# AUSTRALIAN PRODUCT INFORMATION – TRULICITY (DULAGLUTIDE RCH) AUTOINJECTOR

## 1. NAME OF THE MEDICINE

dulaglutide (rch)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TRULICITY contains dulaglutide (rch) 1.5 mg per 0.5 mL solution.

For the full list of excipients, see **6.1 List of excipients.**

## 3. PHARMACEUTICAL FORM

Solution for Injection.

TRULICITY is a clear, colourless, essentially free from particles, sterile and non-pyrogenic solution for subcutaneous administration.

## 4. CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

Type 2 Diabetes Mellitus: glycaemic control

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 medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see section 5.1 for data with respect to different combinations).

Type 2 Diabetes Mellitus: reduction in risk of major adverse cardiovascular events

TRULICITY is indicated as an adjunct to standard of care therapy 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

## 4.2 DOSE 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 can not 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 known hypersensitivity to dulaglutide or any of the excipients in the product.

## 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.

### Severe Gastrointestinal Disease

Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions which include nausea, vomiting and diarrhoea especially at the initiation of treatment (see **4.8 Adverse effects (Undesirable Effects)**). These events may lead to dehydration, which could cause a deterioration in renal function including acute renal failure. Patients treated with dulaglutide should be advised of the potential risk of dehydration, particularly in relation to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Dulaglutide 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.

### Acute Pancreatitis

Acute Pancreatitis has been reported with use of GLP-1 receptor agonists, including dulaglutide. Patients should be informed of the symptoms of acute pancreatitis. If acute pancreatitis is suspected TRULICITY should be discontinued until evaluation is complete. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis (see **4.8 Adverse effects (Undesirable Effects)**). If the diagnosis of acute pancreatitis is confirmed, TRULICITY should be permanently discontinued.

### Risk of hypoglycaemia

Patients receiving TRULICITY in combination with sulfonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of sulfonylurea or insulin.

### Use in Patients with Congestive Heart Failure

There is limited therapeutic experience in patients with congestive heart failure.

### Pulmonary aspiration

Dulaglutide delays gastric emptying. Pulmonary aspiration has been reported in patients receiving long acting GLP-1 receptor agonists undergoing general anaesthesia or deep sedation. This should be considered prior to such procedures.

### Psychiatric disorders

Suicidal behaviour and ideation have been reported with GLP-1 receptor agonists. Monitor patients for the emergence or worsening of depression, suicidal thoughts or behaviours, and/or any unusual changes in mood or behaviour. Consider the benefits and risks for individual patients prior to initiating or continuing therapy in patients with suicidal thoughts or behaviours or have a history of suicidal attempts.

**Use in hepatic impairment**

No dose adjustment is required based on hepatic impairment.

**Use in renal impairment**

There is limited therapeutic experience in patients with end stage renal disease (<15 mL/min requiring dialysis treatment), therefore TRULICITY cannot be recommended in this population. (See **4.2 Dose and method of administration and 5.1 Pharmacodynamic Properties**).

**Use in the Elderly**

No dose adjustment is required based on age.

**Paediatric Use**

The safety and effectiveness of dulaglutide have not been established in patients under 18 years of age.

**Effects on Laboratory Tests**

No information on the effect of dulaglutide on laboratory tests is available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Dulaglutide causes a delay in gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology studies, dulaglutide 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 dulaglutide 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 drugs primarily renally eliminated or metabolised by cytochrome P450 enzymes are not expected.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

**Effects on fertility**

No adverse effects on fertility were observed in male and female rats given subcutaneous doses of dulaglutide at ≤16.3 mg/kg every 3 days, yielding exposure to dulaglutide (based on plasma AUC) ≥30 times higher than that in patients at the maximum recommended human dose.

**Use in Pregnancy**

Pregnancy Category B3.

There are no adequate and well controlled studies of dulaglutide in pregnant women. Administer TRULICITY to pregnant women only if the potential benefit justifies the potential risk to the foetus.

High doses of dulaglutide (11 to 44 times the human clinical exposure following once weekly administration of 1.5 mg dulaglutide) during the period of organogenesis to pregnant rats and rabbits caused increased post-implantation loss, reduced foetal growth, and skeletal and visceral abnormalities (including malformations in rabbits). These findings were observed in association with maternal effects (decreased maternal food intake and decreased weight gain) and are not considered likely to reflect direct embryofoetal toxicity or teratogenicity. Memory deficits were observed in the female offspring of rats treated throughout pregnancy and lactation at 1.63 mg/kg every 3 days (yielding 16 times the human clinical exposure). No adverse effects on embryofoetal development were seen in rats and rabbits at subcutaneous doses of 0.49 mg/kg and ≤0.12 mg/kg, respectively, given every 3 days (yielding exposures approximately 4 times higher than that in patients at the maximum recommended human dose).

**Use in Lactation**

It is not known whether dulaglutide is excreted in human milk. Administer TRULICITY to nursing women only if the potential benefit to the mother justifies the potential risk to the infant. In rats, treatment with dulaglutide throughout pregnancy and lactation at 1.63 mg/kg every 3 days delayed postnatal growth and development and produced memory deficits in the offspring. No adverse effects on postnatal development were observed in rats with subcutaneous dosing at 0.49 mg/kg every 3 days (yielding 4.5 times the exposure in patients at the maximum recommended human dose).

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on ability to drive or use machinery have been performed. When TRULICITY is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving or using machinery.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

**Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

**Clinical Trial Data**

In the completed phase 2 and 3 initial registration studies 4,006 individuals received at least one dose of dulaglutide for a total of 3,531 patient years, 703 received placebo for 284 patient years and 1,541 received active comparator for 1,722 patient years. The 1.5 mg dose of dulaglutide was received by 1,762 individuals for 1,689 patient years. In studies of 26-week duration, 69.9% of patients who received dulaglutide 1.5 mg reported one or more treatment emergent adverse event compared to 66.0% of patients who received placebo.

The safety profile from the long-term cardiovascular outcome study with 4949 patients randomised to dulaglutide and followed for a median of 5.4 years was consistent with the initial phase 2 and phase 3 registration studies.

The following related adverse reactions have been identified based on evaluation of the full duration of Phase 2 and Phase 3 clinical studies, the long-term cardiovascular outcome study and

post-marketing reports. The adverse reactions are listed below as MedDRA preferred term in order of decreasing incidence. Frequencies of adverse reactions have been calculated based on their incidence in the phase 2 and phase 3 registration studies.

**Table 1. Adverse Reactions in Placebo-Controlled Trial Reported in ≥5% of TRULICITY Patients**

| Adverse Reaction | Dulaglutide 1.5 mg N=834 | Placebo N=568 |
|---|---|---|
| Nausea | 21.1% | 5.3% |
| Vomiting[a] | 12.7% | 2.3% |
| Diarrhoea[b] | 12.6% | 6.7% |
| Abdominal Pain[c] | 9.4% | 4.9% |
| Decreased Appetite | 8.6% | 1.6% |
| Dyspepsia | 5.8% | 2.3% |
| Fatigue[d] | 5.6% | 2.6% |

[a] includes retching, vomiting, vomiting projectile.

