Trulicity
(Dulaglutide)

1. NAME OF THE MEDICINAL PRODUCT

Trulicity 1.5mg/0.5ml Single-Dose Pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

*Produced in CHO cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trulicity is indicated in adults with type 2 diabetes mellitus to improve glycaemic control as:

Monotherapy
When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.

Add-on therapy
In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see section 5.1 for data with respect to different combinations).

4.2 Posology and method of administration

Posology

Monotherapy
The recommended dose is 0.75 mg once weekly.

Add-on therapy
The recommended dose is 1.5 mg once weekly.
For potentially vulnerable populations, such as patients ≥ 75 years, 0.75 mg once weekly can be considered as a starting dose.

When Trulicity is added to existing metformin and/or pioglitazone therapy, the current dose of metformin and/or pioglitazone can be continued. When it is added to existing therapy of a sulphonylurea or prandial 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. Self-monitoring may be necessary to adjust the dose of sulphonylurea or prandial insulin.

Elderly patients (> 65 years old)
No dose adjustment is required based on age (see section 5.2). However, the therapeutic experience in patients ≥ 75 years is very limited (see section 5.1), and in these patients 0.75 mg once weekly can be considered as a starting dose.

Patients with renal impairment
No dosage adjustment is required in patients with mild or moderate renal impairment.
There is very limited experience in patients with severe renal impairment (eGFR [by CKD-EPI] < 30 ml/min/1.73 m^2) or end stage renal disease, therefore Trulicity is not recommended in this population (see section 5.2).

Patients with hepatic impairment
No dosage adjustment is required in patients with hepatic impairment.

Paediatric population
The safety and efficacy of dulaglutide in children aged less than 18 years have not yet been established. No data are available.

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.

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.

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

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

Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions. This should be considered when treating patients with impaired renal function since these events, i.e. nausea, vomiting, and/or diarrhoea, may cause dehydration which could cause a deterioration of renal function. Dulaglutide has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.

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).

Populations not studied
There is limited experience in patients with congestive heart failure.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per 1.5 mg dose, i.e. essentially 'sodium- free'.

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. Dulaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption.. For some prolonged release formulations, an increased release due to an extended gastric residence time may slightly increase drug exposure.

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 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 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 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 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 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 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 dose 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.

Sitagliptin
Sitagliptin exposure was unaffected when coadministered with a single dose of dulaglutide. Following coadministration with 2 consecutive 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 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). The increased exposure may enhance the effects of dulaglutide on blood glucose levels.

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 prandial 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 phase II and phase III studies conducted, 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.

Tabulated list of adverse reactions

The following adverse reactions have been identified based on evaluation of the full duration of the phase II and phase III clinical studies and 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.

Table 1: The frequency of adverse reactions of dulaglutide

System Organ Class	Very common	Common	Uncommon	Rare
Metabolism and nutrition disorders	Hypoglycaemia* (when used in combination with prandial insulin, metformin† or metformin plus glimepiride)	Hypoglycaemia* (when used as monotherapy or in combination with metformin plus pioglitazone)		
Gastrointestinal disorders	Nausea, diarrhoea, vomiting†, abdominal pain†	Decreased appetite, dyspepsia, constipation, flatulence, abdominal distention, gastroesophageal reflux disease, eructation		Acute pancreatitis
General disorders and administration site conditions		Fatigue	Injection site reactions	
Investigations		Sinus tachycardia, first degree atrioventricular block (AVB)		

* Documented, symptomatic hypoglycaemia and blood glucose ≤ to 3.9 mmol/L

† Dulaglutide 1.5 mg dose only. For dulaglutide 0.75 mg, adverse reaction met frequency for next lower incidence grouping.

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 (plus 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.

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.

Gastrointestinal adverse reactions
Cumulative reporting of gastrointestinal events up to 104 weeks with dulaglutide 0.75mg and 1.5 mg, respectively, included nausea (12.9% and 21.2 %), diarrhoea (10.7% and 13.7 %) and vomiting (6.9% and 11.5 %). These were typically mild or moderate in severity and were reported to peak during the first 2 weeks of treatment and rapidly declined over the next 4 weeks, after which the rate remained relatively constant.

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

Acute pancreatitis
The incidence of acute pancreatitis in Phase II and III clinical studies was 0.07% for dulaglutide compared to 0.14% for placebo and 0.19% for comparators with or without additional background antidiabetic therapy.

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 0.75mg and 1.5 mg, respectively.

First degree AV block/PR interval prolongation
Small mean increases from baseline in PR interval of 2 to 3 msec and a 1.5% and 2.4 % incidence of first-degree AV block were observed with dulaglutide 0.75 mg and 1.5 mg, respectively.

Immunogenicity
In clinical 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 III data revealed no clear impact of dulaglutide anti-drug antibodies on changes in HbA1c.

