

The incidence of documented symptomatic hypoglycaemia when TRULICITY 1,5 mg was used in combination with insulin glargine was 35,3 % and the rate was 3,38 events/patient/year. The severe hypoglycaemia event incidence was 0,7 % and the rate was 0,01 events/patient/year.

The incidences of documented symptomatic hypoglycaemia when TRULICITY 0,75 mg and 1,5 mg, respectively, were used in combination with prandial insulin were 85,3 % and 80,0 % and rates were 35,66 and 31,06 events/patient/year. The severe hypoglycaemia event incidences were 2,4 % and 3,4 %, and rates were 0,05 and 0,06 events/patient/year.

Gastrointestinal adverse reactions: Cumulative reporting of gastrointestinal events up to 104 weeks with TRULICITY 0,75 mg and 1,5 mg, respectively, included nausea (12,9 % and 21,2 %*)*, diarrhoea (10,7 % and 13,7 %) and vomiting (6,9 % and 11,5 %). These were typically mild or moderate in severity and were reported to peak during the first 2 weeks of treatment and rapidly declined over the next 4 weeks, after which the rate remained relatively constant.

In clinical pharmacology studies conducted in patients with type 2 diabetes mellitus up to 6 weeks, the majority of gastrointestinal events were reported during the first 2-3 days after the initial dose and declined with subsequent doses.

Acute pancreatitis: The incidence of acute pancreatitis in Phase II and III clinical studies was 0,07% for TRULICITY compared to 0,14 % for placebo and 0,19 % for comparators with or without additional background antidiabetic therapy. Acute pancreatitis and pancreatitis have also been reported in the post-marketing setting.

Pancreatic enzymes: TRULICITY is associated with mean increases from baseline in pancreatic enzymes (lipase and/or pancreatic amylase) of 11 % to 21 % (see section 4.4). In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.

Heart rate increase: Small mean increases in heart rate of 2 to 4 beats per minute (bpm) and a 1,3 % and 1,4 % incidence of sinus tachycardia, with a concomitant increase from baseline ≥ 15 bpm, were observed with TRULICITY 0,75 mg and 1,5 mg, respectively.

First degree AV block/PR interval prolongation: Small mean increases from baseline in PR interval of 2 to 3 msec and a 1,5 % and 2,4 % incidence of first-degree AV block were observed with TRULICITY 0,75 mg and 1,5 mg, respectively.

Immunogenicity: In clinical studies, treatment with TRULICITY was associated with a 1,6 % incidence of treatment emergent TRULICITY anti-drug antibodies, indicating that the structural modifications in the GLP-1 and modified IgG4 parts of the dulaglutide molecule, together with high homology with native GLP-1 and native IgG4, minimise the risk of immune response against TRULICITY. Patients with dulaglutide antibodies generally had low titres, and although the number of patients developing dulaglutide antibodies was low, examination of the phase III data revealed no clear impact of dulaglutide antibodies on changes in HbA1c. None of the patients with systemic hypersensitivity developed dulaglutide antibodies.

Hypersensitivity: In the phase II and phase III clinical studies, systemic hypersensitivity events (e.g., urticaria, oedema) were reported in 0,5 % of patients receiving TRULICITY.

Cases of anaphylactic reaction have been rarely reported with marketed use of TRULICITY.

Injection site reactions: Injection site adverse events were reported in 1,9 % of patients receiving TRULICITY. Potentially immune-mediated injection site adverse events (e.g., rash, erythema) were reported in 0,7 % of patients and were usually mild.

Discontinuation due to an adverse event: In studies of 26 weeks duration, the incidence of discontinuation due to adverse events was 2,6 % (0,75 mg) and 6,1 % (1,5 mg) for TRULICITY versus 3,7 % for placebo. Through the full study duration (up to 104 weeks), the incidence of discontinuation due to adverse events was 5,1 % (0,75 mg) and 8,4 % (1,5 mg) for TRULICITY. The most frequent adverse reactions leading to discontinuation for 0,75 mg and 1,5 mg TRULICITY, respectively, were nausea (1,0 %, 1,9 %), diarrhoea (0,5 %, 0,6 %), and vomiting (0,4 %, 0,6 %), and were generally reported within the first 4-6 weeks.