[b] includes diarrhoea, faecal volume increased, frequent bowel movements.

[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 disorders

Gastrointestinal events (nausea, vomiting and diarrhoea) reported were typically mild or moderate in severity. The onset of nausea, vomiting and diarrhoea was observed to peak during the first two weeks of treatment and rapidly decline over the next four weeks, after which they 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.

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

### Cholecystitis

In glycaemic control studies with patients receiving dulaglutide 1.5 mg, the incidence of cholecystitis was 0.1% (*uncommon*).

### General Disorders and Administration Site Conditions

Potentially immune-mediated injection site adverse events (e.g., rash, erythema) have been reported in 0.7% of patients receiving dulaglutide and have usually been mild.

*Immunogenicity*

In clinical studies treatment with dulaglutide at any dose was associated with a 1.6% incidence of treatment emergent dulaglutide anti-drug antibodies.

*Hypersensitivity*

Systemic hypersensitivity events (e.g. urticaria, angiooedema) have been reported in 0.3% of patients receiving dulaglutide 1.5 mg once weekly, compared to 0.7% in placebo. Systemic hypersensitivity events were reported in 0.5% of patients receiving dulaglutide at any dose. In the 1.6% of dulaglutide-treated patients with treatment emergent anti-drug antibodies, there were no systemic hypersensitivity adverse events reported.

**Cardiac arrhythmia**

In the long-term cardiovascular outcome trial, a higher proportion of patients experienced serious adverse events of atrial fibrillation in the dulaglutide group (93 patients [1.9%]) compared to the placebo group (63 patients [1.3%]); p=0.015.

**Investigations**

Dulaglutide is associated with a small mean increase in heart rate of 2 to 4 beats per minute and a 1.4% incidence of sinus tachycardia with a concomitant increase from baseline of ≥15 beats per minute.

Dulaglutide is associated with small mean increases from baseline in PR interval of 2 to 3 msec and a 2.4% incidence of first-degree atrioventricular block.

Dulaglutide is associated with mean increases from baseline in pancreatic enzymes (pancreatic amylase and/or lipase) of 14% to 20% (see **4.4 Special warnings and precautions for use**).

**Discontinuation due to an adverse event**

In studies of 26-week duration the incidence of discontinuation due to adverse events was 6.1% for TRULICITY 1.5 mg versus 3.7% for placebo, which was not statistically different. Through the full study duration (up to 104 weeks) the incidence of discontinuation due to adverse events was 8.4% for dulaglutide 1.5 mg. The most frequent adverse events leading to discontinuation were nausea (1.9%), diarrhoea (0.6%) and vomiting (0.6%), and were generally reported within the first 4-6 weeks.

In the long-term cardiovascular outcome study (median follow-up 5.4 years), a higher proportion of patients in the dulaglutide group permanently discontinued study drug due to an adverse event (dulaglutide: 451 [9.1%]; placebo: 310 [6.3%]; p<0.001). Gastrointestinal events were the most common reason for study drug discontinuation (dulaglutide: 201 [4.1%]; placebo: 54 [1.1%]). The most frequent adverse events leading to discontinuation of study drug in the dulaglutide group were nausea (1.3%), diarrhoea (0.7%) and vomiting (0.6%).

**Metabolic and Nutrition Disorders**

**Table 2. Incidence of Symptomatic Hypoglycaemia in Phase 3 Studies for Dulaglutide (1.5 mg)**

| Study | N | n[a] (%) |
|---|---|---|
| **Monotherapy Study H9X-MC-GBDC** | | |
| Dulaglutide | 269 | 17 (6.3%) |
| Metformin | 268 | 13 (4.9%) |
| **Add on to metformin Study H9X-MC-GBCF** | | |
| Dulaglutide | 304 | 33 (10.9%) |
| Sitagliptin | 315 | 18 (5.7%) |
| **Add on to metformin & TZD Study H9X-MC-GBDA** | | |
| Dulaglutide | 279 | 18 (6.5%) |
| Exenatide BID | 276 | 37 (13.4%) |
| **Add on to metformin & sulfonylurea Study H9X-MC-GBDB** | | |
| Dulaglutide | 273 | 110 (40.3%) |
| Insulin glargine | 262 | 134 (51.1%) |
| **Add on to insulin lispro ± metformin Study H9X-MC-GBDD** | | |
| Dulaglutide | 295 | 236 (80.0%) |
| Insulin glargine | 296 | 247 (83.4%) |

**Abbreviations**: BID = twice daily injections, TZD = thiazolidinedione.

[a] number of patients experiencing at least one episode of documented symptomatic hypoglycaemia (plasma glucose ≤70 mg/dL).

*Combination with insulin secretagogues and/or insulin*

Documented symptomatic hypoglycaemia was reported very commonly when TRULICITY was administered concomitantly with metformin plus glimepiride and when TRULICITY was administered concomitantly with prandial insulin. When dulaglutide was used in combination with metformin and a sulfonylurea or with prandial insulin the rates of hypoglycaemia were 1.67 events/patient/year and 31.06 events/patient/year, respectively. The rates of severe hypoglycaemia events were 0.01 events/patient/year and 0.06 events/patient/year, respectively.

The incidence of documented symptomatic hypoglycaemia when dulaglutide 1.5 mg was used with sulfonylurea 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 dulaglutide 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.

*Combination with non-secretagogues*

Documented symptomatic hypoglycaemia was reported very commonly when TRULICITY was administered concomitantly with metformin and was reported commonly when TRULICITY was administered concomitantly with metformin and pioglitazone. When dulaglutide was used in combination with a non-secretagogue, the rates of hypoglycaemia were 0.19 to 0.26 events/patient/year, and no episodes of severe hypoglycaemia were reported.

*Monotherapy*

Documented symptomatic hypoglycaemia was reported commonly when TRULICITY was administered as monotherapy. The rate of hypoglycaemia was 0.62 events/patient/year and no episodes of severe hypoglycaemia were reported.

**POSTMARKETING DATA**

The following adverse drug reactions are based on post marketing reports:

***Eye disorders -*** Events of non-arteritic anterior ischaemic optic neuropathy (NAION), a rare condition associated with the potential for decreased vision including permanent loss of vision, have been reported in patients treated with products with GLP-1 receptor agonist activity. A sudden loss of vision should lead to ophthalmological examination.

***Gastrointestinal disorders –*** Intestinal obstruction including ileus.

***Hepatobiliary –*** Elevation of liver enzymes.

***Immune system disorders –*** Anaphylactic Reactions: Rare (≥ 0.01%, <0.1%).

***Nervous system disorders*** - Dysaesthesia, Dysgeusia

***Skin and subcutaneous tissue disorders*** – Alopecia

### 4.9 OVERDOSE

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

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

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 TRULICITY 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, as shown in Figure 1. In the same study, a single 1.5 mg dose of TRULICITY 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 **5.2 Pharmacokinetic properties**).

