ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trulicity 0.75 mg solution for injection in pre-filled pen
Trulicity 1.5 mg solution for injection in pre-filled pen
Trulicity 3 mg solution for injection in pre-filled pen
Trulicity 4.5 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Trulicity 0.75 mg solution for injection in pre-filled pen

Each pre-filled pen contains 0.75 mg of dulaglutide* in 0.5 ml solution.

Excipient with known effect:

One ml of solution contains 0.20 mg polysorbate 80.

Trulicity 1.5 mg solution for injection in pre-filled pen

Each pre-filled pen contains 1.5 mg of dulaglutide* in 0.5 ml solution.

Excipient with known effect:

One ml of solution contains 0.20 mg polysorbate 80.

Trulicity 3 mg solution for injection in pre-filled pen

Each pre-filled pen contains 3 mg of dulaglutide* in 0.5 ml solution.

Excipient with known effect:

One ml of solution contains 0.25 mg polysorbate 80.

Trulicity 4.5 mg solution for injection in pre-filled pen

Each pre-filled pen contains 4.5 mg of dulaglutide* in 0.5 ml solution.

Excipient with known effect:

One ml of solution contains 0.25 mg polysorbate 80.

*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 solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Type 2 Diabetes Mellitus

Trulicity is indicated for the treatment of patients 10 years and above with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes.

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

4.2 Posology and method of administration

Posology

Adults

Monotherapy
The recommended dose is 0.75 mg once weekly.

Add-on therapy
The recommended dose is 1.5 mg once weekly.

If needed,

- the 1.5 mg dose can be increased after at least 4 weeks to 3 mg once weekly.
- the 3 mg dose can be increased after at least 4 weeks to 4.5 mg once weekly.

The maximum dose is 4.5 mg once weekly.

Paediatrics

The starting dose for paediatric patients 10 years and above is 0.75 mg once weekly.

If needed, the dose can be increased to 1.5 mg once weekly after at least 4 weeks. The maximum dose is 1.5 mg once weekly.

Combination therapy

When Trulicity is added to existing metformin and/or pioglitazone therapy, the current dose of metformin and/or pioglitazone can be continued. When Trulicity is added to existing metformin and/or sodium-glucose co-transporter 2 inhibitor (SGLT2i) therapy, the current dose of metformin and/or SGLT2i can be continued. When it is added to existing therapy of a sulphonylurea or insulin, a reduction in the dose of sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia (see sections 4.4 and 4.8).

The use of Trulicity does not require blood glucose self-monitoring. Blood glucose self-monitoring is necessary to adjust the dose of sulphonylurea or insulin, particularly when Trulicity therapy is started and insulin is reduced. A stepwise approach to insulin dose reduction is recommended.

Missed doses

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 (72 hours) 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.

Special population

Elderly
No dose adjustment is required based on age (see section 5.2).

Renal impairment
No dose adjustment is required in patients with mild, moderate or severe renal impairment (eGFR < 90 to ≥ 15 mL/min/1.73m^2).

There is very limited experience in patients with end stage renal disease (< 15 ml/min/1.73m^2), therefore Trulicity cannot be recommended in this population (see sections 5.1 and 5.2).

Hepatic impairment
No dose adjustment is required in patients with hepatic impairment.

Paediatric population
The safety and efficacy of dulaglutide in children aged less than 10 years have not been established and no data are available (see sections 5.1 and 5.2).

Method of administration

Trulicity is to be injected subcutaneously in the abdomen, thigh or upper arm. It should not be administered intravenously or intramuscularly.

The dose can be administered at any time of day, with or without meals.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered medicinal product should be clearly recorded.

Type 1 diabetes mellitus or diabetic ketoacidosis

Dulaglutide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Dulaglutide 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).

Severe gastrointestinal disease

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.

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.

Dehydration

Dehydration, sometimes leading to acute renal failure or worsening renal impairment, has been reported in patients treated with dulaglutide, 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 dulaglutide should be advised of the potential risk of dehydration, particularly in relation to gastrointestinal adverse reactions and take precautions to avoid fluid depletion.

Acute pancreatitis

Use of GLP-1 receptor agonists has been associated with a risk of developing acute pancreatitis. In clinical trials, acute pancreatitis has been reported in association with dulaglutide (see section 4.8).

Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, dulaglutide should be discontinued. If pancreatitis is confirmed, dulaglutide should not be restarted. 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

Patients receiving dulaglutide in combination with sulphonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of sulphonylurea or insulin (see sections 4.2 and 4.8).

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium- free’.

Polysorbate

Trulicity 0.75 mg and 1.5 mg, solution for injection in pre-filled pen
This medicinal product contains 0.10 mg of polysorbate 80 in each 0.5 ml dose which is equivalent to 0.20 mg/ml.

Polysorbates may cause allergic reactions.

Trulicity 3 mg and 4.5 mg, solution for injection in pre-filled pen
This medicinal product contains 0.125 mg of polysorbate 80 in each 0.5 ml dose which is equivalent to 0.25 mg/ml.

Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Dulaglutide delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. In the clinical pharmacology studies described below, dulaglutide doses up to 1.5 mg did not affect the absorption of the orally administered medicinal products tested to any clinically relevant degree. For the 4.5 mg dose, absence of major clinically relevant interactions was predicted by physiologically-based pharmacokinetic (PBPK) modelling simulations.

For patients receiving dulaglutide in combination with oral medicinal products with rapid gastrointestinal absorption or prolonged release, there is a potential for altered medicinal product exposure, particularly at the time of dulaglutide treatment initiation.

Sitagliptin

Sitagliptin exposure was unaffected when coadministered with a single 1.5 mg dose of dulaglutide. Following coadministration with 2 consecutive 1.5 mg doses of dulaglutide, sitagliptin $AUC_{(0-\tau)}$ and C_{max} decreased by approximately 7.4 % and 23.1 %, respectively. Sitagliptin t_{max} increased approximately 0.5 hours following coadministration with dulaglutide compared to sitagliptin alone.

Sitagliptin can produce up to 80 % inhibition of DPP-4 over a 24-hour period. Dulaglutide (1.5 mg) coadministration with sitagliptin increased dulaglutide exposure and C_{max} by approximately 38 % and 27 %, respectively, and median t_{max} increased approximately 24 hours. Therefore, dulaglutide does have a high degree of protection against DPP-4 inactivation (see section 5.1, Mechanism of action). The increased exposure may enhance the effects of dulaglutide on blood glucose levels.

Paracetamol

Following a first dose of 1 and 3 mg dulaglutide, paracetamol C_{max} was reduced by 36 % and 50 %, respectively, and the median t_{max} occurred later (3 and 4 hours, respectively). After coadministration with up to 3 mg of dulaglutide at steady state, there were no statistically significant differences on $AUC_{(0-12)}$, C_{max} or t_{max} of paracetamol. No dose adjustment of paracetamol is necessary when administered with dulaglutide.

Atorvastatin

Coadministration of 1.5 mg of dulaglutide with atorvastatin decreased C_{max} and $AUC_{(0-\infty)}$ up to 70 % and 21 %, respectively, for atorvastatin and its major metabolite *o*-hydroxyatorvastatin. The mean $t_{1/2}$ of atorvastatin and *o*-hydroxyatorvastatin were increased by 17 % and 41 %, respectively, following dulaglutide administration. These observations are not clinically relevant. No dose adjustment of atorvastatin is necessary when administered with dulaglutide.

Digoxin

After coadministration of steady state digoxin with 2 consecutive 1.5 mg doses of dulaglutide, overall exposure (AUC_{τ}) and t_{max} of digoxin were unchanged; and C_{max} decreased by up to 22 %. This change

is not expected to have clinical consequences. No dose adjustment is required for digoxin when administered with dulaglutide.

Anti-hypertensives

Coadministration of multiple dulaglutide 1.5 mg doses with steady state lisinopril caused no clinically relevant changes in the AUC or C_{max} of lisinopril. Statistically significant delays in lisinopril t_{max} of approximately 1 hour were observed on Days 3 and 24 of the study. When a single 1.5 mg dose of dulaglutide and metoprolol were coadministered, the AUC and C_{max} of metoprolol increased by19 % and 32 %, respectively. While metoprolol t_{max} was delayed by 1 hour, this change was not statistically significant. These changes were not clinically relevant; therefore, no dose adjustment of lisinopril or metoprolol is necessary when administered with dulaglutide.

Warfarin

Following dulaglutide (1.5 mg) coadministration, S- and R-warfarin exposure and R-warfarin C_{max} were unaffected, and S-warfarin C_{max} decreased by 22 %. AUC_{INR} increased by 2 %, which is unlikely to be clinically significant, and there was no effect on maximum international normalised ratio response (INR_{max}). The time of international normalised ratio response ($tINR_{max}$) was delayed by 6 hours, consistent with delays in t_{max} of approximately 4 and 6 hours for S- and R-warfarin, respectively. These changes are not clinically relevant. No dose adjustment for warfarin is necessary when given together with dulaglutide.

Oral contraceptives

Coadministration of dulaglutide (1.5 mg) with an oral contraceptive (norgestimate 0.18 mg/ethinyl estradiol 0.025 mg) did not affect the overall exposure to norelgestromin and ethinyl estradiol. Statistically significant reductions in C_{max} of 26 % and 13 % and delays in t_{max} of 2 and 0.30 hours were observed for norelgestromin and ethinyl estradiol, respectively. These observations are not clinically relevant. No dose adjustment for oral contraceptives is required when given together with dulaglutide.

Metformin

Following coadministration of multiple 1.5 mg doses of dulaglutide with steady state metformin (immediate release formula [IR]), metformin AUC_{τ} increased up to 15 % and C_{max} decreased up to 12 %, respectively, with no changes in t_{max}. These changes are consistent with the gastric emptying delay of dulaglutide and within the pharmacokinetic variability of metformin and thus are not clinically relevant. No dose adjustment for metformin IR is recommended when given with dulaglutide.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

It is unknown whether dulaglutide is excreted in human milk. A risk to newborns/infants cannot be excluded. Dulaglutide should not be used during breast-feeding.

Fertility

The effect of dulaglutide on fertility in humans is unknown. In the rat, there was no direct effect on mating or fertility following treatment with dulaglutide (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 2 and phase 3 studies to support the initial registration of dulaglutide 0.75 mg and 1.5 mg, 4,006 patients were exposed to dulaglutide alone or in combination with other glucose lowering medicinal products. 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 outcome study with 4,949 patients randomised to dulaglutide 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 2 and phase 3 clinical studies, the long-term cardiovascular outcome 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 2 and phase 3 registration studies.

Table 1. The frequency of adverse reactions of dulaglutide

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 metformin plus glimepiride)	Hypoglycaemia* (when used as monotherapy or in combination with metformin plus pioglitazone)	Dehydration		

Nervous system disorders			Dysgeusia		
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
† For dulaglutide 0.75 mg, adverse reaction met frequency for next lower incidence grouping.
[$] The frequency seen in a paediatric study was common; 3.9 % (2 patients) in the dulaglutide 0.75 mg group, 3.8 % (2 patients) in the dulaglutide 1.5 mg group and 2 % (1 patient) in the placebo group. All events were mild to moderate in severity.

Description of selected adverse reactions

Hypoglycaemia
When dulaglutide 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 dulaglutide 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 dulaglutide 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 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.

The incidences when dulaglutide 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.

In a phase 3 study through to week 52, when dulaglutide 1.5 mg, 3 mg and 4.5 mg were used in combination with metformin, the incidences of documented symptomatic hypoglycaemia were 3.1 %, 2.4 % and 3.1 %, respectively, and rates were 0.07, 0.05 and 0.07 events/patient/year; one episode of severe hypoglycaemia was reported with dulaglutide 1.5 mg and 4.5 mg, respectively.

Gastrointestinal adverse reactions
Cumulative reporting of gastrointestinal events up to 104 weeks with dulaglutide 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 a phase 3 study with 1.5 mg, 3 mg and 4.5 mg dulaglutide doses respectively, cumulative reporting of gastrointestinal events through to 52 weeks included nausea (14.2 %, 16.1 % and 17.3 %), diarrhoea (7.7 %, 12.0 % and 11.6 %) and vomiting (6.4 %, 9.1 % and 10.1 %). 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 2 and 3 registration studies was 0.07 % for dulaglutide 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
Dulaglutide 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 dulaglutide 0.75 mg and 1.5 mg, respectively.

In a phase 3 study with 1.5 mg, 3 mg and 4.5 mg dulaglutide doses, the incidence of sinus tachycardia, with a concomitant increase from baseline ≥ 15 bpm, was 2.6 %, 1.9 % and 2.6 % respectively. Mean increases in heart rate of 1 – 4 beats per minute (bpm) were observed.

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 dulaglutide 0.75 mg and 1.5 mg, respectively.

In a phase 3 study with 1.5 mg, 3 mg and 4.5 mg dulaglutide doses, the incidence of first-degree AV block was 1.2 %, 3.8 % and 1.7 % respectively. Mean increases from baseline in PR interval of 3 – 5 msec were observed.

Immunogenicity
In registration studies, treatment with dulaglutide was associated with a 1.6 % incidence of treatment emergent dulaglutide 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 dulaglutide. Patients with dulaglutide anti-drug antibodies generally had low titres, and although the number of patients developing dulaglutide anti-drug antibodies was low, examination of the phase 3 data revealed no clear impact of dulaglutide anti-drug antibodies on changes in HbA1c. None of the patients with systemic hypersensitivity developed dulaglutide anti-drug antibodies.

Hypersensitivity
In the phase 2 and phase 3 registration studies, systemic hypersensitivity events (e.g., urticaria, edema) were reported in 0.5 % of patients receiving dulaglutide. Cases of anaphylactic reaction have been rarely reported with marketed use of dulaglutide.