***Reporting of suspected adverse reactions*:**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Alternately, report suspected adverse events to the company at ade_za@lilly.com

4.9 OVERDOSE

Effects of overdose with TRULICITY in clinical studies have included gastrointestinal disorders and hypoglycaemia. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medicines used in diabetes, blood glucose lowering medicines, excl. insulins, glucagon-like peptide-1 (GLP-1) analogues ATC code: A10BJ05

Mechanism of Action: Dulaglutide is a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist. The molecule consists of 2 identical disulfide-linked chains, each containing a modified human GLP-1 analogue sequence covalently linked to a modified human immunoglobulin G4 (IgG4) heavy chain fragment (Fc) by a small peptide linker. The GLP-1 analog portion of dulaglutide is approximately 90 % homologous to native human GLP-1 (7-37). Native GLP-1 has a half-life of 1,5-2 minutes due to degradation by DPP-4 and renal clearance. In contrast to native GLP-1, dulaglutide is resistant to degradation by DPP-4, and has a large size that slows absorption and reduces renal clearance. These engineering features result in a soluble formulation and a prolonged half-life of 4,7 days, which makes it suitable for once-weekly subcutaneous administration. In addition, the dulaglutide molecule was engineered to prevent the Fcγ receptor-dependent immune response and to reduce its immunogenic potential.

Dulaglutide exhibits several antihyperglycaemic actions of GLP-1. In the presence of elevated glucose concentrations, dulaglutide increases intracellular cyclic AMP (cAMP) in pancreatic beta cells leading to insulin release. Dulaglutide suppresses glucagon secretion which is known to be inappropriately elevated in patients with type 2 diabetes.

Lower glucagon concentrations lead to decreased hepatic glucose output. Dulaglutide also slows gastric emptying.

Pharmacodynamic effects: Dulaglutide improves glycaemic control through the sustained effects of lowering fasting, pre-meal and postprandial glucose concentrations in patients with type 2 diabetes starting after the first dulaglutide administration and is sustained throughout the once weekly dosing interval.

A pharmacodynamic study with dulaglutide demonstrated, in patients with type 2 diabetes, a restoration of first phase insulin secretion to a level that exceeded levels observed in healthy subjects on placebo and improved second phase insulin secretion in response to an intravenous bolus of glucose. In the same study, a single 1,5 mg dose of dulaglutide appeared to increase maximal insulin secretion from the β-cells, and to enhance β-cell function in subjects with type 2 diabetes mellitus as compared with placebo.

Consistent with the pharmacokinetic profile, dulaglutide has a pharmacodynamic profile suitable for once weekly administration (see section 5.2).

Clinical efficacy and safety

Glycaemic control: The safety and efficacy of dulaglutide were evaluated in nine randomised, controlled, phase III trials involving 6 193 patients with type 2 diabetes. In all studies, dulaglutide produced clinically significant improvements in glycaemic control as measured by glycosylated haemoglobin A1c (HbA1c).

Monotherapy: Dulaglutide was studied in a 52-week active controlled monotherapy study in comparison to metformin. Dulaglutide 1,5 mg and 0,75 mg were superior to metformin (1 500-2 000 mg/day) in the reduction in HbA1c and a significantly greater proportion of

patients reached an HbA1c target of < 7,0 % and ≤ 6,5 % with dulaglutide 1,5 mg and dulaglutide 0,75 mg compared to metformin at 26 weeks.

The rate of documented symptomatic hypoglycaemia with dulaglutide 1,5 mg and 0,75 mg, and metformin were 0,62; 0,15 and 0,09 episodes/patient/year, respectively. No cases of severe hypoglycaemia were observed.