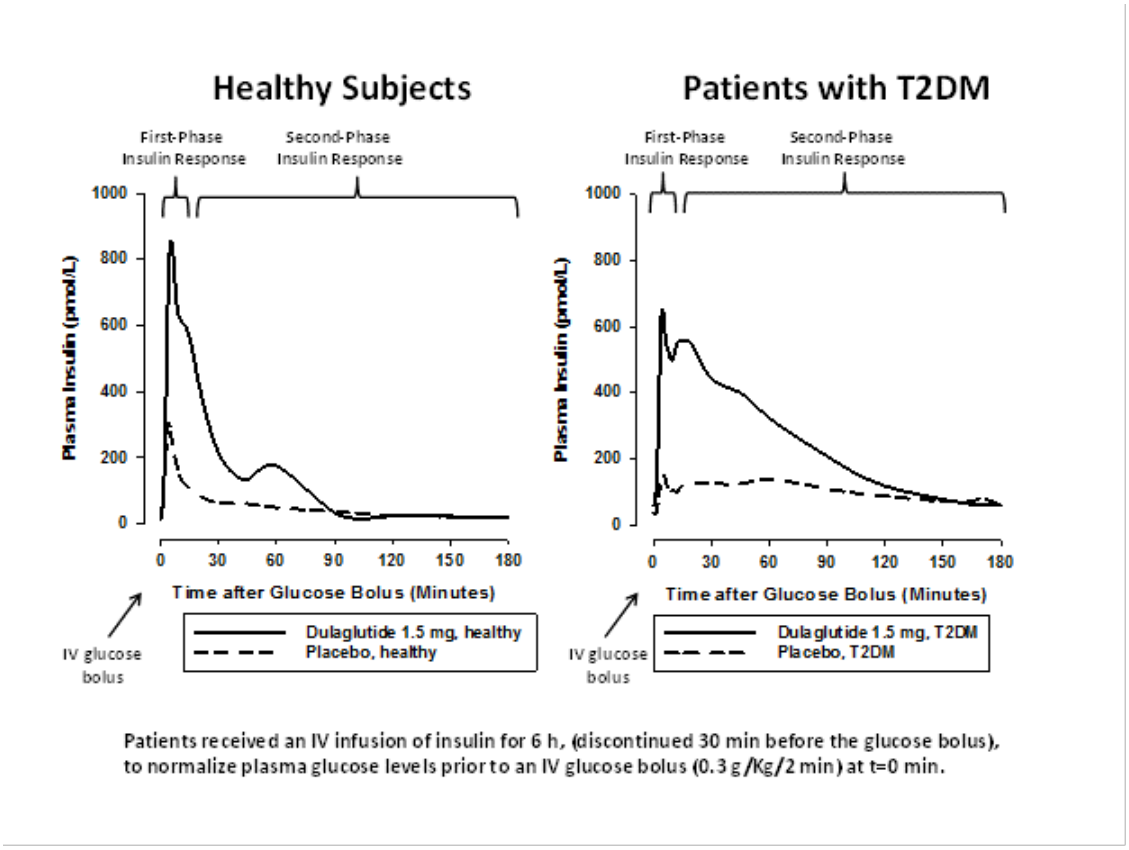



**Figure 1. Effect of dulaglutide on first and second phase insulin secretion**

**Mechanism of action**

Dulaglutide is a long acting GLP-1 receptor agonist. Native GLP-1 has a half-life of 1.5 – 2 minutes due to degradation by dipeptidyl peptidase-4 (DPP-4) and renal clearance. In contrast to native GLP-1, dulaglutide is relatively 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 anti-hyperglycaemic actions of GLP-1. In the presence of elevated glucose concentrations, dulaglutide increases intracellular cyclic AMP 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.

**Clinical trials**

The efficacy of TRULICITY has been established in eight pivotal Phase 3 studies involving 5,770 patients with type 2 diabetes mellitus. These studies were designed to assess safety and efficacy in patients across different stages of the type 2 diabetes mellitus treatment continuum from monotherapy, combination with one or two oral antidiabetic medications, to combination with insulin. These studies included 3,525 patients treated with TRULICITY, of whom 2,108 were treated with TRULICITY 1.5 mg once weekly. In all studies, TRULICITY produced clinically significant improvements in glycaemic control as measured by glycosylated haemoglobin A1c (HbA1c). Superiority of dulaglutide to comparators for HbA1c change from baseline was consistently demonstrated. Treatment with dulaglutide was associated with modest weight loss.

Table 3 provides a summary for five initial registration studies of TRULICITY as monotherapy, add on to metformin, add on to metformin & TZD, add on to metformin & sulfonylurea, and add on to insulin lispro ± metformin. Change in HbA1c (%) was the primary endpoint, other important secondary outcomes included change in fasting blood glucose (FBG), percentage of patients achieving a target HbA1c <7.0%, and change in body weight at the primary and final study time points. The type 2 diabetes mellitus population was well represented by patients participating in the five Phase 3 studies of dulaglutide, with approximately 51% being male and a mean baseline age of 56.2 years. Of the 4,572 patients included in the five studies, 847 (18.5%) were aged ≥ 65 years, of whom 86 were aged ≥ 75 years (1.9%). Across the five studies at baseline, the mean duration of diabetes ranged from 2.6 to 12.7 years, mean baseline HbA1c ranged from 7.6% to 8.5% and mean body mass index ranged from 31.2 kg/m$^2$ to 33.3 kg/m$^2$.

Tables 4, 6 and 7 provide a summary for studies of TRULICITY as add-on to titrated basal insulin, add-on to SGLT2 inhibitor therapy, and add-on to glimepiride, respectively.

Tables 5 and 8 provide a summary for studies of TRULICITY compared to liraglutide, both in combination with metformin, and in comparison to insulin glargine in patients with moderate to severe chronic kidney disease, respectively.