Injection site reactions
Injection site adverse events were reported in 1.9 % of patients receiving dulaglutide. 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 dulaglutide 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 dulaglutide. The most frequent adverse reactions leading to discontinuation for 0.75 mg and 1.5 mg dulaglutide, 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.

In a phase 3 study with 1.5 mg, 3 mg and 4.5 mg dulaglutide doses, the incidence of discontinuation due to adverse events through 52 weeks was 6.0 % (1.5 mg), 7.0 % (3 mg) and 8.5 % (4.5 mg). The most frequent adverse reactions leading to discontinuation for dulaglutide 1.5 mg, 3 mg and 4.5 mg, respectively, were nausea (1.3 %, 1.3 %, 1.5 %), diarrhoea (0.2 %, 1.0 %, 1.0 %), and vomiting (0.0 %, 0.8 %, 1.3 %).

Dulaglutide doses of 3 mg and 4.5 mg
The safety profile in patients treated with dulaglutide 3 mg and 4.5 mg once weekly is consistent with that described above for dulaglutide doses of 0.75 mg and 1.5 mg once weekly.

Paediatric population
The safety profile in paediatric patients aged 10 years and above treated with dulaglutide 0.75 mg and 1.5 mg once-weekly is comparable with that described above for adult patients.

The immunogenicity profile in paediatric patients treated with dulaglutide is consistent with that described above for adult patients. In the paediatric study, 2.1 % and 4.0 % of patients treated with placebo and dulaglutide respectively developed treatment emergent dulaglutide anti-drug antibodies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

Effects of overdose with dulaglutide 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: Drugs used in diabetes, blood glucose lowering drugs, excl. insulins, 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 ten randomised, controlled, phase 3 trials involving 8,035 patients with type 2 diabetes. Of these, 1,644 were ≥ 65 years of which 174 were ≥ 75 years. These studies included 5,650 dulaglutide treated patients, of whom 1,558 were treated

with Trulicity 0.75 mg weekly, 2,862 were treated with Trulicity 1.5 mg weekly, 616 were treated with Trulicity 3 mg weekly and 614 were treated with Trulicity 4.5 mg weekly. 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. Trulicity 1.5 mg and 0.75 mg were superior to metformin (1500 - 2000 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 Trulicity 1.5 mg and Trulicity 0.75 mg compared to metformin at 26 weeks.

Table 2. Results of a 52-week active controlled monotherapy study with two doses of dulaglutide in comparison to metformin

	Baseline HbA1c (%)	**Mean change in HbA1c (%)**	**Patients at target HbA1c**		**Change in FBG (mmol/L)**	**Change in body weight (kg)**
			< 7.0 % (%)[a]	**≤ 6.5 % (%)[b]**		
26 weeks						
Dulaglutide 1.5 mg once weekly (n = 269)	7.63	-0.78[††]	61.5[#]	46.0[##]	-1.61	-2.29
Dulaglutide 0.75 mg once weekly (n = 270)	7.58	-0.71[††]	62.6[#]	40.0[#]	-1.46	-1.36[#]
Metformin 1500 - 2000 mg/day (n = 268)	7.60	-0.56	53.6	29.8	-1.34	-2.22
52 weeks						
Dulaglutide 1.5 mg once weekly (n = 269)	7.63	-0.70[††]	60.0[#]	42.3[##]	-1.56[#]	-1.93
Dulaglutide 0.75 mg once weekly (n = 270)	7.58	-0.55[†]	53.2	34.7	-1.00	-1.09[#]
Metformin 1500 - 2000 mg/day (n = 268)	7.60	-0.51	48.3	28.3	-1.15	-2.20

[†] multiplicity adjusted 1-sided p-value < 0.025, for noninferiority; [††] multiplicity adjusted 1-sided p-value < 0.025, for superiority of dulaglutide to metformin, assessed for HbA1c only
[#] $p < 0.05$, [##] $p < 0.001$ dulaglutide treatment group compared to metformin
[a] HbA1c value of 7.0 % (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)
[b] HbA1c value of 6.5 % (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)
FBG = fasting blood glucose; DCCT = Diabetes Control and Complications Trial; IFCC = International Federation of Clinical Chemistry and Laboratory Medicine

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 Trulicity 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).

Table 3. Results of a 104-week placebo and active controlled study with two doses of dulaglutide in comparison to sitagliptin

	Baseline HbA1c (%)	**Mean change in HbA1c (%)**	**Patients at target HbA1c**		**Change in FBG (mmol/L)**	**Change in body weight (kg)**
			< 7.0 % (%)[a]	**≤ 6.5 % (%)[b]**		
26 weeks						
Dulaglutide 1.5 mg once weekly (n = 304)	8.12	-1.22‡‡,##	60.9**,##	46.7**,##	-2.38**,##	-3.18**,##
Dulaglutide 0.75 mg once weekly (n = 302)	8.19	-1.01‡‡,##	55.2**,##	31.0**,##	-1.97**,##	-2.63**,##
Placebo (n = 177)	8.10	0.03	21.0	12.5	-0.49	-1.47
Sitagliptin 100 mg once daily (n = 315)	8.09	-0.61	37.8	21.8	-0.97	-1.46
52 weeks						
Dulaglutide 1.5 mg once weekly (n = 304)	8.12	-1.10††	57.6##	41.7##	-2.38##	-3.03##
Dulaglutide 0.75 mg once weekly (n = 302)	8.19	-0.87††	48.8##	29.0##	-1.63##	-2.60##
Sitagliptin 100 mg once daily (n = 315)	8.09	-0.39	33.0	19.2	-0.90	-1.53
104 weeks						
Dulaglutide 1.5 mg once weekly (n = 304)	8.12	-0.99††	54.3##	39.1##	-1.99##	-2.88##
Dulaglutide 0.75 mg once weekly (n = 302)	8.19	-0.71††	44.8##	24.2##	-1.39##	-2.39
Sitagliptin 100 mg once daily (n = 315)	8.09	-0.32	31.1	14.1	-0.47	-1.75

†† multiplicity adjusted 1-sided p-value < 0.025, for superiority of dulaglutide compared to sitagliptin, assessed only for HbA1c at 52 and 104 weeks

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

** p < 0.001 dulaglutide treatment group compared to placebo

p < 0.001 dulaglutide treatment group compared to sitagliptin

[a] HbA1c value of 7.0 % (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)

[b] HbA1c value of 6.5 % (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

The rates of documented symptomatic hypoglycaemia with dulaglutide 1.5 mg and 0.75 mg, and sitagliptin were 0.19, 0.18, and 0.17 episodes/patient/year, respectively. No cases of severe hypoglycaemia with dulaglutide were observed.

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 Trulicity 1.5 mg resulted in similar lowering of HbA1c and patients achieving HbA1c targets of < 7.0 % and ≤ 6.5 % compared to liraglutide.

Table 4. Results of a 26-week active controlled study of one dose of dulaglutide in comparison to liraglutide

	Baseline HbA1c (%)	**Mean change in HbA1c (%)**	**Patients at target HbA1c**		**Change in FBG (mmol/L)**	**Change in body weight (kg)**
			< 7.0 % (%)[a]	**≤ 6.5 % (%)[b]**		
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.

[a] HbA1c value of 7.0 % (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)

[b] HbA1c value of 6.5 % (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

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, Trulicity 1.5 mg demonstrated superior lowering in HbA1c to insulin glargine which was maintained at 78 weeks; whereas lowering in HbA1c with Trulicity 0.75 mg was non-inferior to insulin glargine. With Trulicity 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.

Table 5. Results of a 78-week active controlled study with two doses of dulaglutide in comparison to insulin glargine

	Baseline HbA1c (%)	Mean change in HbA1c (%)	Patients at target HbA1c < 7.0 % (%)[a]	Patients at target HbA1c ≤ 6.5 % (%)[b]	Change in FBG (mmol/L)	Change in body weight (kg)
52 weeks						
Dulaglutide 1.5 mg once weekly (n = 273)	8.18	-1.08††	53.2##	27.0##	-1.50	-1.87##
Dulaglutide 0.75 mg once weekly (n = 272)	8.13	-0.76†	37.1	22.5#	-0.87##	-1.33##
Insulin glargine+ once daily (n = 262)	8.10	-0.63	30.9	13.5	-1.76	1.44
78 weeks						
Dulaglutide 1.5 mg once weekly (n = 273)	8.18	-0.90††	49.0##	28.1##	-1.10#	-1.96##
Dulaglutide 0.75 mg once weekly (n = 272)	8.13	-0.62†	34.1	22.1	-0.58##	-1.54##
Insulin glargine+ once daily (n = 262)	8.10	-0.59	30.5	16.6	-1.58	1.28

† multiplicity adjusted 1-sided p-value < 0.025, for noninferiority; †† multiplicity adjusted 1-sided p-value < 0.025, for superiority of dulaglutide to insulin glargine, assessed for HbA1c only

# $p < 0.05$, ## $p < 0.001$ dulaglutide treatment group compared to insulin glargine

+ Insulin glargine doses were adjusted utilising an algorithm with a fasting plasma glucose target of < 5.6 mmol/L

[a] HbA1c value of 7.0 % (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)

[b] HbA1c value of 6.5 % (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

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 Trulicity 1.5 mg 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 6. 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 < 7.0 % (%)[a]	Patients at target HbA1c ≤ 6.5 % (%)[b]	Change in FBG (mmol/L)	Change in body weight (kg)
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

[a] HbA1c value of 7.0 % (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)

[b] HbA1c value of 6.5 % (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

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 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 7. 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 < 7. 0%^ (%)[a]	Patients at target HbA1c ≤ 6.5 % (%)[b]	Change in FBG (mmol/L)	Change in body weight (kg)
24 weeks						
Dulaglutide 0.75 mg once weekly (n = 141)	8.05	-1.19‡‡	58.8‡‡	38.9**	-1.44	-2.6
Dulaglutide 1.5 mg once weekly (n = 142)	8.04	-1.33‡‡	67.4‡‡	50.8**	-1.77	-3.1
Placebo (n = 140)	8.05	-0.51	31.2	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

^ Patients who withdrew from randomised treatment before 24 weeks were considered as not meeting the target

[a] HbA1c value of 7.0 % (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)
[b] HbA1c value of 6.5 % (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

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, Trulicity 1.5 mg and 0.75 mg demonstrated superiority for HbA1c reduction in comparison to placebo and exenatide, accompanied by a significantly a greater percentage of patients achieving HbA1c targets of < 7.0 % or ≤ 6.5 %

Table 8. Results of a 52-week active controlled study with two doses of dulaglutide in comparison to exenatide

	Baseline HbA1c (%)	**Mean change in HbA1c (%)**	**Patients at target HbA1c**		**Change in FBG (mmol/L)**	**Change in body weight (kg)**
			< 7.0 % (%)[a]	**≤ 6.5 % (%)[b]**		
26 weeks						
Dulaglutide 1.5 mg once weekly (n = 279)	8.10	-1.51‡‡,††	78.2**,##	62.7**,##	-2.36**,##	-1.30**
Dulaglutide 0.75 mg once weekly (n = 280)	8.05	-1.30‡‡/††	65.8**/##	53.2**/##	-1.90**/##	0.20 */##
Placebo (n = 141)	8.06	-0.46	42.9	24.4	-0.26	1.24
Exenatide+ 10 mcg twice daily (n = 276)	8.07	-0.99	52.3	38.0	-1.35	-1.07
52 weeks						
Dulaglutide 1.5 mg once weekly (n = 279)	8.10	-1.36††	70.8##	57.2##	-2.04##	-1.10
Dulaglutide 0.75 mg once weekly (n = 280)	8.05	-1.07††	59.1#	48.3##	-1.58#	0.44#
Exenatide+ 10 mcg twice daily (n = 276)	8.07	-0.80	49.2	34.6	-1.03	-0.80

†† multiplicity adjusted 1-sided p-value < 0.025, for superiority of dulaglutide to exenatide, assessed for HbA1c only
‡‡ multiplicity adjusted 1-sided p-value < 0.001 for superiority of dulaglutide compared to placebo, assessed for HbA1c only
* $p < 0.05$, ** $p < 0.001$ dulaglutide treatment group compared to placebo
# $p < 0.05$, ## $p < 0.001$ dulaglutide treatment group compared to exenatide
+ Exenatide dose was 5 mcg twice daily for first 4 weeks and 10 mcg twice daily thereafter
[a] HbA1c value of 7.0 % (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)

[b] HbA1c value of 6.5 % (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

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, Trulicity1.5 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 1.5 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 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 9).

Table 9. 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 (mmol/L)**	**Change in body weight (kg)**
			< 7.0 % (%)[a]	**≤ 6.5 % (%)[b]**		
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
[a] HbA1c value of 7.0 % (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)
[b] HbA1c value of 6.5 % (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

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 prestudy 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 Trulicity 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.

Table 10. Results of a 52-week active controlled study with two doses of dulaglutide in comparison to insulin glargine

	Baseline HbA1c (%)	**Mean change in HbA1c (%)**	**Patients at target HbA1c**		**Change in FBG (mmol/L)**	**Change in body weight (kg)**
			< 7.0 % (%)[a]	**≤ 6.5 % (%)[b]**		
26 weeks						
Dulaglutide 1.5 mg once weekly (n = 295)	8.46	-1.64[††]	67.6[#]	48.0[#]	-0.27[##]	-0.87[##]
Dulaglutide 0.75 mg once weekly (n = 293)	8.40	-1.59[††]	69.0[#]	43.0	0.22[##]	0.18[##]
Insulin glargine[+] once daily (n = 296)	8.53	-1.41	56.8	37.5	-1.58	2.33
52 weeks						
Dulaglutide 1.5 mg once weekly (n = 295)	8.46	-1.48[††]	58.5[#]	36.7	0.08[##]	-0.35[##]
Dulaglutide 0.75 mg once weekly (n = 293)	8.40	-1.42[††]	56.3	34.7	0.41[##]	0.86[##]
Insulin glargine[+] once daily (n = 296)	8.53	-1.23	49.3	30.4	-1.01	2.89

[††] multiplicity adjusted 1-sided p-value < 0.025, for superiority of dulaglutide to insulin glargine, assessed for HbA1c only

[#] $p < 0.05$, [##] $p < 0.001$ dulaglutide treatment group compared to insulin glargine

[+] Insulin glargine doses were adjusted utilizing an algorithm with a fasting plasma glucose target of < 5.6 mmol/L

[a] HbA1c value of 7.0 % (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)

[b] HbA1c value of 6.5 % (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

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
Trulicity 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 Trulicity 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.