Combination therapy with metformin: The safety and efficacy of dulaglutide was investigated in a placebo and active controlled (sitagliptin 100 mg daily) study of 104 weeks duration, all in combination with metformin. Treatment with dulaglutide 1,5 mg and 0,75 mg resulted in a superior reduction in HbA1c compared to sitagliptin at 52 weeks, accompanied by a significantly greater proportion of patients achieving HbA1c targets of < 7,0 % and ≤ 6,5 %. These effects were sustained to the end of the study (104 weeks).

The safety and efficacy of dulaglutide was also investigated in an active controlled study (liraglutide 1,8 mg daily) of 26 weeks duration, both in combination with metformin. Treatment with dulaglutide 1,5 mg resulted in similar lowering of HbA1c and patients achieving HbA1c targets of < 7,0 % and ≤ 6,5 % compared to liraglutide.

The rate of documented symptomatic hypoglycaemia with dulaglutide 1,5 mg was 0,12 episodes/patient/year and with liraglutide was 0,29 episodes/patient/year. No cases of severe hypoglycaemia were observed.

Combination therapy with metformin and sulphonylurea: In an active controlled study of 78 weeks duration, dulaglutide was compared to insulin glargine, both on a background of metformin and a sulphonylurea. At 52 weeks, dulaglutide 1,5 mg demonstrated superior lowering in HbA1c to insulin glargine which was maintained at 78 weeks; whereas lowering in HbA1c with dulaglutide 0,75 mg was non-inferior to insulin glargine. With dulaglutide

1,5 mg a significantly higher percentage of patients reached a target HbA1c of < 7,0 % or ≤ 6,5 % at 52 and 78 weeks compared to insulin glargine.

The rates of documented symptomatic hypoglycaemia with dulaglutide 1,5 mg and 0,75 mg, and insulin glargine were 1,67; 1,67; and 3,02 episodes/patient/year, respectively. Two cases of severe hypoglycaemia were observed with dulaglutide 1,5 mg and two cases of severe hypoglycaemia were observed with insulin glargine.

Combination therapy with sulphonylurea: The safety and efficacy of dulaglutide as add-on to a sulphonylurea was investigated in a placebo-controlled study of 24 weeks duration. Treatment with dulaglutide 1,5 mg in combination with glimepiride resulted in a statistically significant reduction in HbA1c compared to placebo with glimepiride at 24 weeks. With dulaglutide 1,5 mg, a significantly higher percentage of patients reached a target HbA1c of < 7,0 % and ≤ 6,5 % at 24 weeks compared to placebo.

The rates of documented symptomatic hypoglycaemia with dulaglutide 1,5 mg and placebo were 0,90 and 0,04 episodes/patient/year, respectively. No cases of severe hypoglycaemia were observed for dulaglutide or placebo.

Combination therapy with SGLT2 inhibitor with or without metformin: The safety and efficacy of dulaglutide as add-on to sodium-glucose co-transporter 2 inhibitor (SGLT2i) therapy (96 % with and 4 % without metformin) were investigated in a placebo-controlled study of 24 weeks duration. Treatment with dulaglutide 0,75 mg or dulaglutide 1,5 mg in combination with SGLT2i therapy resulted in a statistically significant reduction in HbA1c compared to placebo with SGLT2i therapy at 24 weeks. With both dulaglutide 0,75 mg and 1,5 mg, a significantly higher percentage of patients reached a target HbA1c of < 7,0 % and ≤ 6,5 % at 24 weeks compared to placebo.

The rates of documented symptomatic hypoglycaemia with dulaglutide 0,75 mg, dulaglutide 1,5 mg, and placebo were 0,15; 0,16 and 0,12 episodes/patient/year, respectively. One patient reported severe hypoglycaemia with dulaglutide 0,75 mg in combination with SGLT2i therapy and none with dulaglutide 1,5 mg or placebo.