**Table 3. Summary of Efficacy Results from Dulaglutide Phase 3 studies (Intention to Treat)**

| | Study | N | HbA1c (%) | | Change FBG (mmol/L) | %Patients at target <7.0% | Change body weight (kg) |
|---|---|---|---|---|---|---|---|
| | | | Change | Endpoint | | | |
| **Monotherapy Study H9X-MC-GBDC** | | | | | | | |
| Primary Time Point 26 weeks | Dulaglutide 1.5 mg | 269 | -0.78†† | 6.81†† | -1.61 | 61.5# | -2.29 |
| | Metformin | 268 | -0.56 | 7.03 | -1.34 | 53.6 | -2.22 |
| Final Time Point 52 weeks | Dulaglutide 1.5 mg | 269 | -0.70†† | 6.89†† | -1.56# | 60.0# | -1.93 |
| | Metformin | 268 | -0.51 | 7.08 | -1.15 | 48.3 | -2.20 |
| **Add on to metformin Study H9X-MC-GBCF** | | | | | | | |
| Primary Time Point 52 weeks | Dulaglutide 1.5 mg | 304 | -1.10†† | 7.02†† | -2.38## | 57.6## | -3.03## |
| | Sitagliptin | 315 | -0.39 | 7.73 | -0.90 | 33.0 | -1.53 |
| Final Time Point 104 weeks | Dulaglutide 1.5 mg | 304 | -0.99†† | 7.13†† | -1.99## | 54.3## | -2.88## |
| | Sitagliptin | 315 | -0.32 | 7.80 | -0.47 | 31.1 | -1.75 |
| **Add on to metformin & TZD Study H9X-MC-GBDA** | | | | | | | |
| Primary Time Point 26 weeks | Dulaglutide 1.5 mg | 279 | -1.51‡‡,†† | 6.55‡‡,†† | -2.36**,## | 78.2**,## | -1.30** |
| | Placebo | 141 | -0.46 | 7.44 | -0.26 | 42.9 | 1.24 |
| | Exenatide BID | 276 | -0.99** | 7.05** | -1.35** | 52.3* | -1.07** |
| Final Time Point 52 weeks | Dulaglutide 1.5 mg | 279 | -1.36†† | 6.66†† | -2.04## | 70.8## | -1.10 |
| | Exenatide BID | 276 | -0.80 | 7.23 | -1.03 | 49.2 | -0.80 |
| **Add on to metformin & sulfonylurea Study H9X-MC-GBDB** | | | | | | | |
| Primary Time Point 52 weeks | Dulaglutide 1.5 mg | 273 | -1.08†† | 7.05†† | -1.50 | 53.2## | -1.87## |
| | Insulin glargine | 262 | -0.63 | 7.50 | -1.76 | 30.9 | 1.44 |
| Final Time Point 78 weeks | Dulaglutide 1.5 mg | 273 | -0.90†† | 7.23†† | -1.10# | 49.0# | -1.96## |
| | Insulin glargine | 262 | -0.59 | 7.54 | -1.58 | 30.5 | 1.28 |
| **Add on to insulin lispro ± metformin Study H9X-MC-GBDD** | | | | | | | |
| Primary Time Point 26 weeks | Dulaglutide 1.5 mg | 295 | -1.64†† | 6.83†† | -0.27## | 67.6# | -0.87## |
| | Insulin glargine | 296 | -1.41 | 7.05 | -1.58 | 56.8 | 2.33 |
| Final Time Point 52 weeks | Dulaglutide 1.5 mg | 295 | -1.48†† | 6.99†† | 0.08## | 58.5# | -0.35## |
| | Insulin glargine | 296 | -1.23 | 7.23 | -1.01 | 49.3 | 2.89 |

**Abbreviations**: BID = twice daily injections, HbA1c = glycosylated haemoglobin A1c, TZD = thiazolidinedione.

† multiplicity adjusted 1-sided p-value <0.025 for noninferiority of dulaglutide compared to comparator, assessed only for HbA1c.

†† multiplicity adjusted 1-sided p-value <0.025 for superiority of dulaglutide compared to comparator, assessed only for HbA1c.

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

*p<0.05 dulaglutide or exenatide BID compared to placebo.

**p<0.001 dulaglutide or exenatide BID compared to placebo.

#p<0.05 dulaglutide compared to active comparator.

## p<0.001 dulaglutide compared to active comparator.

*Monotherapy*

Study GBDC was a 52-week Phase 3, randomised, parallel-arm, double-blind, double-dummy, active-comparator trial to assess the safety and efficacy of 2 doses of once weekly dulaglutide (1.5 mg and 0.75 mg) as monotherapy in patients with early type 2 diabetes mellitus. In this study, patients discontinued their prior oral antidiabetic medication and were then randomised to TRULICITY once weekly or metformin following a two week lead in period. TRULICITY 1.5 mg was superior to metformin (1500-2000 mg/day) in the reduction in HbA1c from baseline (mean baseline 7.6%) and a significantly greater proportion of patients reached an HbA1c target of <7.0% ($p< 0.05$) and ≤6.5% ($p< 0.001$) with TRULICITY compared to metformin at 26 weeks. These effects were sustained for up to 52 weeks of treatment. The rate of documented symptomatic hypoglycaemia with TRULICITY 1.5 mg alone was 0.62 episodes/patient/year and with metformin was 0.09 episodes/patient/year. No cases of severe hypoglycaemia were observed.

*Combination therapy with titrated basal insulin, with or without metformin*

In a 28 week placebo controlled study, TRULICITY 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 TRULICITY 1.5mg. 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 TRULICITY 1.5 mg, respectively. At 28 weeks, treatment with once weekly TRULICITY 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 % (Table 4).

**Table 4. Results of a 28 week study of dulaglutide compared to placebo as add-on to titrated insulin glargine**

| | **Baseline HbA1c** | **Mean change in HbA1c** | **Patients at target HbA1c** | | **Change in FBG** | **Change in body weight** |
|---|---|---|---|---|---|---|
| | **(%)** | **(%)** | **<7.0% (%)** | **≤6.5% (%)** | **(mmol/L)** | **(kg)** |
| **28 weeks** | | | | | | |
| Dulaglutide 1.5 mg once weekly and insulin glargine (n=150) | 8.41 | -1.44‡‡ | 66.7‡‡ | 50.0** | -2.48‡‡ | -1.91‡‡ |
| Placebo once weekly and insulin glargine (n=150) | 8.32 | -0.67 | 33.3 | 16.7 | -1.55 | 0.50 |

‡‡ $p < 0.001$ for superiority of dulaglutide compared to placebo, overall type I error controlled

** $p < 0.001$ dulaglutide treatment group compared to placebo

The rates of documented symptomatic hypoglycaemia with TRULICITY 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 TRULICITY 1.5 mg in combination with insulin glargine and none with placebo.

*Combination with Oral Antidiabetic Medications*

Combination with metformin

Study GBCF was a 104-week, adaptive, Phase 2/3, placebo-controlled, safety, and efficacy study of once weekly dulaglutide compared to sitagliptin in patients on metformin. In the initial dose-finding portion of the study, 7 doses of dulaglutide (0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 3.0 mg), sitagliptin, and placebo were assessed. An optimal or maximum utility dose was to be selected based on the use of a pre-defined clinical utility index combining efficacy (HbA1c and weight) and safety (diastolic blood pressure and heart rate) measures. At the completion of the dose-finding portion, the dulaglutide 1.5 mg dose was selected as the optimal dose. The dulaglutide 0.75 mg dose was additionally selected to move forward as a contingency dose. Following completion of the dose-finding stage, evaluation of the safety and efficacy of these 2 doses and comparator arms continued in Study GBCF. Treatment with TRULICITY 1.5 mg resulted in a superior reduction in HbA1c compared to placebo (at 26 weeks). TRULICITY was also superior to sitagliptin for reduction in HbA1c at 52 weeks accompanied by a significantly ($p< 0.001$) greater proportion of patients achieving HbA1c targets of < 7.0% and ≤ 6.5%. Treatment with TRULICITY also resulted in significantly ($p< 0.001$) greater reductions in fasting plasma glucose and body weight than observed for sitagliptin. These effects were sustained to the end of the study (104 weeks). The rate of documented symptomatic hypoglycaemia with TRULICITY 1.5 mg was 0.19 episodes/patient/year and with sitagliptin was 0.17 episodes/patient/year. No cases of severe hypoglycaemia with TRULICITY were observed.