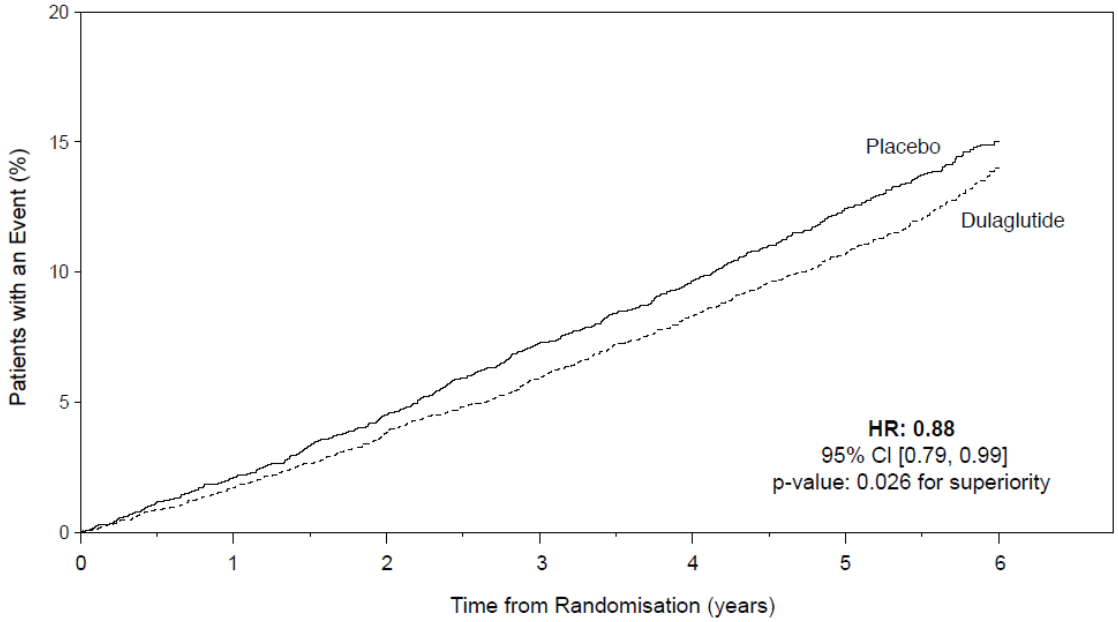
Cardiovascular Evaluation

Meta-analysis of phase 2 and 3 studies
In a meta-analysis of phase 2 and 3 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 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 0.75 mg dose was not administered in this study). 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. 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 from randomisation to first occurrence of any major adverse cardiovascular events (MACE): CV death, non-fatal myocardial infarction, or non-fatal stroke. Trulicity was superior in preventing MACE compared to placebo (Figure 1). Each MACE component contributed to the reduction of MACE, as shown in Figure 2.



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 outcome study

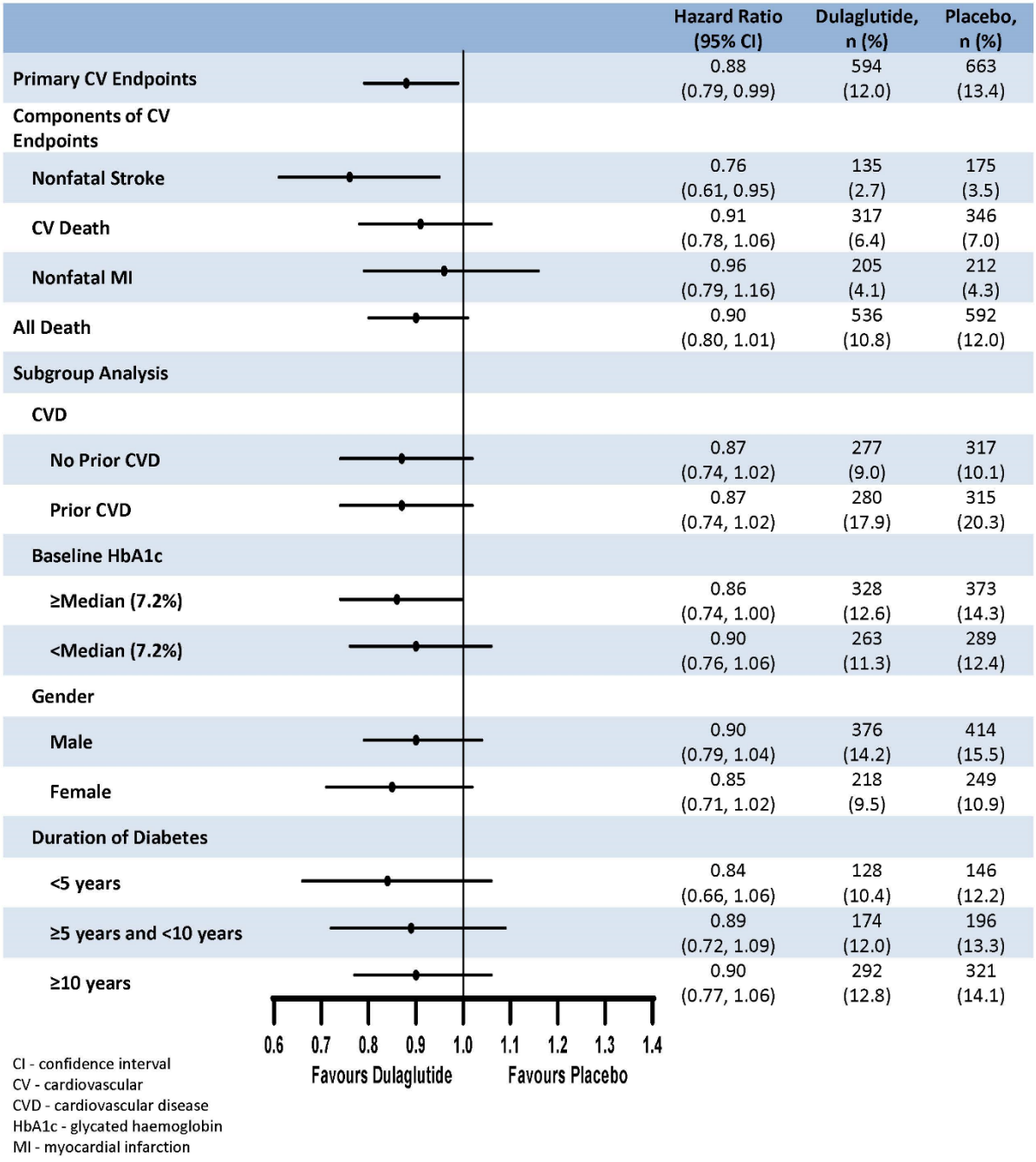


Figure 2. Forest plot of analyses of individual cardiovascular event types, all cause death, and consistency of effect across subgroups for the primary endpoint

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 %]; $p < 0.001$).

Combination of dulaglutide 4.5 mg, 3 mg and 1.5 mg therapy with metformin
The safety and efficacy of dulaglutide 3 mg and 4.5 mg once weekly compared to dulaglutide 1.5 mg once weekly as add-on to metformin were investigated in a 52 weeks study. At 36 weeks, both Trulicity 3 mg and 4.5 mg were superior to Trulicity 1.5 mg in lowering of HbA1c and body weight.

A greater percentage of patients achieved HbA1c targets of < 7.0 % or ≤ 6.5 % at 36 weeks with Trulicity 3 mg and Trulicity 4.5 mg. The proportions of patients that achieved ≥ 5 % body weight reduction from baseline were 31 %, 40 % and 49 % for Trulicity 1.5 mg, 3 mg and 4.5 mg respectively. These effects were sustained through 52 weeks.

Table 11. Results of an active controlled study comparing three doses of dulaglutide

	Baseline HbA1c (%)	**Mean change in HbA1c (%)**	**Patients at target HbA1c**		**Change in FBG (mmol/L)**	**Change in body weight (kg)**
			< 7.0 % (%)[a]	**≤ 6.5 % (%)[b]**		
36 weeks						
Dulaglutide 1.5 mg once weekly (n = 612)	8.64	-1.53	57.0	38.1	-2.45	-3.1
Dulaglutide 3 mg once weekly (n = 616)	8.63	-1.71#	64.7#	48.4‡‡	-2.66	-4.0#
Dulaglutide 4.5 mg once weekly (n = 614)	8.64	-1.87##	71.5#	51.7‡‡	-2.90#	-4.7##
52 weeks						
Dulaglutide 1.5 mg once weekly (n = 612)	8.64	-1.52	58.6	40.4	-2.39	-3.5
Dulaglutide 3 mg once weekly (n = 616)	8.63	-1.71‡	65.4‡	49.2‡	-2.70‡	-4.3‡
Dulaglutide 4.5 mg once weekly (n = 614)	8.64	-1.83‡‡	71.7‡‡	51.3‡‡	-2.92‡‡	-5.0‡‡

# $p < 0.05$, ## $p < 0.001$ for superiority compared to dulaglutide 1.5 mg, adjusted p-values with overall type I error controlled

‡ $p < 0.05$, ‡‡ $p < 0.001$ compared to dulaglutide 1.5 mg

[a] HbA1c value of 7.0 % (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)

[b] HbA1c value of 6.5 % (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

Results target the on-treatment effect (analysis is based on mixed models for repeated measurements or longitudinal logistic regression).

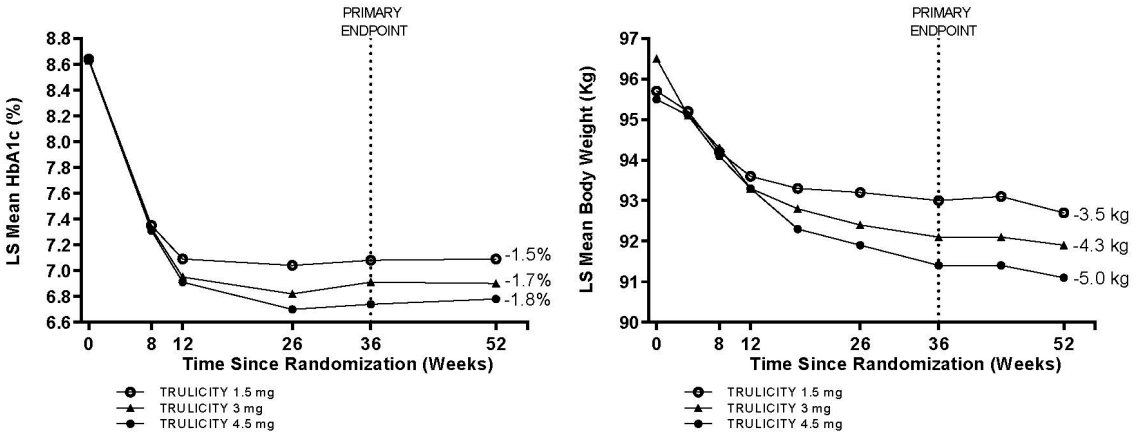


Figure 3. Mean change in HbA1c (%) and body weight (kg) from baseline to week 52

The rates of documented symptomatic hypoglycaemia with dulaglutide 1.5 mg, 3 mg and 4.5 mg were 0.07, 0.05 and 0.07 episodes/patient/year respectively. One patient reported severe hypoglycaemia with dulaglutide 1.5 mg, no patient with dulaglutide 3 mg, and one patient with dulaglutide 4.5 mg.

Special populations

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 pre-study 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 12. 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 % (%)[a]**	**Change in FBG (mmol/L)**	**Change in body weight (kg)**
26 weeks					
Dulaglutide 1.5 mg once weekly (n = 192)	8.60	-1.19[†]	78.3	1.28[##]	-2.81[##]
Dulaglutide 0.75 mg once weekly (n = 190)	8.58	-1.12[†]	72.6	0.98[##]	-2.02[##]
Insulin glargine[+] once daily (n = 194)	8.56	-1.13	75.3	-1.06	1.11
52 weeks					
Dulaglutide 1.5 mg once weekly (n = 192)	8.60	-1.10[†]	69.1	1.57[##]	-2.66[##]
Dulaglutide 0.75 mg once weekly (n = 190)	8.58	-1.10[†]	69.5	1.15[##]	-1.71[##]
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

[a] HbA1c value of 8.0 % (DCCT) corresponds to 63.9 mmol/mol (IFCC) (average blood glucose: 10.1 mmol/L)

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.

Use in the paediatric population

The safety and efficacy of dulaglutide 0.75 mg and 1.5 mg once weekly in children and adolescents aged 10 years and above were compared to placebo added to diet and exercise alone, with or without metformin and/or basal insulin. The double-blind placebo-controlled period lasted for 26 weeks, after which patients assigned to placebo started 26 weeks of open-label treatment with dulaglutide 0.75 mg once weekly and patients assigned to dulaglutide continued open-label dulaglutide at their assigned dose. At 26 weeks, dulaglutide was superior to placebo treatment in lowering HbA1c.