Combination therapy with metformin and pioglitazone: In a placebo and active (exenatide twice daily) controlled study, both in combination with metformin and pioglitazone, dulaglutide 1,5 mg and 0,75 mg demonstrated superiority for HbA1c reduction in comparison to placebo and exenatide, accompanied by a significantly greater percentage of patients achieving HbA1c targets of < 7,0 % or ≤ 6,5 %.
The rates of documented symptomatic hypoglycaemia with dulaglutide 1,5 mg and 0,75 mg, and exenatide twice daily were 0,19; 0,14 and 0,75 episodes/patient/year, respectively. No cases of severe hypoglycaemia were observed for dulaglutide and two cases of severe hypoglycaemia were observed with exenatide twice daily.

Combination therapy with titrated basal insulin, with or without metformin: In a 28-week placebo-controlled study, dulaglutide 1,5 mg was compared to placebo as add-on to titrated basal insulin glargine (88 % with and 12 % without metformin) to evaluate the effect on glycaemic control and safety. To optimise the insulin glargine dose, both groups were titrated to a target fasting serum glucose of <5,6 mmol/L. The mean baseline dose of insulin glargine was 37 units/day for patients receiving placebo and 41 units/day for patients receiving dulaglutide 1,5 mg. The initial insulin glargine doses in patients with HbA1c <8,0 % were reduced by 20 %. At the end of the 28-week treatment period the dose was 65 units/day and 51 units/day, for patients receiving placebo and dulaglutide 1,5 mg, respectively. At 28 weeks, treatment with once weekly dulaglutide 1,5 mg resulted in

a statistically significant reduction in HbA1c compared to placebo and a significantly greater percentage of patients achieving HbA1c targets of < 7,0 % and ≤ 6,5 %.

The rates of documented symptomatic hypoglycaemia with dulaglutide 1,5 mg and insulin glargine were 3,38 episodes/patient/year compared to placebo and insulin glargine 4,38 episodes/patient/year. One patient reported severe hypoglycaemia with dulaglutide 1,5 mg in combination with insulin glargine and none with placebo.

Combination therapy with prandial insulin with or without metformin: In this study, patients on 1 or 2 insulin injections per day prior to study entry, discontinued their pre-study insulin regimen and were randomised to dulaglutide once weekly or insulin glargine once daily, both in combination with prandial insulin lispro three times daily, with or without metformin. At 26 weeks, both dulaglutide 1,5 mg and 0,75 mg were superior to insulin glargine in lowering of HbA1c and this effect was sustained at 52 weeks. A greater percentage of patients achieved HbA1c targets of < 7,0 % or ≤ 6,5 % at 26 weeks and < 7,0 % at 52 weeks than with insulin glargine.

The rates of documented symptomatic hypoglycaemia with dulaglutide 1,5 mg and 0,75 mg, and insulin glargine were 31,06; 35,66 and 40,95 episodes/patient/year, respectively. Ten patients reported severe hypoglycaemia with dulaglutide 1,5 mg, seven with dulaglutide 0,75 mg, and fifteen with insulin glargine

Fasting blood glucose: Treatment with dulaglutide resulted in significant reductions from baseline in fasting blood glucose. The majority of the effect on fasting blood glucose concentrations occurred by 2 weeks. The improvement in fasting glucose was sustained through the longest study duration of 104 weeks.

Postprandial glucose: Treatment with dulaglutide resulted in significant reductions in mean post prandial glucose from baseline (changes from baseline to primary time point: -1,95 mmol/L to -4,23 mmol/L).

Beta-cell function: Clinical studies with dulaglutide have indicated enhanced beta-cell function as measured by homeostasis model assessment (HOMA2-%B). The durability of effect on beta-cell function was maintained through the longest study duration of 104 weeks.