The safety and efficacy of TRULICITY 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 compared to liraglutide.

**Table 5. Results of a 26 week study of dulaglutide compared to liraglutide, both in combination with metformin**

| | **Baseline HbA1c (%)** | **Mean change in HbA1c (%)** | **Patients at target HbA1c** | | **Change in FBG (mmol/L)** | **Change in body weight (kg)** |
|---|---|---|---|---|---|---|
| | | | **<7.0 % (%)** | **≤6.5 % (%)** | | |
| **26 weeks** | | | | | | |
| Dulaglutide 1.5 mg once weekly (n=299) | 8.06 | -1.42‡ | 68.3 | 54.6 | -1.93 | -2.90# |
| Liraglutide+ 1.8 mg daily (n=300) | 8.05 | -1.36 | 67.9 | 50.9 | -1.90 | -3.61 |

‡ 1-sided p-value $p < 0.001$, for noninferiority of dulaglutide compared to liraglutide, assessed only for HbA1c.

# $p < 0.05$ dulaglutide treatment group compared to liraglutide.

+ Patients randomised to liraglutide were initiated at a dose of 0.6 mg/day. After Week 1, patients were up-titrated to 1.2 mg/day and then at Week 2 to 1.8 mg/day.

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. The most frequent adverse events were gastrointestinal, including nausea, diarrhoea, dyspepsia, and vomiting, and were similar between the groups.

Combination with metformin and thiazolidinedione

Study GBDA was a 52-week, Phase 3, randomized, parallel-arm, placebo-controlled, open-label to active-comparator (exenatide twice daily) trial. It was double-blind with respect to dulaglutide 1.5 mg, dulaglutide 0.75 mg, and placebo treatment assignment to 26 weeks. For those patients randomized to placebo who were then switched to dulaglutide after 26 weeks, it was also double-blind with respect to the dulaglutide dose assignment (1.5 mg or 0.75 mg) to 52 weeks. This study was designed to assess the safety and efficacy of dulaglutide 1.5 mg and dulaglutide 0.75 mg in patients who were on stable doses of metformin and pioglitazone. In this study, TRULICITY 1.5 mg demonstrated a significant improvement in HbA1c change compared to placebo at 26 weeks. TRULICITY also demonstrated superiority for HbA1c reduction in comparison to exenatide at 26 weeks and at 52 weeks. This was accompanied by significantly ($p< 0.001$) greater reductions in fasting serum glucose and a greater percentage of patients achieving HbA1c targets of < 7.0% or ≤ 6.5% at 26 and 52 weeks. Weight loss with TRULICITY was comparable to exenatide. The rate of documented symptomatic hypoglycaemia with TRULICITY 1.5 mg was 0.19 episodes/patient/year and with exenatide twice daily was 0.75 episodes/patient/year ($p=0.006$ by paired stepwise comparison). No cases of severe hypoglycaemia were observed for TRULICITY and two cases of severe hypoglycaemia were observed with exenatide twice daily.

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 TRULICITY 0.75 mg or TRULICITY 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 TRULICITY 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.

**Table 6. Results of a 24 week placebo controlled study of dulaglutide as add-on to SGLT2i therapy**

| | **Baseline HbA1c (%)** | **Mean change in HbA1c (%)** | **Patients at target HbA1c** | | **Change in FBG (mmol/L)** | **Change in body weight (kg)** |
|---|---|---|---|---|---|---|
| | | | **<7.0% (%)** | **≤6.5% (%)** | | |
| **24 weeks** | | | | | | |
| Dulaglutide 0.75 mg once weekly (n=141) | 8.05 | -1.19‡‡ | 61.8‡‡ | 38.9** | -1.44 | -2.6 |
| Dulaglutide 1.5 mg once weekly (n=142) | 8.04 | -1.33‡‡ | 71.5‡‡ | 50.8** | -1.77 | -3.1 |
| Placebo (n=140) | 8.05 | -0.51 | 32.5 | 14.6 | -0.29 | -2.3 |

‡‡ $p < 0.001$ for superiority of dulaglutide compared to placebo, with overall type I error controlled

** $p < 0.001$ for dulaglutide treatment group compared to placebo

The rates of documented symptomatic hypoglycaemia with TRULICITY 0.75 mg, TRULICITY 1.5 mg, and placebo were 0.15, 0.16 and 0.12 episodes/patient/year, respectively. One patient reported severe hypoglycaemia with TRULICITY 0.75 mg in combination with SGLT2i therapy and none with TRULICITY 1.5 mg or placebo.

Combination with metformin and sulfonylurea

Study GBDB was a 78-week Phase 3, randomised, parallel-arm, open-label (double-blind with respect to dulaglutide dose assignment), active comparator (insulin glargine) trial to assess the safety and efficacy of 2 doses of once weekly dulaglutide (1.5 mg and 0.75 mg) in patients who were on stable doses of metformin and glimepiride. At 52 weeks, TRULICITY 1.5 mg demonstrated superior lowering in HbA1c to insulin glargine which was maintained at 78 weeks. This was accompanied by a significantly ($p< 0.001$) higher percentage of subjects reaching a target HbA1c of < 7.0 % or ≤ 6.5% at primary (52 weeks) and final (78 weeks) time points. Subjects treated with TRULICITY lost a mean of 1.87 kg in comparison to a gain of 1.44 kg in the insulin glargine arm ($p< 0.001$) in the first 52 weeks and this effect was sustained to 78 weeks. The rate of documented symptomatic hypoglycaemia with TRULICITY 1.5 mg was 1.67 episodes/patient/year and with insulin glargine was 3.03 episodes/patient/year ($p=0.012$). Two cases of severe hypoglycaemia were observed with TRULICITY and two cases of severe hypoglycaemia were observed with insulin glargine.

Combination therapy with sulfonylurea

The safety and efficacy of dulaglutide as add-on to a sulfonylurea was investigated in a placebo controlled study of 24 weeks duration. Treatment with TRULICITY 1.5mg in combination with glimepiride resulted in a statistically significant reduction in HbA1c compared to placebo with glimepiride at 24 weeks. With TRULICITY 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.