Table 13. Glycemic results in paediatric patients aged 10 years and above with type 2 diabetes, with inadequate glycemic control despite diet and exercise (with or without metformin and/or basal insulin)

	Baseline HbA1c (%)	**Mean change in HbA1c (%)**	**Patients at target HbA1c**		**Mean change in FBG (mmol/L)**	**Mean change in body mass index (kg/m^2)**
			< 7.0 % (%)[a]	**≤ 6.5 % (%)[b]**		
26 weeks						
Dulaglutide pooled[c] (n = 103)	8.0	-0.8[##]	51.5[##]	41.8[‡‡]	-1.1[##]	-0.1
Dulaglutide 0.75 mg once weekly (n = 51)	7.9	-0.6[##]	54.9[##]	43.1[‡‡]	-0.7[#]	-0.2
Dulaglutide 1.5 mg once weekly (n = 52)	8.2	-0.9[##]	48.1[##]	40.4[‡‡]	-1.4[##]	-0.1
Placebo once weekly (n = 51)	8.1	0.6	13.7	9.8	1.0	0.0
52 weeks[d]						
Dulaglutide pooled[c] (n = 103)	8.0	-0.4	59.5	45.2	-0.63	0.1
Dulaglutide 0.75 mg once weekly (n = 51)	7.9	-0.2	65.0	55.0	-0.21	0.0
Dulaglutide 1.5 mg once weekly (n = 52)	8.2	-0.6	54.6	36.4	-0.95	0.1
Placebo/dulaglutide 0.75 mg once weekly[e] (n = 51)	8.1	-0.1	50.0	29.4	0.24	-0.2

[#] $p < 0.05$, [##] $p < 0.001$ for superiority compared to placebo, adjusted p-values with overall type I error controlled.

[‡] $p < 0.05$, [‡‡] $p < 0.001$ for superiority compared to placebo.

[a] HbA1c value of 7.0 % (DCCT) corresponds to 53.0 mmol/mol (IFCC) (average blood glucose: 8.6 mmol/L)

[b] HbA1c value of 6.5 % (DCCT) corresponds to 47.5 mmol/mol (IFCC) (average blood glucose: 7.8 mmol/L)

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

[d] Efficacy estimates at the primary endpoint (26 weeks) are based on the treatment regimen estimand while estimates at the end of the open label extension (52 weeks) are based on the efficacy estimand.

[e] Patients assigned to placebo for the initial 26 week double-blind period started treatment with dulaglutide 0.75 mg once weekly for the follow-on 26 week open-label period.

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. Absolute bioavailabilities for 3 mg and 4.5 mg doses were estimated to be similar to 1.5 mg although they have not been specifically studied. Over the dose range 0.75 mg to 4.5 mg, the increase in dulaglutide concentration is approximately proportional.

Distribution

The apparent population mean central volume of distribution was 3.09 L and the apparent population mean peripheral volume of distribution was 5.98 L.

Biotransformation

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

Elimination

Apparent population mean clearance of dulaglutide was 0.142 L/h. and the elimination half-life was approximately 5 days.

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 Trulicity 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
A population pharmacokinetic analysis was conducted for dulaglutide 0.75 mg and 1.5 mg using data from 128 paediatric patients (10 to < 18 years of age) with type 2 diabetes. The AUC in paediatric patients was approximately 37 % lower than that in adult patients. However, this difference was not determined to be clinically meaningful.

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 6 month carcinogenicity study in transgenic mice, there was no tumorigenic response. In a 2 year carcinogenicity study in rats, at ≥ 3 times the human clinical exposure following 4.5 mg dulaglutide per week, dulaglutide caused statistically significant, dose-related increases in the incidence of thyroid C-cell tumours (adenomas and carcinomas combined). The clinical relevance of these findings is currently unknown.

During the fertility studies, a reduction in the number of corpora lutea and prolonged oestrous cycle were observed at dose levels that were associated with decreased food intake and body weight gain in maternal animals; however, no effects on indices of fertility and conception or embryonic development were observed. In reproductive toxicology studies, skeletal effects and a reduction in foetal growth were observed in the rat and rabbit at exposures of dulaglutide 5- to 18-fold higher than those proposed clinically, but no foetal malformations were observed. Treatment of rats throughout pregnancy and lactation produced memory deficits in female offspring at exposures that were 7-fold higher than those proposed clinically. Dulaglutide dosing of male and female juvenile rats did not produce memory deficits at 38-fold the highest human exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Citric acid
Mannitol
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2 ºC – 8 ºC).
Do not freeze.
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.

6.5 Nature and contents of container

Glass syringe (type I) encased in a disposable pen.
Each pre-filled pen contains 0.5 ml of solution.
Packs of 2 and 4 pre-filled pens and multipack of 12 (3 packs of 4) pre-filled pens. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product 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.
Trulicity that has been frozen must not be used.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland BV., Orteliuslaan 1000, 3528 BD Utrecht, The Netherlands.

8. MARKETING AUTHORISATION NUMBER

EU/1/14/956/001
EU/1/14/956/002
EU/1/14/956/003
EU/1/14/956/006
EU/1/14/956/007
EU/1/14/956/008
EU/1/14/956/011
EU/1/14/956/012
EU/1/14/956/013
EU/1/14/956/014
EU/1/14/956/015
EU/1/14/956/016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 November 2014
Date of latest renewal: 23 August 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Eli Lilly Kinsale Limited
Dunderrow
Kinsale
Co. Cork
Ireland

ImClone Systems, LLC
33 ImClone Drive
Branchburg, New Jersey 08876
USA

Name and address of the manufacturer(s) responsible for batch release

Eli Lilly Italia S.p.A.
Via Gramsci 731/733
50019, Sesto Fiorentino
Firenze (FI)
Italy

Lilly France
2, rue du Colonel Lilly
67640 Fegersheim
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Trulicity 0.75 mg solution for injection in pre-filled pen
dulaglutide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 0.75 mg of dulaglutide in 0.5 ml solution

3. LIST OF EXCIPIENTS

Excipients: sodium citrate, citric acid, mannitol, polysorbate 80, water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
2 pre-filled pens of 0.5 ml solution
4 pre-filled pens of 0.5 ml solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Once weekly.

Mark the day of the week you want to use your medicine to help you remember.

	Mon	Tues	Wed	Thu	Fri	Sat	Sun
Week 1							
Week 2							

	Mon	Tues	Wed	Thu	Fri	Sat	Sun
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/956/001 2 pre-filled pens
EU/1/14/956/002 4 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TRULICITY 0.75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (with Blue Box) – multipack - PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Trulicity 0.75 mg solution for injection in pre-filled pen
dulaglutide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 0.75 mg of dulaglutide in 0.5 ml solution

3. LIST OF EXCIPIENTS

Excipients: sodium citrate, citric acid, mannitol, polysorbate 80, water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
Multi-pack: 12 (3 packs of 4) pre-filled pens of 0.5 ml solution.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Once weekly.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/956/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TRULICITY 0.75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON (without Blue Box) component of a multipack - PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Trulicity 0.75 mg solution for injection in pre-filled pen
dulaglutide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 0.75 mg of dulaglutide in 0.5 ml solution

3. LIST OF EXCIPIENTS

Excipients: sodium citrate, citric acid, mannitol, polysorbate 80, water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
4 pre-filled pens of 0.5 ml solution. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Once weekly.

Mark the day of the week you want to use your medicine to help you remember.

	Mon	Tues	Wed	Thu	Fri	Sat	Sun
Week 1							
Week 2							

	Mon	Tues	Wed	Thu	Fri	Sat	Sun
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/956/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TRULICITY 0.75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Trulicity 0.75 mg solution for injection in pre-filled pen
dulaglutide
Subcutaneous use

2. METHOD OF ADMINISTRATION

Once weekly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Trulicity 1.5 mg solution for injection in pre-filled pen
dulaglutide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 1.5 mg of dulaglutide in 0.5 ml solution

3. LIST OF EXCIPIENTS

Excipients: sodium citrate, citric acid, mannitol, polysorbate 80, water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
2 pre-filled pens of 0.5ml solution
4 pre-filled pens of 0.5ml solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Once weekly.

Mark the day of the week you want to use your medicine to help you remember.

	Mon	Tues	Wed	Thu	Fri	Sat	Sun
Week 1							
Week 2							

	Mon	Tues	Wed	Thu	Fri	Sat	Sun
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/956/006 2 pre-filled pens
EU/1/14/956/007 4 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TRULICITY 1.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (with Blue Box) multipack - PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Trulicity 1.5 mg solution for injection in pre-filled pen
dulaglutide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 1.5 mg of dulaglutide in 0.5 ml solution

3. LIST OF EXCIPIENTS

Excipients: sodium citrate, citric acid, mannitol, polysorbate 80, water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
Multi-pack: 12 (3 packs of 4) pre-filled pens of 0.5 ml solution.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Once weekly.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/956/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TRULICITY 1.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON (without Blue Box) component of a multipack - PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Trulicity 1.5 mg solution for injection in pre-filled pen
dulaglutide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 1.5 mg of dulaglutide in 0.5 ml solution

3. LIST OF EXCIPIENTS

Excipients: sodium citrate, citric acid, mannitol, polysorbate 80, water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
4 pre-filled pens of 0.5 ml solution. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Once weekly.

Mark the day of the week you want to use your medicine to help you remember.

	Mon	Tues	Wed	Thu	Fri	Sat	Sun
Week 1							
Week 2							

	Mon	Tues	Wed	Thu	Fri	Sat	Sun
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/956/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TRULICITY 1.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Trulicity 1.5 mg solution for injection in pre-filled pen
dulaglutide
Subcutaneous use

2. METHOD OF ADMINISTRATION

Once weekly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Trulicity 3 mg solution for injection in pre-filled pen
dulaglutide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 3 mg of dulaglutide in 0.5 ml solution

3. LIST OF EXCIPIENTS

Excipients: sodium citrate, citric acid, mannitol, polysorbate 80, water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
2 pre-filled pens of 0.5ml solution
4 pre-filled pens of 0.5ml solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Once weekly.

Mark the day of the week you want to use your medicine to help you remember.

	Mon	Tues	Wed	Thu	Fri	Sat	Sun
Week 1							
Week 2							

	Mon	Tues	Wed	Thu	Fri	Sat	Sun
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/956/011 2 pre-filled pens
EU/1/14/956/012 4 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TRULICITY 3 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (with Blue Box) multipack - PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Trulicity 3 mg solution for injection in pre-filled pen
dulaglutide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 3 mg of dulaglutide in 0.5 ml solution

3. LIST OF EXCIPIENTS

Excipients: sodium citrate, citric acid, mannitol, polysorbate 80, water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
Multi-pack: 12 (3 packs of 4) pre-filled pens of 0.5 ml solution.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Once weekly.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/956/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TRULICITY 3 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON (without Blue Box) component of a multipack - PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Trulicity 3 mg solution for injection in pre-filled pen
dulaglutide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 3 mg of dulaglutide in 0.5 ml solution

3. LIST OF EXCIPIENTS

Excipients: sodium citrate, citric acid, mannitol, polysorbate 80, water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
4 pre-filled pens of 0.5 ml solution. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Once weekly.

Mark the day of the week you want to use your medicine to help you remember.

	Mon	Tues	Wed	Thu	Fri	Sat	Sun
Week 1							
Week 2							

	Mon	Tues	Wed	Thu	Fri	Sat	Sun
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/956/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TRULICITY 3 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Trulicity 3 mg solution for injection
dulaglutide
Subcutaneous use

2. METHOD OF ADMINISTRATION

Once weekly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Trulicity 4.5 mg solution for injection in pre-filled pen
dulaglutide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 4.5 mg of dulaglutide in 0.5 ml solution

3. LIST OF EXCIPIENTS

Excipients: sodium citrate, citric acid, mannitol, polysorbate 80, water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
2 pre-filled pens of 0.5ml solution
4 pre-filled pens of 0.5ml solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Once weekly.

Mark the day of the week you want to use your medicine to help you remember.

	Mon	Tues	Wed	Thu	Fri	Sat	Sun
Week 1							
Week 2							

	Mon	Tues	Wed	Thu	Fri	Sat	Sun
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/956/014 2 pre-filled pens
EU/1/14/956/015 4 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TRULICITY 4.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (with Blue Box) multipack - PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Trulicity 4.5 mg solution for injection in pre-filled pen
dulaglutide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 4.5 mg of dulaglutide in 0.5 ml solution

3. LIST OF EXCIPIENTS

Excipients: sodium citrate, citric acid, mannitol, polysorbate 80, water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
Multi-pack: 12 (3 packs of 4) pre-filled pens of 0.5 ml solution.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Once weekly.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/956/016

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TRULICITY 4.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON (without Blue Box) component of a multipack - PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Trulicity 4.5 mg solution for injection in pre-filled pen
dulaglutide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 4.5 mg of dulaglutide in 0.5 ml solution

3. LIST OF EXCIPIENTS

Excipients: sodium citrate, citric acid, mannitol, polysorbate 80, water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
4 pre-filled pens of 0.5 ml solution. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Once weekly.

Mark the day of the week you want to use your medicine to help you remember.

	Mon	Tues	Wed	Thu	Fri	Sat	Sun
Week 1							
Week 2							

	Mon	Tues	Wed	Thu	Fri	Sat	Sun
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/956/016

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TRULICITY 4.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Trulicity 4.5 mg solution for injection
dulaglutide
Subcutaneous use

2. METHOD OF ADMINISTRATION

Once weekly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Trulicity 0.75 mg solution for injection in pre-filled pen
Trulicity 1.5 mg solution for injection in pre-filled pen
Trulicity 3 mg solution for injection in pre-filled pen
Trulicity 4.5 mg solution for injection in pre-filled pen
dulaglutide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Trulicity is and what it is used for
2. What you need to know before you use Trulicity
3. How to use Trulicity
4. Possible side effects
5. How to store Trulicity
6. Contents of the pack and other information

1. What Trulicity is and what it is used for

Trulicity contains an active substance called dulaglutide and is used to lower blood sugar (glucose) in adults and children aged 10 years and above, with type 2 diabetes mellitus and can help prevent heart disease.

Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should.