Body weight: Dulaglutide 1,5 mg was associated with sustained weight reduction over the duration of studies (from baseline to final time point -0,35 kg to -2,90 kg). Changes in body weight with dulaglutide 0,75 mg ranged from 0,86 kg to -2,63 kg. Reduction in body weight was observed in patients treated with dulaglutide irrespective of nausea, though the reduction was numerically larger in the group with nausea.

Patient reported outcomes: Dulaglutide significantly improved total treatment satisfaction compared to exenatide twice daily. In addition, there was significantly lower perceived frequency of hyperglycaemia and hypoglycaemia compared to exenatide twice daily.

Blood pressure: The effect of dulaglutide on blood pressure as assessed by Ambulatory Blood Pressure Monitoring was evaluated in a study of 755 patients with type 2 diabetes. Treatment with dulaglutide provided reductions in systolic blood pressure (SBP) (-2,8 mmHg difference compared to placebo) at 16 weeks. There was no difference in diastolic blood pressure (DBP). Similar results for SBP and DBP were demonstrated at the final 26-week time point of the study.

Cardiovascular Evaluation: In a meta-analysis of phase II and III registration studies, a total of 51 patients (dulaglutide: 26 [N = 3,885]; all comparators: 25 [N = 2,125]) experienced at least one cardiovascular (CV) event (death due to CV causes, nonfatal MI, nonfatal stroke, or hospitalisation for unstable angina). The results showed that there was no increase in CV risk with dulaglutide compared with control therapies (HR: 0,57; CI: [0,30; 1,10]).

Cardiovascular outcomes study: The TRULICITY long-term cardiovascular outcomes study was a placebo-controlled, double-blind clinical trial. Type 2 diabetes patients with established cardiovascular (CV) disease or multiple cardiovascular risk factors were randomly allocated to either TRULICITY 1,5 mg (4 949) or placebo (4 952) both in addition to standards of care for type 2 diabetes. The median study follow-up time was 5,4 years.

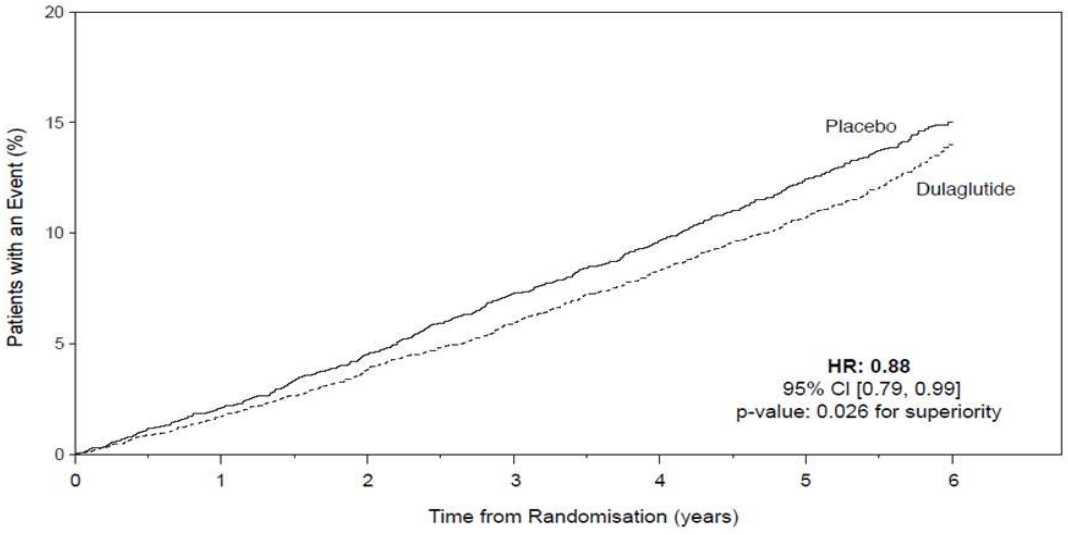
The mean age was 66,2 years, the mean BMI was 32,3 kg/m², and 46,3 % of patients were female. There were 3 114 (31,5 %) patients with established CV disease. Patients confirmed to be without established CV disease, but with multiple CV risk factors, comprised 62,8 % of the randomized trial population.