**Table 7. Results of a 24 week placebo controlled study of dulaglutide as add-on to glimepiride**

| | **Baseline HbA1c (%)** | **Mean change in HbA1c (%)** | **Patients at target HbA1c** | | **Change in FBG (mmol/L)** | **Change in body weight (kg)** |
|---|---|---|---|---|---|---|
| | | | **<7.0% (%)** | **≤6.5% (%)** | | |
| **24 weeks** | | | | | | |
| Dulaglutide 1.5 mg once weekly (n=239) | 8.39 | -1.38‡‡ | 55.3‡‡ | 40.0** | -1.70‡‡ | -0.91 |
| Placebo (n=60) | 8.39 | -0.11 | 18.9 | 9.4 | 0.16 | -0.24 |

‡‡ $p < 0.001$ for superiority of dulaglutide compared to placebo, with overall type I error controlled

** $p < 0.001$ for dulaglutide treatment group compared to placebo

The rates of documented symptomatic hypoglycaemia with TRULICITY 1.5 mg and placebo were 0.90 and 0.04 episodes/patient/year, respectively. No cases of severe hypoglycaemia were observed for TRULICITY or placebo.

*Combination with Prandial Insulin*

Study GBDD was a 52-week Phase 3, randomised, parallel-arm, open-label (double-blind with respect to dulaglutide dose assignment), active comparator (insulin glargine) trial to assess the safety and efficacy of 2 doses of once weekly dulaglutide (1.5 mg and 0.75 mg), both in combination with insulin lispro, with or without metformin, in patients previously treated with a stable, conventional insulin regimen for at least 3 months. 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 TRULICITY once weekly or insulin glargine once daily, both in combination with prandial insulin lispro three times daily, with or without metformin. At 26 weeks, TRULICITY 1.5 mg was superior to insulin glargine in lowering of HbA1c and this effect was sustained at 52 weeks. This was accompanied by a significant ($p< 0.001$) weight loss in comparison to insulin glargine, where weight gain was observed over the course of the study. A greater percentage of patients also achieved HbA1c targets of < 7.0 % or ≤ 6.5% at 26 weeks ($p< 0.05$) and <7.0 % at 52 weeks ($p< 0.05$) when treated with TRULICITY than with insulin glargine. The rate of documented symptomatic hypoglycaemia with TRULICITY 1.5 mg was 31.06 episodes/patient/year and with insulin glargine was 40.95 episodes/patient/year. Ten patients reported severe hypoglycaemia with TRULICITY and fifteen with insulin glargine.

*Use in patients with renal impairment*

In a 52 week study, TRULICITY 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 TRULICITY 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.

**Table 8. Results of a 52 week active controlled study with two doses of dulaglutide in comparison to insulin glargine (in patients with moderate to severe chronic kidney disease)**

| | Baseline HbA1c (%) | Mean change in HbA1c (%) | Patients at target HbA1c <8.0% (%) | Change in FBG (mmol/L) | Change in body weight (kg) |
|---|---|---|---|---|---|
| **26 weeks** | | | | | |
| Dulaglutide 0.75 mg once weekly (n=190) | 8.58 | -1.12† | 72.6 | 0.98## | -2.02## |
| Dulaglutide 1.5 mg once weekly (n=192) | 8.60 | -1.19† | 78.3 | 1.28## | -2.81## |
| Insulin glargine+ once daily (n=194) | 8.56 | -1.13 | 75.3 | -1.06 | 1.11 |
| **52 weeks** | | | | | |
| Dulaglutide 0.75 mg once weekly (n=190) | 8.58 | -1.10† | 69.5 | 1.15## | -1.71## |
| Dulaglutide 1.5 mg once weekly (n=192) | 8.60 | -1.10† | 69.1 | 1.57## | -2.66## |
| Insulin glargine+ once daily (n=194) | 8.56 | -1.00 | 70.3 | -0.35 | 1.57 |

† 1-sided p-value < 0.025, for non-inferiority of dulaglutide to insulin glargine

## p < 0.001 dulaglutide treatment group compared to insulin glargine

+ Insulin glargine doses were adjusted utilizing an algorithm with a fasting plasma glucose target of ≤ 8.3 mmol/L

The rates of documented symptomatic hypoglycaemia with TRULICITY 1.5 mg and TRULICITY 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 TRULICITY 1.5 mg, six with TRULICITY 0.75 mg, and seventeen with insulin glargine. The safety profile of TRULICITY in patients with renal impairment was similar to that observed in other studies with TRULICITY.

Fasting Blood glucose

Treatment with TRULICITY 1.5 mg resulted in significant reductions from baseline in fasting blood glucose (least-square mean changes from baseline to primary time point -0.27 mmol/L to -2.38 mmol/L). 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 TRULICITY 1.5 mg resulted in significant reductions in self-monitored mean post prandial glucose from baseline (least-square mean changes from baseline to primary time point -1.95 mmol/L to -4.23 mmol/L).

Beta cell function

Clinical studies with TRULICITY 1.5 mg 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

TRULICITY 1.5 mg was associated with sustained weight reduction over the duration of studies (least square mean change from baseline to final time point -0.35 kg to -2.88 kg). This was significant ($p< 0.001$) in comparison to sitagliptin and insulin glargine and comparable to exenatide twice daily and metformin. Reduction in body weight was observed in patients treated with TRULICITY irrespective of nausea, though the reduction was numerically larger in the group with nausea.

Patient Reported Outcomes

TRULICITY 1.5 mg significantly improved ($p< 0.05$) total treatment satisfaction as measured by the Diabetes Treatment Satisfaction Questionnaire (DTSQs) compared to exenatide twice daily. In addition, there was significantly ($p< 0.05$) lower perceived frequency of hyperglycaemia and hypoglycaemia compared to exenatide twice daily.

Blood Pressure

The effect of TRULICITY 1.5 mg on blood pressure as assessed by Ambulatory Blood Pressure Monitoring was evaluated in a study of 755 patients with type 2 diabetes. Treatment with TRULICITY 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.

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-neutralising antibodies, and 36 patients (0.9% of the overall population) developed antibodies against native GLP-1.

Patients with dulaglutide ADAs generally had low titres and although the number of patients developing dulaglutide ADAs was low, examination of the phase III data revealed no clear impact of dulaglutide ADAs on changes in HbA1c.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising 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.