When this happens, sugar (glucose) builds up in the blood.

Trulicity is used:
- on its own if your blood sugar is not properly controlled by diet and exercise alone, and you can’t take metformin (another diabetes medicine).
- or with other medicines for diabetes when they are not enough to control your blood sugar levels. These other medicines may be medicines taken by mouth and/or insulin given by injection.

It is important to continue to follow the advice on diet and exercise given to you by your doctor, pharmacist or nurse.

2. What you need to know before you use Trulicity

Do not use Trulicity
- if you are allergic to dulaglutide or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Trulicity if:
- you are on dialysis as this medicine is not recommended.
- you have type 1 diabetes (the type when your body does not produce any insulin) as this medicine may not be right for you.
- you have diabetic ketoacidosis (a complication of diabetes that occurs when the body is unable to break down glucose because there is not enough insulin). The signs include rapid weight loss, feeling sick or being sick, a sweet smell to your breath, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat.
- you have severe problems with food digestion or food remaining in your stomach for longer than normal (including gastroparesis).
- you have ever had pancreatitis (inflammation of the pancreas) which causes severe pain in the stomach and back which does not go away.
- you are taking a sulphonylurea or insulin for your diabetes, as low blood sugar (hypoglycaemia) can occur. Your doctor may need to change your dose of these other medicines to reduce this risk.

Trulicity is not an insulin and should therefore not be used as a substitute for insulin.

Symptoms, sometimes severe, of delayed emptying of stomach contents such as feeling of fullness, nausea and/or vomiting have been reported in patients using Trulicity. Tell your doctor if you develop severe problems with your stomach emptying that will not go away while using Trulicity.

If you know that you are due to have surgery where you will be under anesthesia (sleeping), please tell your doctor that you are using Trulicity.

When initiating treatment with Trulicity, you may in some cases experience loss of fluids/dehydration, e.g. in case of vomiting, nausea and/or diarrhoea which may lead to a decrease in kidney function. It is important to avoid dehydration by drinking plenty of fluids. Contact your doctor if you have any questions or concerns.

Children and adolescents
Trulicity can be used in children and adolescents aged 10 years and above. Data is not available in children below 10 years of age.

Other medicines and Trulicity
Because Trulicity can slow stomach emptying which could affect other medicines, tell your doctor, pharmacist or nurse if you are using, have recently used or might use any other medicine.

Pregnancy
It is not known if dulaglutide could harm your unborn child. Women who could become pregnant should use contraception during treatment with dulagutide. Tell your doctor if you are pregnant, think you may be pregnant or are planning to have a baby, as Trulicity should not be used during pregnancy. Talk to your doctor about the best way to control your blood sugar while you are pregnant.

Breast-feeding
Talk to your doctor if you would like to or are breast-feeding before taking this medicine. Do not use Trulicity if you are breast-feeding. It is not known if dulaglutide passes into human breast milk.

Driving and using machines
Trulicity has no to little effect on the ability to drive or use machines. However, if you use Trulicity in combination with a sulphonylurea or insulin, low blood sugar (hypoglycaemia) may occur which may reduce your ability to concentrate. Avoid driving or using machines if you get any signs of low blood sugar. See section 2, ‘Warning and precautions’ for information on increased risk of low blood sugar and section 4 for the warning signs of low blood sugar. Talk to your doctor for further information.

Trulicity contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Trulicity contains polysorbate
Trulicity 0.75 mg and 1.5 mg, solution for injection in pre-filled pen
This medicine contains 0.10 mg of polysorbate 80 in each pre-filled pen, which is equivalent to 0.20 mg/ml.

Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

Trulicity 3 mg and 4.5 mg, solution for injection in pre-filled pen
This medicine contains 0.125 mg of polysorbate 80 in each pre-filled pen, which is equivalent to 0.25 mg/ml.

Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Trulicity

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure how to use this medicine.

Adults
Your doctor may recommend a dose of 0.75 mg once a week for the treatment of your diabetes when Trulicity is used alone.

When used with other medicines for diabetes, your doctor may recommend a dose of 1.5 mg once a week.

If your blood sugar is not controlled well enough, your doctor may increase your dose to 3 mg once a week.

If further blood sugar control is needed the dose may be increased again to 4.5 mg once a week.

Children and adolescents
The starting dose for children and adolescents aged 10 years and above is 0.75 mg once a week. If your blood sugar is not controlled well enough after at least 4 weeks, your doctor may increase your dose to 1.5 mg once a week.

Each pen contains one weekly dose of Trulicity (0.75 mg, 1.5 mg, 3 mg or 4.5 mg). Each pen delivers only one dose.

You can use your pen at any time of the day, with or without meals. You should use it on the same day each week if you can. To help you remember, you may wish to tick the day of the week when you inject your first dose on the box that your pen comes in, or on a calendar.

Trulicity is injected under the skin (subcutaneous injection) of your stomach area (abdomen) or upper leg (thigh). If the injection is given by someone else, they may inject in your upper arm.

If you want to do so, you can use the same area of your body each week. But be sure to choose a different injection site within that area.

It is important that you test your blood glucose levels as instructed by your doctor, pharmacist or nurse, if you are taking Trulicity with a sulphonylurea or insulin.

Read the “Instructions for Use” for the pen carefully before using Trulicity.

If you use more Trulicity than you should
If you use more Trulicity than you should talk to your doctor immediately. Too much of this medicine may make your blood sugar too low (hypoglycaemia) and can make you feel sick or be sick.

If you forget to use Trulicity
If you forget to inject a dose, and if there are **at least 3 days** before your next dose is due, then inject your dose as soon as possible. Inject your next dose on your regular scheduled day.

If there are **less than 3 days** before your next dose is due, skip the dose and inject the next one on your regular scheduled day.

Do not use a double dose to make up for a forgotten dose.

You can also change the day of the week on which you inject Trulicity if necessary, as long as it has been at least 3 days since your last dose of Trulicity.

If you stop using Trulicity
Do not stop using Trulicity without talking with your doctor. If you stop using Trulicity, your blood sugar levels can increase.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Severe side effects
Rare: may affect up to 1 in 1,000 people
- Severe allergic reactions (anaphylactic reactions, angioedema).
  You should see a doctor immediately if you experience symptoms such as rashes, itching and rapid swelling of the tissues of the neck, face, mouth or throat, hives and difficulties breathing.

- Inflamed pancreas (acute pancreatitis) which could cause severe pain in the stomach and back which does not go away.
  You should see a doctor immediately if you experience such symptoms.

Not known: the frequency cannot be estimated from the available data
- Bowel obstruction - a severe form of constipation with additional symptoms such as stomach ache, bloating or vomiting.
  You should see a doctor immediately if you experience such symptoms.

Other side effects
Very common: may affect more than 1 in 10 people
- Feeling sick (nausea) – this usually goes away over time
- Being sick (vomiting) – this usually goes away over time
- Diarrhoea – this usually goes away over time
- Stomach (abdominal) pain.

These side effects are usually not severe. They are most common when first starting dulaglutide but decrease over time in most patients.

- Low blood sugar (hypoglycaemia) is very common when dulaglutide is used with medicines that contain metformin, a sulphonylurea and/or insulin. If you are taking a sulphonylurea or insulin, the dose may need to be lowered while you use dulaglutide.
- Symptoms of low blood sugar may include headache, drowsiness, weakness, dizziness, feeling hungry, confusion, irritability, fast heartbeat and sweating. Your doctor should tell you how to treat low blood sugar.

Common: may affect up to 1 in 10 people
- Low blood sugar (hypoglycaemia) is common when dulaglutide is used alone, or with both metformin and pioglitazone together, or with a sodium-glucose co-transporter 2 inhibitor (SGLT2i) with or without metformin. For a list of possible symptoms, see above under very common affects.
- Feeling less hungry (decreased appetite)
- Indigestion
- Constipation
- Gas (flatulence)
- Bloating of the stomach
- Reflux or heartburn (also called gastroesophageal reflux disease – GERD) - a disease caused by stomach acid coming up into the tube from your stomach to your mouth
- Burping
- Feeling tired
- Increased heart rate
- Slowing of the electrical currents in the heart

Uncommon: may affect up to 1 in 100 people
- Injection site reactions (e.g. rash or redness)
- Allergic reactions (hypersensitivity) (e.g. swelling, raised itchy skin rash (hives))
- Dehydration, often associated with nausea, vomiting and/or diarrhoea
- Gallstones
- Inflamed gallbladder
- Change in the way food or drink tastes

Rare: may affect up to 1 in 1,000 people
- A delay in the emptying of the stomach

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Trulicity

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pen label and on the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze.

Store in the original packaging in order to protect from light.

Trulicity can be taken out of the fridge for up to 14 days at a temperature not above 30 ºC.

Do not use this medicine if you notice that the pen is damaged, or the medicine is cloudy, discoloured or has particles in it.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Trulicity contains
The active substance is dulaglutide.
- *Trulicity 0.75 mg:* Each pre-filled pen contains 0.75 mg of dulaglutide in 0.5 ml solution.
- *Trulicity 1.5 mg:* Each pre-filled pen contains 1.5 mg of dulaglutide in 0.5 ml solution.
- *Trulicity 3 mg:* Each pre-filled pen contains 3 mg of dulaglutide in 0.5 ml solution.
- *Trulicity 4.5 mg:* Each pre-filled pen contains 4.5 mg of dulaglutide in 0.5 ml solution.

The other ingredients are sodium citrate (see section 2 under 'Trulicity contains sodium' for further information); citric acid; mannitol; polysorbate 80 and water for injections.

What Trulicity looks like and contents of the pack
Trulicity is a clear, colourless, solution for injection in a pre-filled pen.
Each pre-filled pen contains 0.5 ml solution.
The pre-filled pen is for single-use only.
Pack sizes of 2, 4 or multipacks of 12 (3 packs of 4) pre-filled pens. Not all pack sizes may be available in your country.

Marketing Authorisation Holder
Eli Lilly Nederland BV., Orteliuslaan 1000, 3528 BD Utrecht, The Netherlands.

Manufacturer
Eli Lilly Italia S.p.A.,Via Gramsci 731/733, 50019, Sesto Fiorentino, Firenze (FI), Italy
Lilly France, 2, rue du Colonel Lilly, 67640 Fegersheim, France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Belgique/België/Belgien
Eli Lilly Benelux S.A./N.V.
Tél/Tel: + 32-(0)2 548 84 84

България
ТП "Ели Лили Недерланд" Б.В. - България
тел. + 359 2 491 41 40

Česká republika
ELI LILLY ČR, s.r.o.
Tel: + 420 234 664 111

Danmark
Eli Lilly Danmark A/S
Tlf.: +45 45 26 60 00

Deutschland
Lilly Deutschland GmbH
Tel. + 49-(0) 6172 273 2222

Lietuva
Eli Lilly Lietuva
Tel. +370 (5) 2649600

Luxembourg/Luxemburg
Eli Lilly Benelux S.A./N.V.
Tél/Tel: + 32-(0)2 548 84 84

Magyarország
Lilly Hungária Kft.
Tel: + 36 1 328 5100

Malta
Charles de Giorgio Ltd.
Tel: + 356 25600 500

Nederland
Eli Lilly Nederland B.V.
Tel: + 31-(0) 30 60 25 800

Eesti
Eli Lilly Nederland B.V.
Tel: +372 6 817 280

Ελλάδα
ΦΑΡΜΑΣΕΡΒ-ΛΙΛΛΥ Α.Ε.Β.Ε.
Τηλ: +30 210 629 4600

España
Lilly S.A.
Tel: + 34-91 663 50 00

France
Lilly France
Tél: +33-(0) 1 55 49 34 34

Hrvatska
Eli Lilly Hrvatska d.o.o.
Tel: +385 1 2350 999

Ireland
Eli Lilly and Company (Ireland) Limited
Tel: + 353-(0) 1 661 4377

Ísland
Icepharma hf.
Sími + 354 540 8000

Italia
Eli Lilly Italia S.p.A.
Tel: + 39- 055 42571

Κύπρος
Phadisco Ltd
Τηλ: +357 22 715000

Latvija
Eli Lilly (Suisse) S.A Pārstāvniecība Latvijā
Tel: +371 67364000

Norge
Eli Lilly Norge A.S.
Tlf: + 47 22 88 18 00

Österreich
Eli Lilly Ges.m.b.H.
Tel: + 43-(0) 1 711 780

Polska
Eli Lilly Polska Sp. z o.o.
Tel: +48 22 440 33 00

Portugal
Lilly Portugal Produtos Farmacêuticos, Lda
Tel: + 351-21-4126600

România
Eli Lilly România S.R.L.
Tel: + 40 21 4023000

Slovenija
Eli Lilly farmacevtska družba, d.o.o.
Tel: +386 (0)1 580 00 10

Slovenská republika
Eli Lilly Slovakia s.r.o.
Tel: + 421 220 663 111

Suomi/Finland
Oy Eli Lilly Finland Ab
Puh/Tel: + 358-(0) 9 85 45 250

Sverige
Eli Lilly Sweden AB
Tel: + 46-(0) 8 7378800

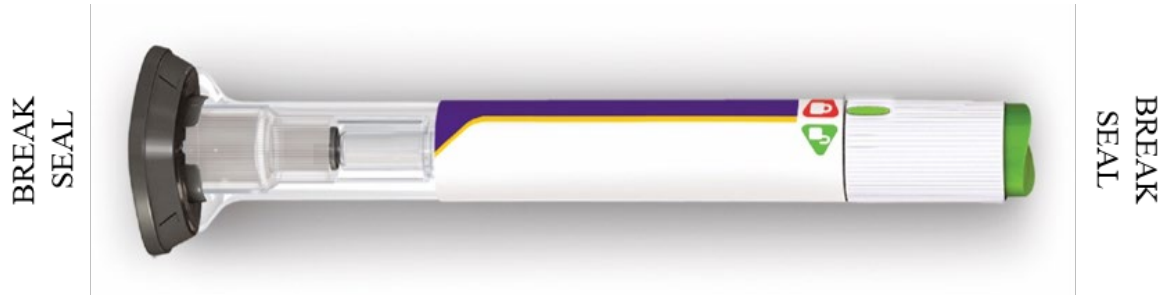
This leaflet was last revised in Month YYYY

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Instructions for use

Trulicity 0.75 mg solution for injection in pre-filled pen
dulaglutide



← Unfold and lay flat →



Read both sides for full instructions

ABOUT TRULICITY PRE-FILLED PEN

Please read these instructions for use and the information for the patient in the package leaflet carefully and completely before using your pre-filled pen. Talk to your doctor, pharmacist or nurse about how to inject Trulicity correctly.