The median baseline HbA1c was 7,2 %. The Trulicity treatment arm included patients ≥ 65 years (n = 2 619) and ≥ 75 years (n = 484), and patients with mild (n = 2 435), moderate (n = 1 031) or severe (n = 50) renal impairment.

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.

TRULICITY was superior in preventing MACE compared to placebo (Figure 1).

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).



Number of patients at risk

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

Figure 1. Kaplan-Meier plot of time to first occurrence of the composite outcome: CV death, non-fatal myocardial infarction or non-fatal stroke, in the dulaglutide long-term cardiovascular outcomes study

Each MACE component contributed to the reduction of MACE, as shown in Figure 2.

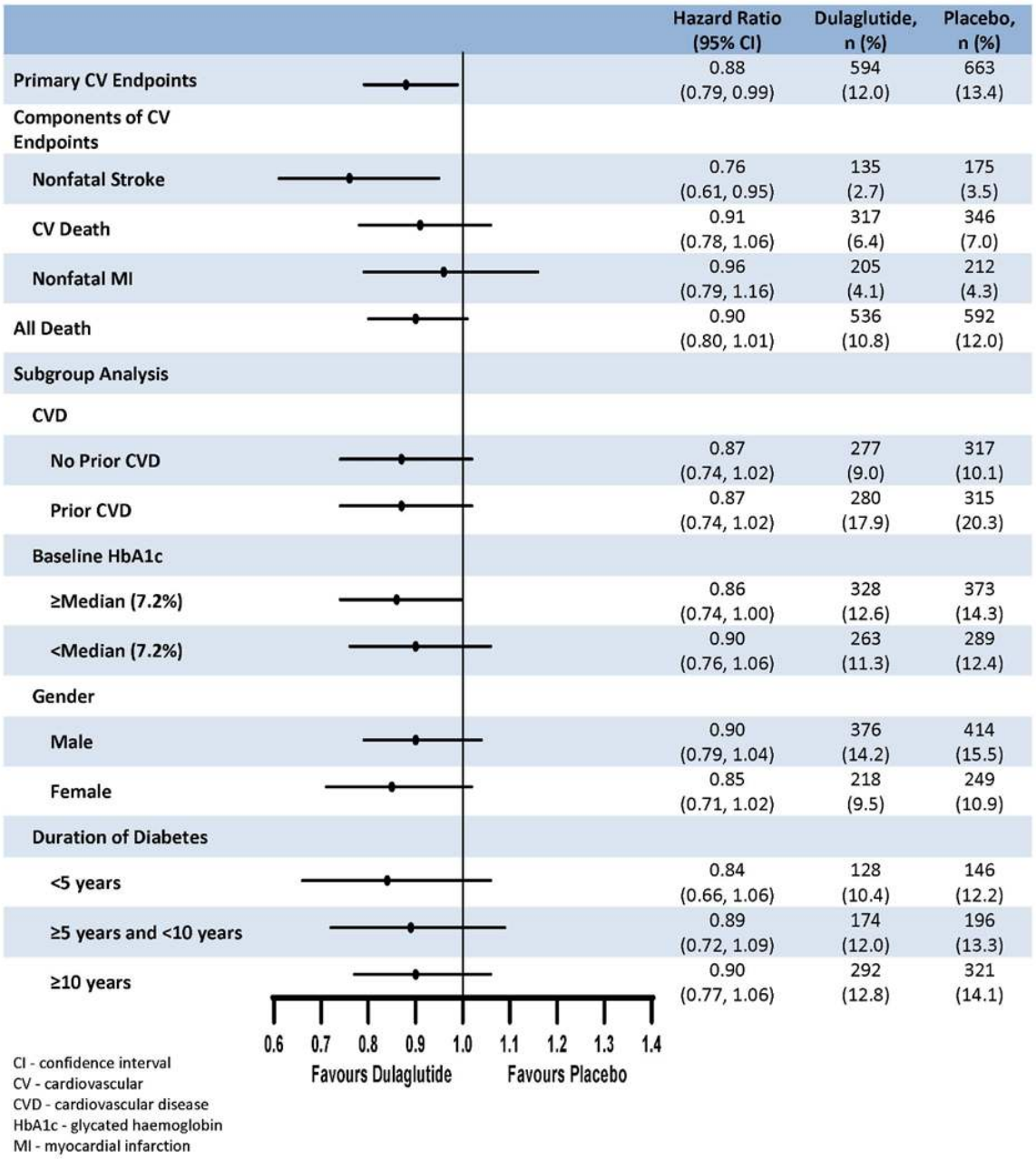


Figure 2: Forest plot of analyses of individual cardiovascular event types, all cause death, and consistency of effect across subgroups for the primary endpoint

A significant and sustained reduction in HbA1c levels from baseline to month 60 was observed with TRULICITY vs placebo, in addition to standard of care (-0,29 % vs 0,22 %; estimated treatment difference -0,51 % [-0,57; -0,45]; p < 0,001). There were significantly

fewer patients in the TRULICITY group who received an additional glycaemic intervention compared to placebo (TRULICITY: 2 086 [42,2 %]; placebo: 2 825 [57,0 %]; p < 0,001).

Special populations

Use in patients with renal impairment: In a 52-week study, dulaglutide 1,5 mg and 0,75 mg were compared to titrated insulin glargine as add-on to prandial insulin lispro to evaluate the effect on glycaemic control and safety of patients with moderate to severe chronic kidney disease (eGFR [by CKD-EPI] < 60 and ≥ 15 mL/min/1,73 m^2). Patients discontinued their prestudy insulin regimen at randomisation. 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.