Hypersensitivity

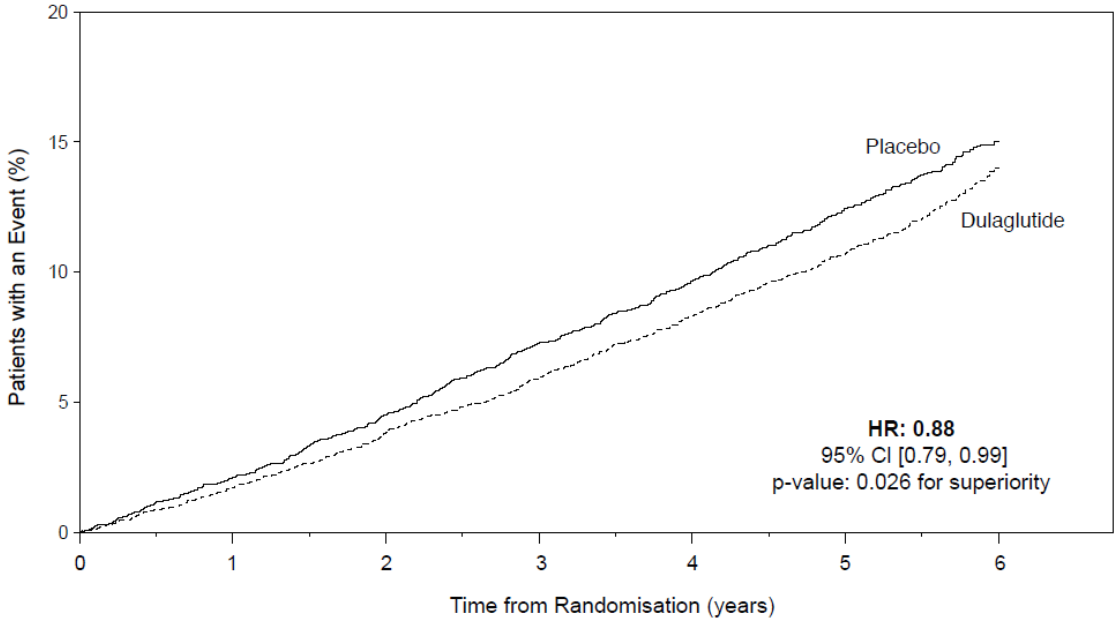
In the Phase 2 and Phase 3 clinical studies, systemic hypersensitivity events (e.g., urticaria, angiooedema) have been reported in 0.5% of patients receiving dulaglutide at any dose for any duration. None of the patients with systemic hypersensitivity developed dulaglutide anti-drug antibodies.

*Cardiovascular outcome study*

The TRULICITY long-term cardiovascular outcome study was a placebo-controlled, double-blind clinical trial. Type 2 diabetes patients 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/m$^2$, and 46.3 % of patients were female. There were 6,221 (62.8 %) patients with multiple cardiovascular (CV) risk factors but without established CV disease, and 3,114 (31.5 %) patients with established CV disease. The median baseline HbA1c was 7.2 %. The majority of patients had a baseline HbA1c ranging from 6.0 % - 8.9 % (10$^{th}$ - 90$^{th}$ percentile). The mean duration of diabetes was 10.5 years. The TRULICITY treatment arm included patients ≥ 65 years (n = 2,619; 52.9 %) and ≥ 75 years (n = 484; 9.7 %), and patients with mild (n = 2,435; 50.2 %), moderate (n = 1,031; 21.3 %) or severe (n = 50; 1.1 %) renal impairment.

The primary endpoint was the time from randomisation to first occurrence of any major adverse cardiovascular events (MACE): CV death, non-fatal myocardial infarction, or non-fatal stroke. Primary outcome status or vital status at the end of study was available for 99.7 % of participants randomised to TRULICITY and placebo. TRULICITY was superior in preventing MACE compared to placebo (Figure 2). TRULICITY-treated patients had a lower rate of MACE as compared to placebo [HR: 0.88; 95 % CI (0.79, 0.99]). Each MACE component contributed to the reduction of MACE, as shown in Figure 3. The efficacy of TRULICITY on MACE was consistent across major demographic and disease subgroups, including prior cardiovascular disease status, baseline HbA1c, gender, duration of diabetes, age, and eGFR.




**Number of patients at risk**

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

**Figure 2**: **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 outcome study**

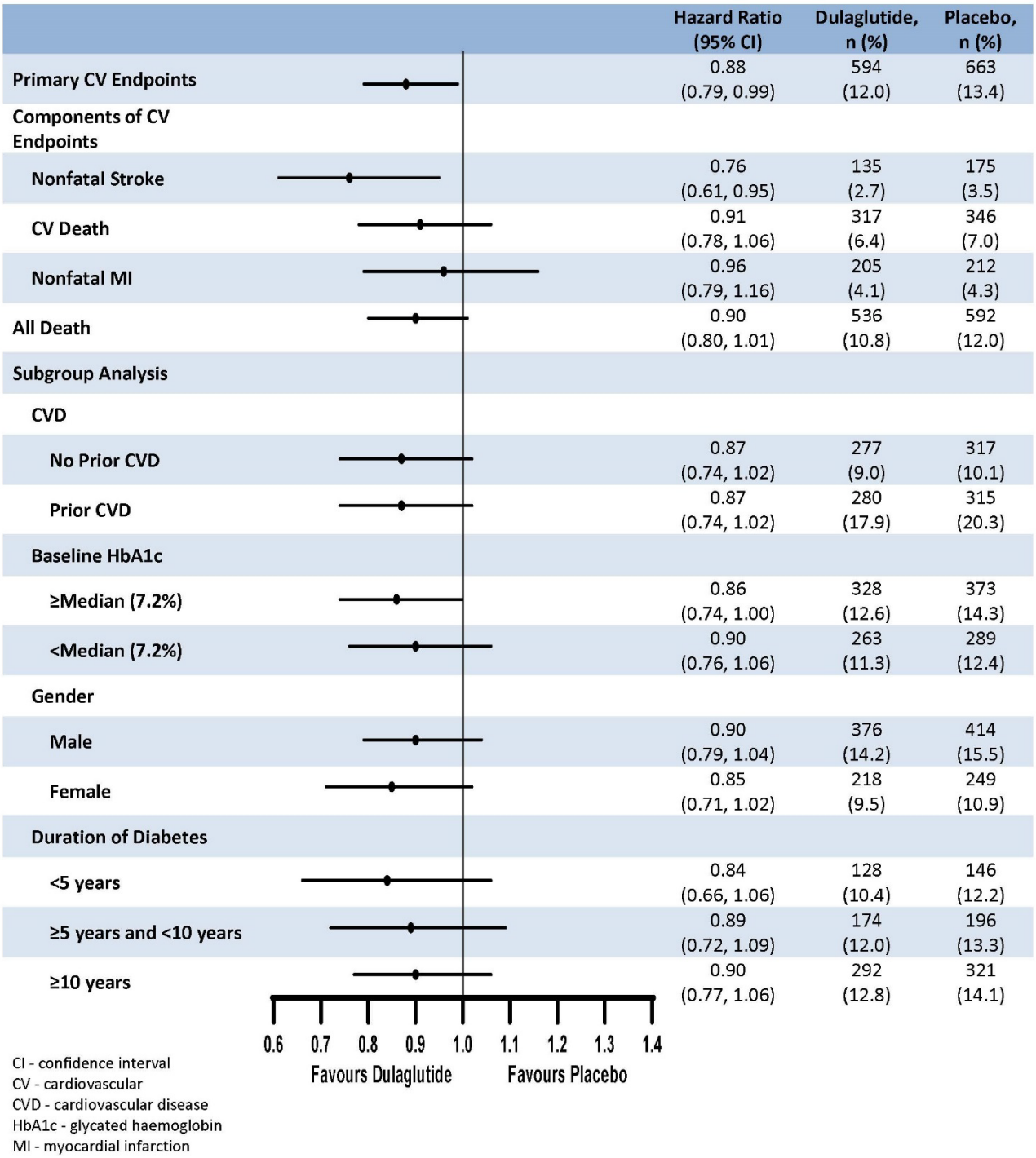



**Figure 3**: **Forest plot of analyses of individual cardiovascular event types, all cause death, and subgroups for the primary endpoint**

A significant and sustained reduction in HbA1c 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 %]; $p < 0.001$).