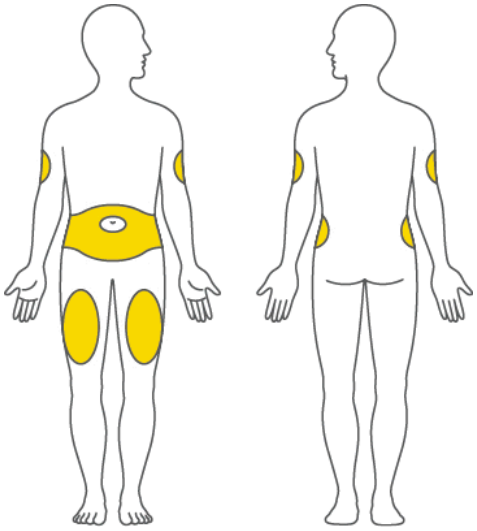
- The pen is a disposable, pre-filled delivery device that is ready to use. Each pen contains one weekly dose of Trulicity (0.75 mg). Each pen delivers one dose only.
- **Trulicity is administered <u>once a week</u>.** You may want to mark your calendar to remind you when to inject your next dose.
- When you press the green injection button, the pen will automatically insert the needle **into your skin,** inject the medicine, and pull back (retract) the needle **after the injection is complete.**

BEFORE YOU GET STARTED

Remove	Check	Inspect	Prepare
from the refrigerator. Leave the base cap on until you are ready to inject.	the label to make sure you have the correct medicine and it has not expired.	the pen. Do not use if you notice that the pen is damaged, or the medicine is cloudy, discoloured or has particles in it.	by washing your hands.

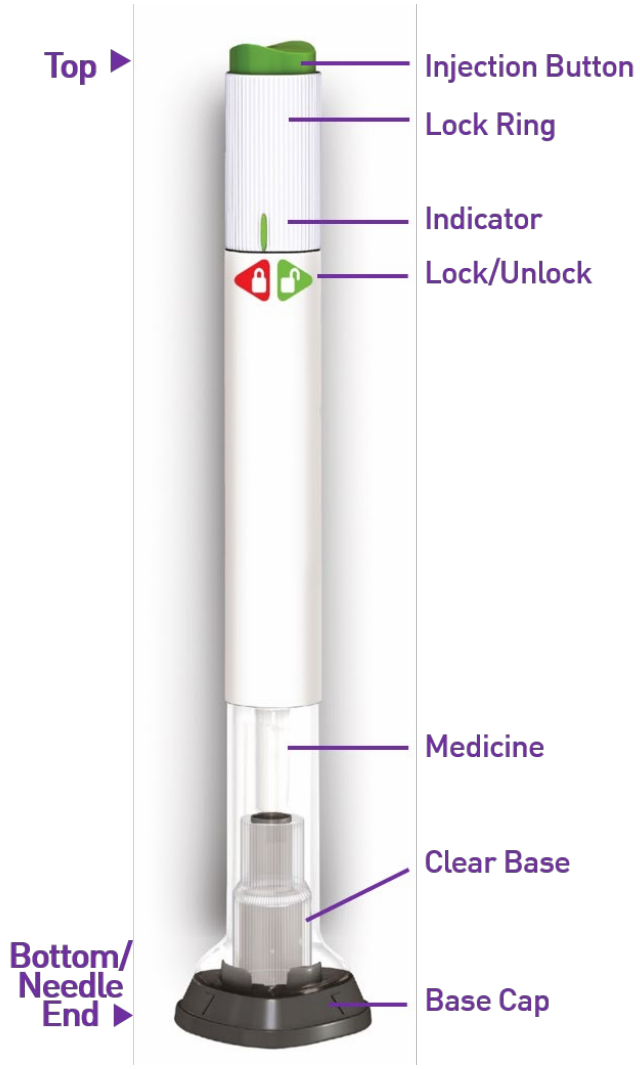
CHOOSE YOUR INJECTION SITE

- Your doctor, pharmacist or nurse can help you choose the injection site that is best for you.
- You may inject the medicine into your stomach (abdomen) or thigh.
- Another person may give you the injection in your upper arm.
- Change (rotate) your injection site each week. You may use the same area of your body, but be sure to choose a different injection site in that area.



FRONT BACK

1. **UNCAP**
2. **PLACE AND UNLOCK**
3. **PRESS AND HOLD**



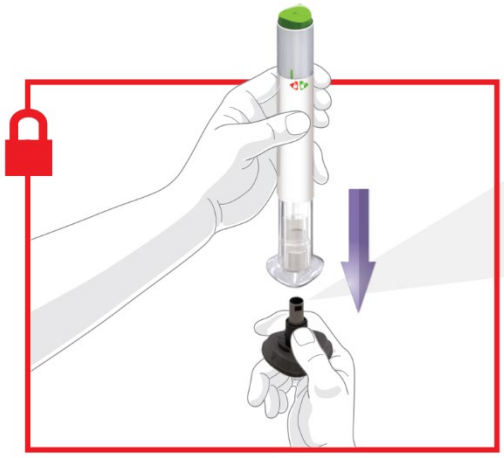
1 UNCAP

Make sure the pen is **locked**.

- Pull off the grey base cap.

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

- When removed, the grey base cap appears as shown and can be discarded.





Grey base cap

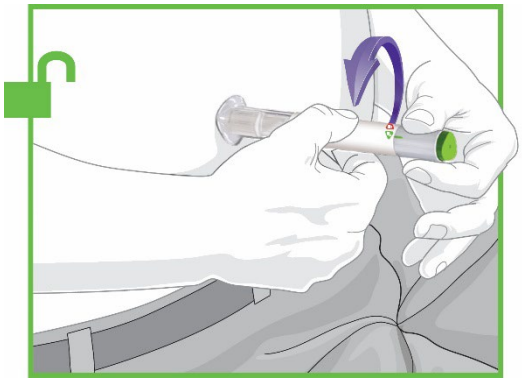
If the grey base cap does not look like the image above:

- **Do not** use the Pen.
- Safely store the Pen and cap and contact Lilly.
- Use a new Pen.

2 PLACE AND UNLOCK

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

Unlock by turning the lock ring.

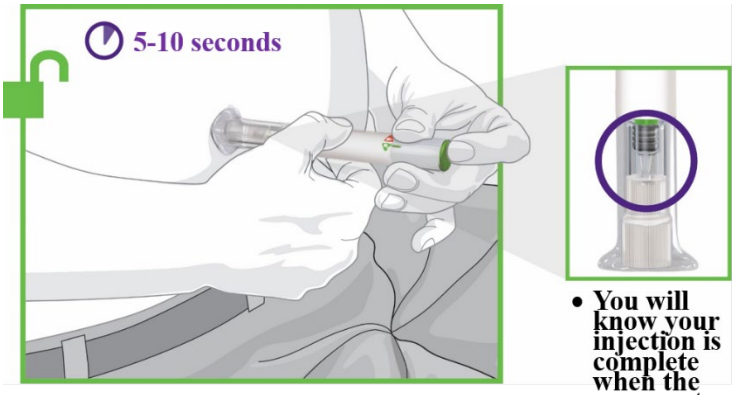


3 PRESS AND HOLD

- Press and hold the green injection button; you will hear a loud click.

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

- Remove the pen from your skin.



IMPORTANT INFORMATION

Storage and Handling
Disposal of Pen
Commonly Asked Questions
Other Information
Where to Learn More

STORAGE AND HANDLING

- The pen contains glass parts. Handle it carefully. If you drop it on a hard surface, do not use it. Use a new pen for your injection.
- Store your pen in the refrigerator.
- When refrigeration is not possible, you can keep your pen at room temperature (below 30°C) for up to a total of 14 days.
- Do not freeze your pen. If the pen has been frozen, DO NOT USE.
- Store the pen in the original package in order to protect from light.
- Keep the pen out of sight and reach of children.
- For complete information about proper storage, read the Information for the patient.

DISPOSAL OF PEN

- Dispose of the pen in a sharps container or as directed by your doctor, pharmacist or nurse.
- Do not recycle the filled sharps container.
- Ask your doctor, pharmacist or nurse about how to dispose of medicines you no longer use.



COMMONLY ASKED QUESTIONS

What if I see an air bubble in my pen?

Air bubbles are normal. They will not harm you or affect your dose.

What if I unlock the pen and press the green injection button before pulling off the base cap?

Do not remove the base cap and do not use the pen. Dispose of the pen as directed by your doctor, pharmacist or nurse. Inject your dose using another pen.

What if there is a drop of liquid on the tip of the needle when I remove the base cap?

A drop of liquid on the tip of the needle is not unusual and will not affect your dose.

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

This is not necessary, but it may help you keep the pen steady and firm against your skin.

I heard more than two clicks during my injection - two louder clicks and a soft one. Did I get my complete injection?

Some patients may hear a soft click right before the second loud click. That is the normal operation of the pen. Do not remove the pen from your skin until you hear the second louder click.

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

This is not unusual and will not affect your dose.

I'm not sure my pen worked correctly.

Check to see if you have received your dose. Your dose was delivered correctly if the grey part is visible (see step 3.) Also contact your local Lilly office listed in the Information for the patient for further instructions. Until then, store your pen safely to avoid an accidental needle stick injury.

OTHER INFORMATION

- If you have vision problems, DO NOT use your pen without help from a person trained to use the Trulicity pen.

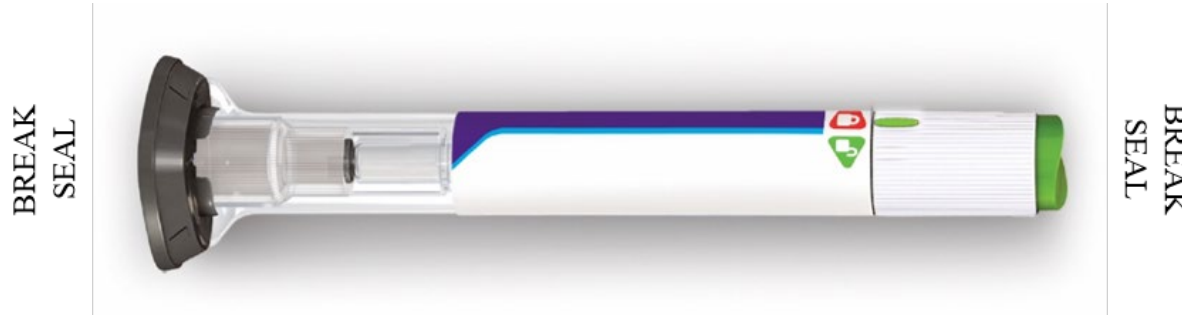
WHERE TO LEARN MORE

- If you have any questions or problems with your Trulicity pen, contact your doctor, pharmacist or nurse.

Last revised in Month YYYY

Instructions for use

Trulicity 1.5 mg solution for injection in pre-filled pen
dulaglutide



← Unfold and lay flat →



Read both sides for full instructions

ABOUT TRULICITY PRE-FILLED PEN

Please read these instructions for use and the information for the patient in the package leaflet carefully and completely before using your pre-filled pen. Talk to your doctor, pharmacist or nurse about how to inject Trulicity correctly.

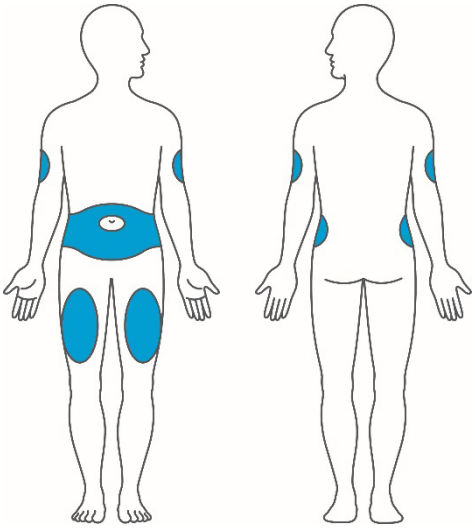
- The pen is a disposable, pre-filled delivery device that is ready to use. Each pen contains one weekly dose of Trulicity (1.5 mg). Each pen delivers one dose only.
- **Trulicity is administered once a week.** You may want to mark your calendar to remind you when to inject your next dose.
- When you press the green injection button, the pen will automatically insert the needle **into your skin,** inject the medicine, and pull back (retract) the needle **after the injection is complete.**

BEFORE YOU GET STARTED

Remove	Check	Inspect	Prepare
from the refrigerator. Leave the Base Cap on until you are ready to inject.	the label to make sure you have the correct medicine and it has not expired.	the pen. Do not use if you notice that the pen is damaged, or the medicine is cloudy, discoloured or has particles in it.	by washing your hands.