At 26 weeks, both dulaglutide 1,5 mg and 0,75 mg were non-inferior to insulin glargine in lowering of HbA1c and this effect was sustained at 52 weeks. A similar percentage of patients achieved HbA1c targets of < 8,0 % at 26 and 52 weeks with both dulaglutide doses as well as insulin glargine.

The rates of documented symptomatic hypoglycaemia with dulaglutide 1,5 mg and dulaglutide 0,75 mg, and insulin glargine were 4,44; 4,34 and 9,62 episodes/patient/year, respectively. No patients reported cases of severe hypoglycaemia with dulaglutide 1,5 mg, six with dulaglutide 0,75 mg, and seventeen with insulin glargine. The safety profile of dulaglutide in patients with renal impairment was similar to that observed in other studies with dulaglutide.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following subcutaneous administration to patients with type 2 diabetes, dulaglutide reaches peak plasma concentrations in 48 hours. The mean peak (C_{max}) and total (AUC) exposures were approximately 114 ng/mL and 14 000 ngh/mL, respectively, after multiple

subcutaneous 1,5 mg doses of dulaglutide in patients with type 2 diabetes. Steady-state plasma concentrations were achieved between 2 to 4 weeks of once-weekly administration of dulaglutide (1,5 mg). Exposures after subcutaneous administration of single dulaglutide (1,5 mg) doses in the abdomen, thigh, or upper arm were comparable. The mean absolute bioavailability of dulaglutide following single-dose subcutaneous administration of single 1,5 mg and 0,75 mg doses was 47 % and 65 %, respectively.

Distribution

The mean volume of distribution after subcutaneous administration of dulaglutide 0,75 mg and 1,5 mg at steady state in patients with type 2 diabetes mellitus were approximately 19,2 L and 17,4 L.

Biotransformation

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

Elimination

The mean apparent clearance of dulaglutide 0,75 mg and 1,5 mg at steady state was 0,111 L/h and 0,107 L/h with an elimination half-life of 4,5 and 4,7 days, respectively.