QTc Interval

Dulaglutide did not prolong QTc interval at supratherapeutic doses of 4 mg and 7 mg as assessed in a thorough QTc study.

## 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 ng·h/mL, respectively after multiple subcutaneous 1.5 mg doses of dulaglutide in patients with type 2 diabetes. Steady state plasma concentrations were achieved after 2 to 4 weeks of once-weekly administration of dulaglutide 1.5 mg. Exposures after subcutaneous administration of single 1.5 mg dulaglutide doses in the abdomen, thigh or upper arm were comparable. The mean absolute bioavailability of dulaglutide following a single dose subcutaneous administration of one 1.5 mg dose was approximately 47%.

### Distribution

The mean volume of distribution after subcutaneous administration of dulaglutide 1.5 mg to steady state in patients with type 2 diabetes mellitus was approximately 17.4 L.

### Metabolism

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

### Elimination

The mean apparent clearance of dulaglutide in humans at steady state was 0.107 L/h with an elimination half- life of 4.7 days.

### Special Populations

No dose adjustment is needed based on age, gender, race, ethnicity, body weight, or renal or hepatic impairment.

*Elderly*

Age had no clinically relevant effect on the pharmacokinetics or pharmacodynamics of dulaglutide.

*Gender and race*

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

*Renal Impairment*

The pharmacokinetics of dulaglutide were evaluated in subjects with varying degrees of renal impairment, and were generally similar between healthy subjects and patients with mild (creatinine clearance 60 to <90 mL/min) to severe renal impairment (creatinine clearance <30 mL/min not requiring dialysis), including end stage renal disease (creatinine clearance <15 mL/min requiring dialysis treatment) 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 TRULICITY 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 subjects with varying degrees of hepatic impairment. Subjects with hepatic impairment had statistically significant decreases in dulaglutide exposure of up to 30% and 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 clinically relevant.

*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.

### 5.3 PRECLINICAL SAFETY DATA

**Genotoxicity**

The genotoxic potential of dulaglutide has not been assessed. As a large molecular weight protein, dulaglutide is not expected to interact with DNA or other chromosomal material.

**Carcinogenicity**

In a 93-week carcinogenicity study in rats, dulaglutide caused statistically significant, dose-related increases in the incidence of thyroid C-cell tumours (adenomas and carcinomas combined) with subcutaneous administration at ≥0.5 mg/kg twice weekly, yielding ≥ 7 times the human clinical exposure following once weekly administration of 1.5 mg dulaglutide. Exposure (plasma AUC) at the no observable effect level for carcinogenicity in the rat (0.05 mg/kg) was subclinical. The human relevance of these findings is unknown. There was no tumourgenic response in a 6-month carcinogenicity study in transgenic mice with subcutaneous doses ≤3 mg/kg twice weekly, yielding exposures up to 5 times higher than that in patients at the maximum recommended human dose.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

TRULICITY contains the excipients sodium citrate dihydrate, citric acid, mannitol, polysorbate 80 and water for injections.

### 6.2 INCOMPATIBILITIES

Incompatibilities were not identified as part of the registration of this medicine (see **4.5 Interactions with other medicines and other forms of interactions**).

## 6.3 SHELF-LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

TRULICITY ready-to-use pre-filled pens should be stored at 2°C - 8°C. Refrigerate. Do not freeze. TRULICITY may be stored unrefrigerated for up to 14 days at temperatures up to 30°C. Protect from light.

## 6.5 NATURE AND CONTENTS OF CONTAINER

TRULICITY is available as a single dose, ready-to-use pre-filled pen (autoinjector). The product is contained in a 1 mL-long, Type 1 borosilicate glass syringe with a bromobutyl plunger. The syringe has a 29G thin wall ½" staked needle.

TRULICITY is available in pack sizes of 2 or 4 ready-to-use pre-filled pens.

Not all pack sizes may be marketed.

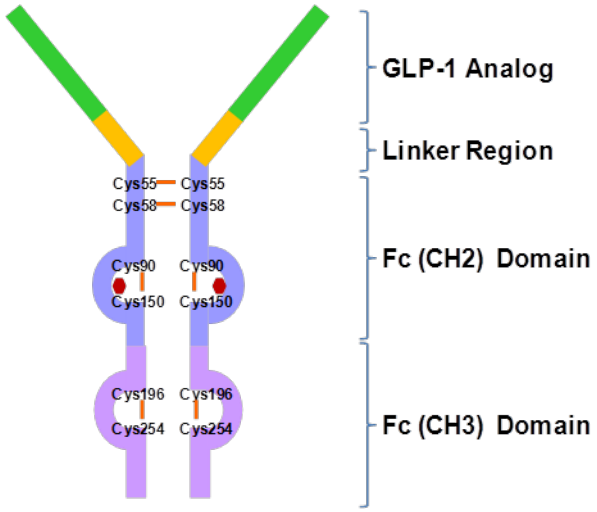
## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

### Chemical structure

Dulaglutide (rch) consists of 2 identical disulfide-linked chains, each containing a modified human glucagon-like peptide 1 (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 analogue portion of dulaglutide is approximately 90% homologous to native human GLP-1 (7-37).



The GLP-1 analogue, linker region, and IgG4 Fc CH2 and CH3 domains are depicted above. The 12 Cys residues that are involved in the inter-chain and intra-chain disulfide bonding are also shown. The hexagonal symbol represents the *N*-linked glycosylation at Asn126 in each polypeptide chain.

The molecular weight of dulaglutide with the predominant form of *N*-linked glycosylation is 62,561 Da.

**CAS number**

923950-08-7

## 7. MEDICINE SCHEDULE

S4 – Prescription Medicine

## 8. SPONSOR

Eli Lilly Australia Pty Ltd
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## 9. DATE OF FIRST APPROVAL

19 January 2015

## 10. DATE OF REVISION

28 May 2026

**SUMMARY TABLE OF CHANGES**

| Section changed | Summary of new information |
|---|---|
| 4.8 | Safety information included in Postmarketing Data section for NAION, dysaesthesia, dysgeusia, and alopecia to harmonise information across the GLP-1 receptor agonist class. |