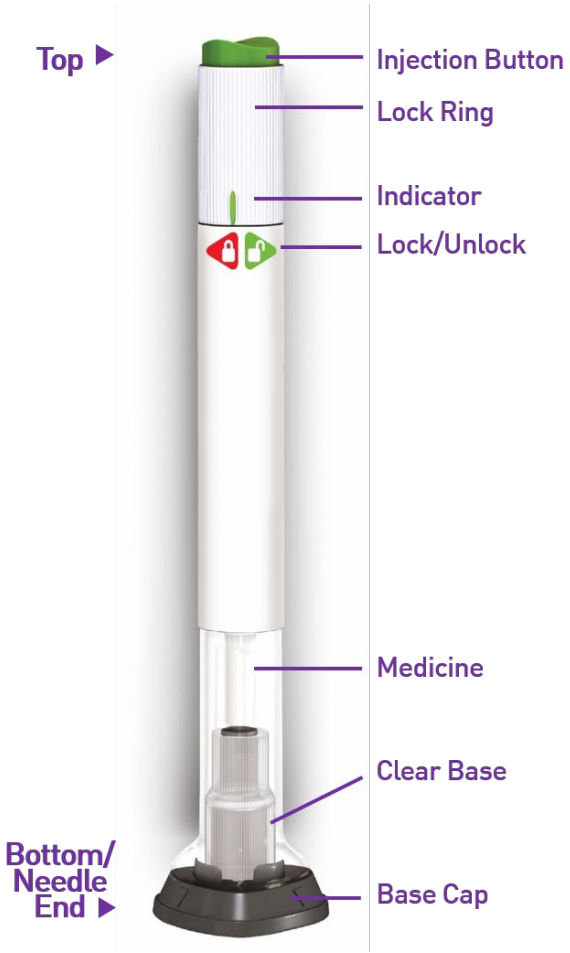
CHOOSE YOUR INJECTION SITE

- Your doctor, pharmacist or nurse can help you choose the injection site that is best for you.
- You may inject the medicine into your stomach (abdomen) or thigh.
- Another person may give you the injection in your upper arm.
- Change (rotate) your injection site each week. You may use the same area of your body, but be sure to choose a different injection site in that area.



FRONT BACK

1. **UNCAP**
2. **PLACE AND UNLOCK**
3. **PRESS AND HOLD**



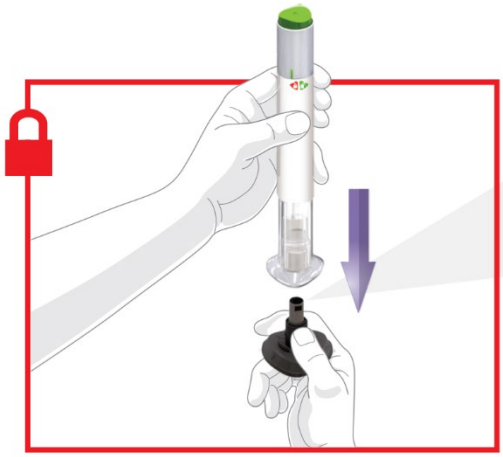
1 UNCAP

Make sure the pen is **locked**.

- Pull off the grey base cap.

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

- When removed, the grey base cap appears as shown and can be discarded.





Grey base cap

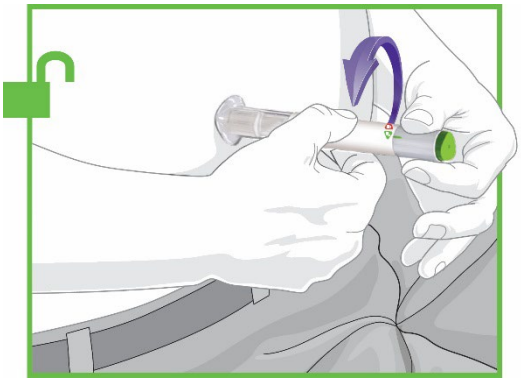
If the grey base cap does not look like the image above:

- **Do not** use the Pen.
- Safely store the Pen and cap and contact Lilly.
- Use a new Pen.

2 PLACE AND UNLOCK

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

Unlock by turning the lock ring.

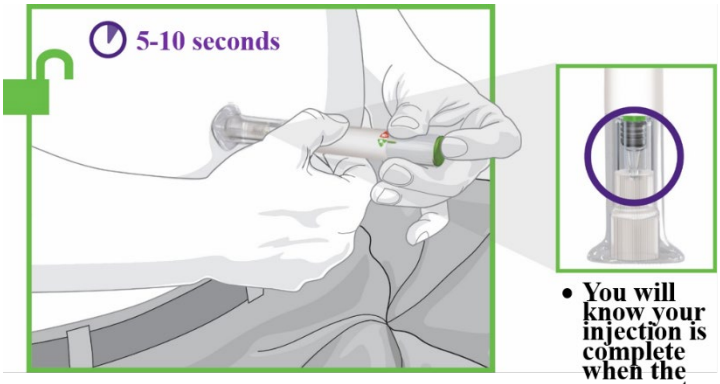


3 PRESS AND HOLD

- Press and hold the green injection button; you will hear a loud click.

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

- Remove the pen from your skin.



- **You will know your injection is complete when the grey part is visible.**

IMPORTANT INFORMATION

Storage and Handling
Disposal of Pen
Commonly Asked Questions
Other Information
Where to Learn More

STORAGE AND HANDLING

- The pen contains glass parts. Handle it carefully. If you drop it on a hard surface, do not use it. Use a new pen for your injection.
- Store your pen in the refrigerator.
- When refrigeration is not possible, you can keep your pen at room temperature (below 30°C) for up to a total of 14 days.
- Do not freeze your pen. If the pen has been frozen, DO NOT USE.
- Store the pen in the original package in order to protect from light.
- Keep the pen out of sight and reach of children.
- For complete information about proper storage, read the Information for the patient.

DISPOSAL OF PEN

- Dispose of the pen in a sharps container or as directed by your doctor, pharmacist or nurse.
- Do not recycle the filled sharps container.
- Ask your doctor, pharmacist or nurse about how to dispose of medicines you no longer use.



COMMONLY ASKED QUESTIONS

What if I see an air bubble in my pen?

Air bubbles are normal. They will not harm you or affect your dose.

What if I unlock the pen and press the green injection button before pulling off the base cap?

Do not remove the base cap and do not use the pen. Dispose of the pen as directed by your doctor, pharmacist or nurse. Inject your dose using another pen.

What if there is a drop of liquid on the tip of the needle when I remove the base cap?

A drop of liquid on the tip of the needle is not unusual and will not affect your dose.

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

This is not necessary, but it may help you keep the pen steady and firm against your skin.

I heard more than two clicks during my injection - two louder clicks and a soft one. Did I get my complete injection?

Some patients may hear a soft click right before the second loud click. That is the normal operation of the pen. Do not remove the pen from your skin until you hear the second louder click.

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

This is not unusual and will not affect your dose.

I'm not sure my pen worked correctly.

Check to see if you have received your dose. Your dose was delivered correctly if the grey part is visible (see step 3.) Also contact your local Lilly office listed in the Information for the patient for further instructions. Until then, store your pen safely to avoid an accidental needle stick injury.

OTHER INFORMATION

- If you have vision problems, DO NOT use your pen without help from a person trained to use the Trulicity pen.

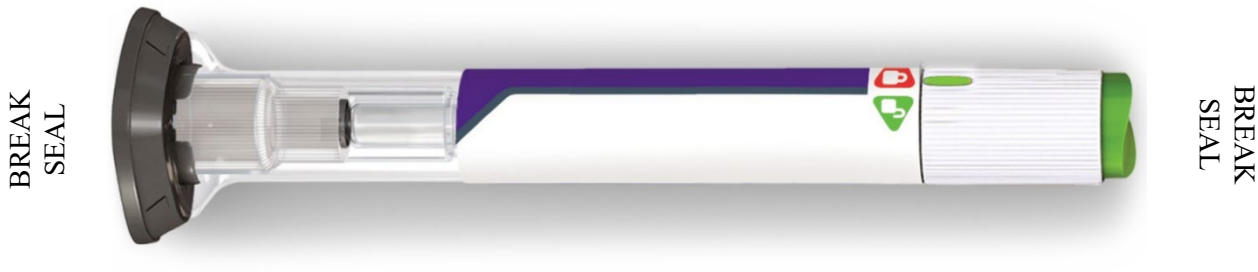
WHERE TO LEARN MORE

- If you have any questions or problems with your Trulicity pen, contact your doctor, pharmacist or nurse.

Last revised in Month YYYY

Instructions for use

Trulicity 3 mg solution for injection in pre-filled pen
dulaglutide



← Unfold and lay flat →



Read both sides for full instructions

ABOUT TRULICITY PRE-FILLED PEN

Please read these instructions for use and the information for the patient in the package leaflet carefully and completely before using your pre-filled pen. Talk to your doctor, pharmacist or nurse about how to inject Trulicity correctly.

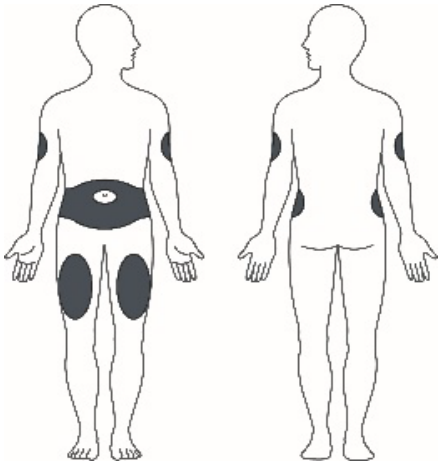
- The pen is a disposable, pre-filled delivery device that is ready to use. Each pen contains one weekly dose of Trulicity (3 mg). Each pen delivers one dose only.
- **Trulicity is administered <u>once a week</u>.** You may want to mark your calendar to remind you when to inject your next dose.
- When you press the green injection button, the pen will automatically insert the needle **into your skin,** inject the medicine, and pull back (retract) the needle **after the injection is complete.**

BEFORE YOU GET STARTED

Remove	**Check**	**Inspect**	**Prepare**
from the refrigerator. Leave the Base Cap on until you are ready to inject.	the label to make sure you have the correct medicine and it has not expired.	the pen. Do not use if you notice that the pen is damaged, or the medicine is cloudy, discoloured or has particles in it.	by washing your hands.

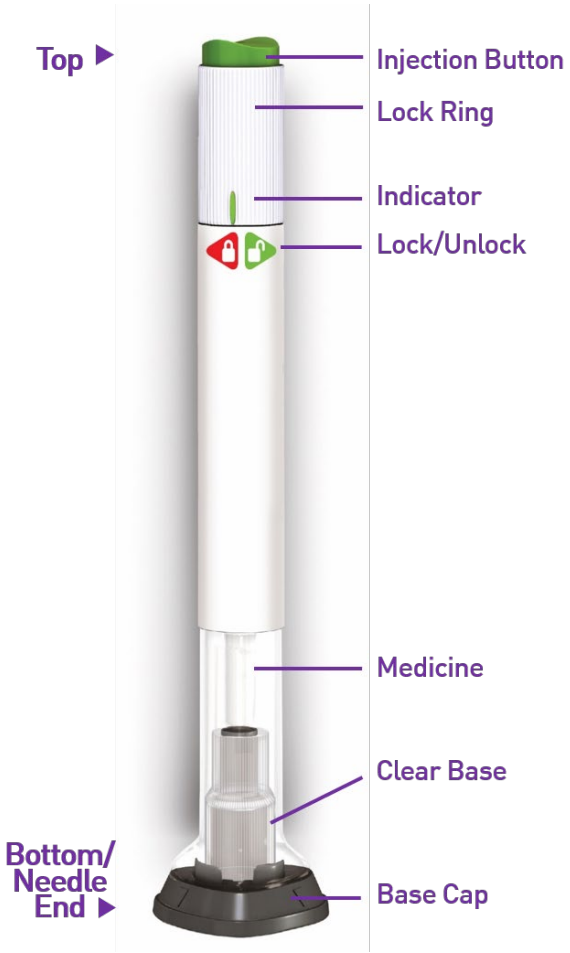
CHOOSE YOUR INJECTION SITE

- Your doctor, pharmacist or nurse can help you choose the injection site that is best for you.
- You may inject the medicine into your stomach (abdomen) or thigh.
- Another person may give you the injection in your upper arm.
- Change (rotate) your injection site each week. You may use the same area of your body, but be sure to choose a different injection site in that area.



FRONT BACK

1. **UNCAP**
2. **PLACE AND UNLOCK**
3. **PRESS AND HOLD**



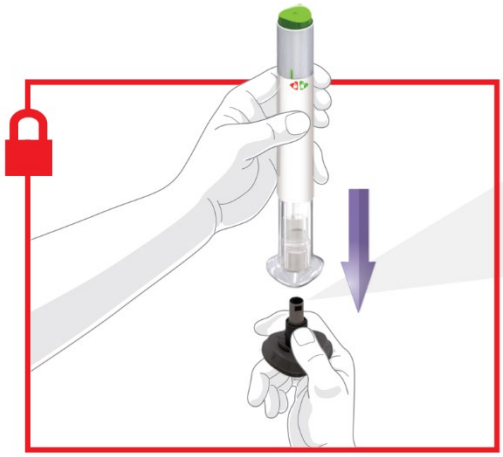
1 UNCAP

Make sure the pen is **locked**.

- Pull off the grey base cap.

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

- When removed, the grey base cap appears as shown and can be discarded.





Grey base cap

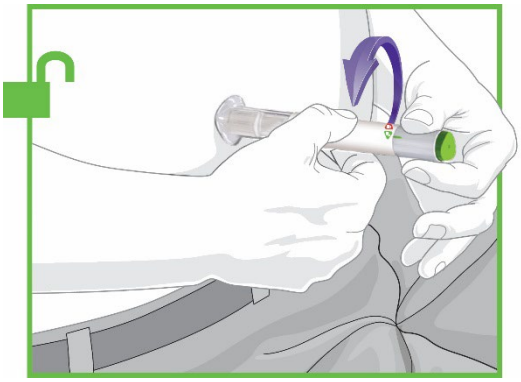
If the grey base cap does not look like the image above:

- **Do not** use the Pen.
- Safely store the Pen and cap and contact Lilly.
- Use a new Pen.