Special populations

Elderly: Age had no clinically relevant effect on the pharmacokinetic and pharmacodynamic properties of dulaglutide.

Gender and race: Gender and race had no clinically meaningful effect on the pharmacokinetics of dulaglutide.

Body weight or body mass index: Pharmacokinetic analyses have demonstrated a statistically significant inverse relationship between body weight or body mass index (BMI) and dulaglutide exposure, although there was no clinically relevant impact of weight or BMI on glycaemic control.

Renal impairment: The pharmacokinetics of dulaglutide were evaluated in a clinical pharmacology study and were generally similar between healthy subjects and patients with mild to severe renal impairment (CrCl < 30 mL/min), including end stage renal disease (requiring dialysis). Additionally, in a 52-week clinical study in patients with type 2 diabetes and moderate to severe renal impairment (eGFR [by CKD-EPI] <60 and ≥15 mL/min/1,73 m^2), the pharmacokinetic profile of dulaglutide 0,75 mg and 1,5 mg once weekly was similar to that demonstrated in previous clinical studies. This clinical study did not include patients with end stage renal disease.

Hepatic impairment: The pharmacokinetics of dulaglutide were evaluated in a clinical pharmacology study, where subjects with hepatic impairment had statistically significant decreases in dulaglutide exposure of up to 30 % to 33 % for mean C_{max} and AUC, respectively, compared to healthy controls. There was a general increase in t_{max} of dulaglutide with increased hepatic impairment. However, no trend in dulaglutide exposure was observed relative to the degree of hepatic impairment. These effects were not considered to be clinically relevant.

Paediatric population: Studies characterising the pharmacokinetics of dulaglutide in paediatric patients have not been performed.

5.3 PRECLINICAL SAFETY DATA

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology or repeat-dose toxicity.

In a 2-year carcinogenicity study in rats, dulaglutide caused statistically significant, dose-related increases in the incidence of thyroid C-cell tumours (adenomas and carcinomas combined) at ≥7 times the human clinical exposure following once weekly administration of 1,5 mg dulaglutide. The human relevance of these findings is currently unknown. There was no tumourigenic response in a 6-month carcinogenicity study in transgenic mice. Animal studies with dulaglutide did not indicate direct harmful effects with respect to fertility. In reproductive toxicology studies, high doses of dulaglutide caused skeletal effects and reduced foetal growth (see 4.6 for use during Pregnancy and Lactation).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trisodium citrate dihydrate

Citric acid, anhydrous

Mannitol

Polysorbate 80

Water for injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies TRULICITY must not be mixed with other medicines.

6.3 SHELF LIFE

2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2 ºC – 8 ºC).

Do not freeze. Do not use TRULICITY if it has been frozen.

TRULICITY is photosensitive and must be protected from light until administration. Store in original package in order to protect from light.

In use: TRULICITY may be stored unrefrigerated for up to 14 days at a temperature not above 30 ºC.

Store all medicines out of reach of children.

6.5 NATURE AND CONTENTS OF CONTAINER

Prefilled Pens: Clear, type 1 glass syringe with staked needle and closed with a grey rubber plunger and rigid needle shield, is assembled into the single-use pen. Each pre-filled pen contains 0,5 mL solution.

Available in packs of 2 and 4. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Any unused medicines or waste material should be disposed of in accordance with local requirements.

Instructions for use: The pre-filled pen is for single-use only.

The instructions for using the pen, included with the package leaflet, must be followed carefully. TRULICITY should not be used if particles appear or if the solution is cloudy and/or discoloured.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Eli Lilly (S.A.) (Pty) Limited

Golden Oak House (Building E), Ballyoaks Office Park,

35 Ballyclare Drive

Bryanston, 2191

8. REGISTRATION NUMBER(S)

51/21.13/0344

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 March 2020

10. DATE OF REVISION OF THE TEXT

08 September 2025