2 PLACE AND UNLOCK

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

Unlock by turning the lock ring.

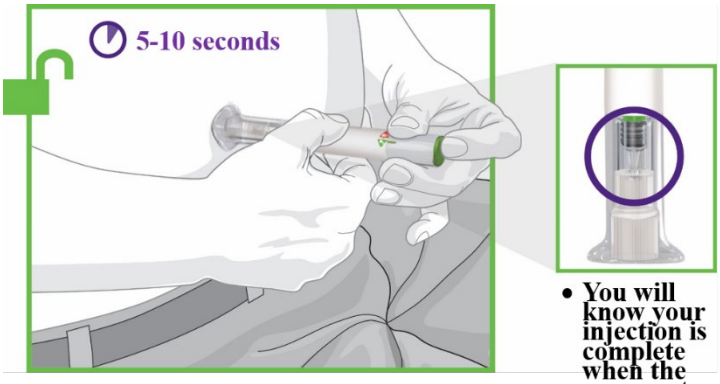


3 PRESS AND HOLD

- Press and hold the green injection button; you will hear a loud click.

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

- Remove the pen from your skin.



- **You will know your injection is complete when the grey part is visible.**

IMPORTANT INFORMATION

Storage and Handling
Disposal of Pen
Commonly Asked Questions
Other Information
Where to Learn More

STORAGE AND HANDLING

- The pen contains glass parts. Handle it carefully. If you drop it on a hard surface, do not use it. Use a new pen for your injection.
- Store your pen in the refrigerator.
- When refrigeration is not possible, you can keep your pen at room temperature (below 30°C) for up to a total of 14 days.
- Do not freeze your pen. If the pen has been frozen, DO NOT USE.
- Store the pen in the original package in order to protect from light.
- Keep the pen out of sight and reach of children.
- For complete information about proper storage, read the Information for the patient.

DISPOSAL OF PEN

- Dispose of the pen in a sharps container or as directed by your doctor, pharmacist or nurse.
- Do not recycle the filled sharps container.
- Ask your doctor, pharmacist or nurse about how to dispose of medicines you no longer use.



COMMONLY ASKED QUESTIONS

What if I see an air bubble in my pen?

Air bubbles are normal. They will not harm you or affect your dose.

What if I unlock the pen and press the green injection button before pulling off the base cap?

Do not remove the base cap and do not use the pen. Dispose of the pen as directed by your doctor, pharmacist or nurse. Inject your dose using another pen.

What if there is a drop of liquid on the tip of the needle when I remove the base cap?

A drop of liquid on the tip of the needle is not unusual and will not affect your dose.

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

This is not necessary, but it may help you keep the pen steady and firm against your skin.

I heard more than two clicks during my injection - two louder clicks and a soft one. Did I get my complete injection?

Some patients may hear a soft click right before the second loud click. That is the normal operation of the pen. Do not remove the pen from your skin until you hear the second louder click.

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

This is not unusual and will not affect your dose.

I'm not sure my pen worked correctly.

Check to see if you have received your dose. Your dose was delivered correctly if the grey part is visible (see step 3.) Also contact your local Lilly office listed in the Information for the patient for further instructions. Until then, store your pen safely to avoid an accidental needle stick injury.

OTHER INFORMATION

- If you have vision problems, DO NOT use your pen without help from a person trained to use the Trulicity pen.

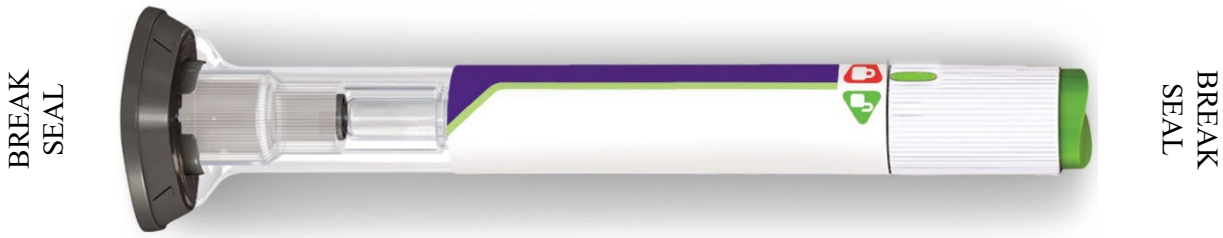
WHERE TO LEARN MORE

- If you have any questions or problems with your Trulicity pen, contact your doctor, pharmacist or nurse.

Last revised in Month YYYY

Instructions for use

Trulicity 4.5 mg solution for injection in pre-filled pen
dulaglutide



← Unfold and lay flat →



Read both sides for full instructions

ABOUT TRULICITY PRE-FILLED PEN

Please read these instructions for use and the information for the patient in the package leaflet carefully and completely before using your pre-filled pen. Talk to your doctor, pharmacist or nurse about how to inject Trulicity correctly.

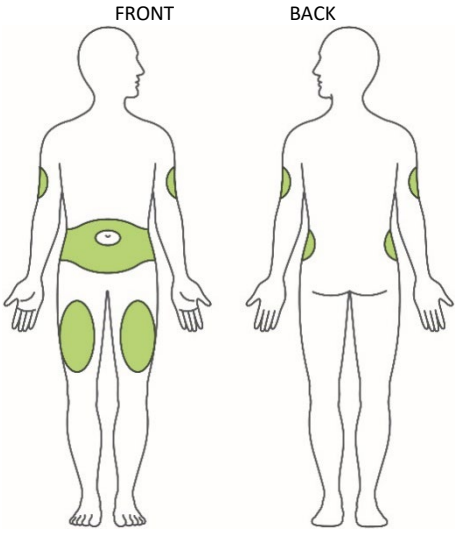
- The pen is a disposable, pre-filled delivery device that is ready to use. Each pen contains one weekly dose of Trulicity (4.5 mg). Each pen delivers one dose only.
- **Trulicity is administered once a week.** You may want to mark your calendar to remind you when to inject your next dose.
- When you press the green injection button, the pen will automatically insert the needle **into your skin,** inject the medicine, and pull back (retract) the needle **after the injection is complete.**

BEFORE YOU GET STARTED

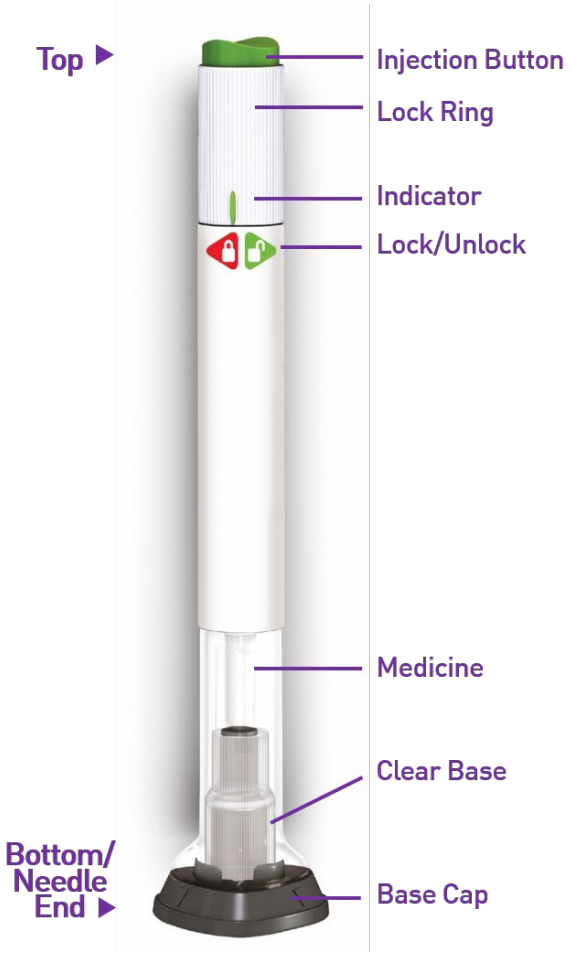
Remove	Check	Inspect	Prepare
from the refrigerator. Leave the base cap on until you are ready to inject.	the label to make sure you have the correct medicine and it has not expired.	the pen. Do not use if you notice that the pen is damaged, or the medicine is cloudy, discoloured or has particles in it.	by washing your hands.

CHOOSE YOUR INJECTION SITE

- Your doctor, pharmacist or nurse can help you choose the injection site that is best for you.
- You may inject the medicine into your stomach (abdomen) or thigh.
- Another person may give you the injection in your upper arm.
- Change (rotate) your injection site each week. You may use the same area of your body, but be sure to choose a different injection site in that area.



1. **UNCAP**
2. **PLACE AND UNLOCK**
3. **PRESS AND HOLD**



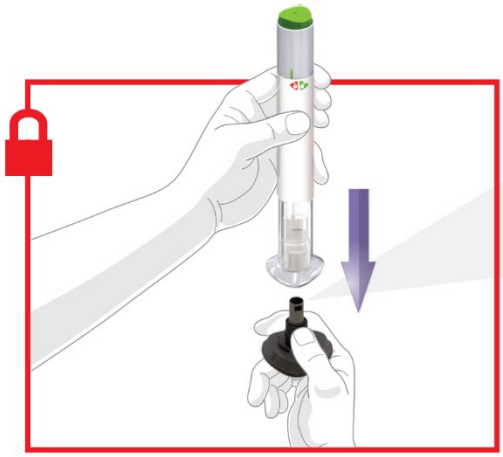
1 UNCAP

Make sure the pen is **locked**.

- Pull off the grey base cap.

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

- When removed, the grey base cap appears as shown and can be discarded.





Grey base cap

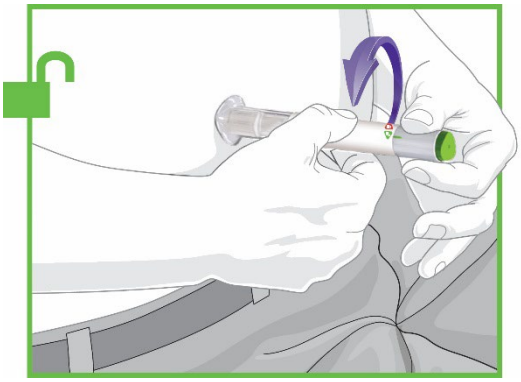
If the grey base cap does not look like the image above:

- **Do not** use the Pen.
- Safely store the Pen and cap and contact Lilly.
- Use a new Pen.

2 PLACE AND UNLOCK

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

Unlock by turning the lock ring.

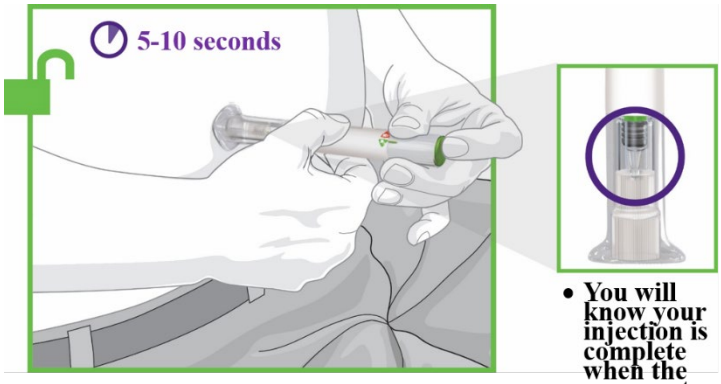


3 PRESS AND HOLD

- Press and hold the green injection button; you will hear a loud click.

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

- Remove the pen from your skin.



- **You will know your injection is complete when the grey part is visible.**

IMPORTANT INFORMATION

Storage and Handling
Disposal of Pen
Commonly Asked Questions
Other Information
Where to Learn More

STORAGE AND HANDLING

- The pen contains glass parts. Handle it carefully. If you drop it on a hard surface, do not use it. Use a new pen for your injection.
- Store your pen in the refrigerator.
- When refrigeration is not possible, you can keep your pen at room temperature (below 30°C) for up to a total of 14 days.
- Do not freeze your pen. If the pen has been frozen, DO NOT USE.
- Store the pen in the original package in order to protect from light.
- Keep the pen out of sight and reach of children.
- For complete information about proper storage, read the Information for the patient.

DISPOSAL OF PEN

- Dispose of the pen in a sharps container or as directed by your doctor, pharmacist or nurse.
- Do not recycle the filled sharps container.
- Ask your doctor, pharmacist or nurse about how to dispose of medicines you no longer use.



COMMONLY ASKED QUESTIONS

What if I see an air bubble in my pen?

Air bubbles are normal. They will not harm you or affect your dose.

What if I unlock the pen and press the green injection button before pulling off the base cap?

Do not remove the base cap and do not use the pen. Dispose of the pen as directed by your doctor, pharmacist or nurse. Inject your dose using another pen.

What if there is a drop of liquid on the tip of the needle when I remove the base cap?

A drop of liquid on the tip of the needle is not unusual and will not affect your dose.

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

This is not necessary, but it may help you keep the pen steady and firm against your skin.

I heard more than two clicks during my injection - two louder clicks and a soft one. Did I get my complete injection?

Some patients may hear a soft click right before the second loud click. That is the normal operation of the pen. Do not remove the pen from your skin until you hear the second louder click.

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

This is not unusual and will not affect your dose.

I'm not sure my pen worked correctly.

Check to see if you have received your dose. Your dose was delivered correctly if the grey part is visible (see step 3.) Also contact your local Lilly office listed in the Information for the patient for further instructions. Until then, store your pen safely to avoid an accidental needle stick injury.

OTHER INFORMATION

- If you have vision problems, DO NOT use your pen without help from a person trained to use the Trulicity pen.

WHERE TO LEARN MORE

- If you have any questions or problems with your Trulicity pen, contact your doctor, pharmacist or nurse.

Last revised in Month YYYY