Hypersensitivity
In the phase II and phase III clinical studies, systemic hypersensitivity events (e.g., urticaria, edema) were reported in 0.5 % of patients receiving dulaglutide. None of the patients with systemic hypersensitivity developed dulaglutide anti-drug antibodies.

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.

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.

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

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 was evaluated in six randomised, controlled, phase III trials involving 5,171 patients with type 2 diabetes. Of these, 958 were ≥ 65 years of which 93 were ≥ 75 years. These studies included 3,136 dulaglutide-treated patients, of whom 1,719 were treated with Trulicity 1.5 mg weekly and 1,417 were treated with Trulicity 0.75 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**	**Change in body weight**
	(%)	**(%)**	**<7.0% (%)**	**≤6.5% (%)**	**(mmol/L)**	**(kg)**
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

The rate of documented symptomatic hypoglycaemia with Trulicity 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**	**Change in body weight**
	(%)	**(%)**	**<7.0 %(%)**	**≤6.5 %(%)**	**(mmol/L)**	**(kg)**
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

The rates of documented symptomatic hypoglycaemia with Trulicity 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 <7.0 %(%)	Patients at target HbA1c ≤6.5 %(%)	Change in FBG (mmol/L)	Change in body weight (kg)
26 weeks						
Dulaglutide 1.5 mg once weekly (n=299)	8.06	-1.42‡	68.3	54.6	-1.93	-2.90#
Liraglutide+ 1.8 mg daily (n=300)	8.05	-1.36	67.9	50.9	-1.90	-3.61

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

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

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

The rate of documented symptomatic hypoglycaemia with Trulicity 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% (%)	Patients at target HbA1c ≤6.5% (%)	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

The rates of documented symptomatic hypoglycaemia with Trulicity 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 Trulicity 1.5mg and two cases of severe hypoglycaemia were observed with insulin glargine.

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 6: 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**	**Change in body weight**
	(%)	**(%)**	**<7.0% (%)**	**≤6.5% (%)**	**(mmol/L)**	**(kg)**
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

The rates of documented symptomatic hypoglycaemia with Trulicity 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 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 0.75mg 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 7: 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**	**Change in body weight**
	(%)	**(%)**	**<7.0% (%)**	**≤6.5% (%)**	**(mmol/L)**	**(kg)**
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

The rates of documented symptomatic hypoglycaemia with Trulicity 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 Trulicity 1.5 mg, seven with Trulicity 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 dulglutide provided reductions in systolic blood pressure (SBP) (-2.8 mmHg difference compared to placebo) at 16 weeks. There was no difference in diastolic blood pressure (DBP). Similar results for SBP and DBP were demonstrated at the final 26 week time point of the study.

Cardiovascular Evaluation
In a meta-analysis of phase II and III 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**]**).

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with dulaglutide in one or more subsets of the paediatric population in the treatment of type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Following subcutaneous administration to patients with type 2 diabetes, dulaglutide reaches peak plasma concentrations in 48 hours. The mean peak (C_{max}) and total (AUC) exposures were approximately 114 ng/ml and 14,000 ngh/ml, respectively, after multiple subcutaneous 1.5 mg doses of dulaglutide in patients with type 2 diabetes. Steady-state plasma concentrations were achieved between 2 to 4 weeks of once-weekly administration of dulaglutide (1.5 mg). Exposures after subcutaneous administration of single dulaglutide (1.5 mg) doses in the abdomen, thigh, or upper arm were comparable. The mean absolute bioavailability of dulaglutide following single-dose subcutaneous administration of single 1.5 mg and 0.75 mg doses was 47 % and 65%, respectively.

Distribution
The mean volume of distribution after subcutaneous administration of dulaglutide 0.75 mg and 1.5 mg at steady state in patients with type 2 diabetes mellitus were approximately 19.2 L and 17.4 L.

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

Elimination
The mean apparent clearance of dulaglutide 0.75 mg and 1.5 mg at steady state was 0.073 L/h and 0.107 L/h with an elimination half-life of 4.5 and 4.7 days, respectively.

Special populations

Elderly patients (> 65 years old)
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.

Patients with 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). In clinical studies, the dulaglutide safety profile in patients with moderate renal impairment was similar to the overall T2DM population. These studies did not include patients with severe renal impairment or end stage renal disease.

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

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

5.3 Preclinical safety data

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

In a 6-month carcinogenicity study in transgenic mice, there was no tumorigenic response. In a 2-year carcinogenicity study in rats, at ≥ 7 times the human clinical exposure following 1.5 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 11- to 44-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 16-fold higher than those proposed clinically.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Citric acid, anhydrous
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

Please see on the Carton

6.4 Special precautions for storage

Store in a refrigerator (2ºC – 8ºC).
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 30ºC.

6.5 Nature and contents of container

Glass syringe (type I) encased in a disposable pen.
Each pen contains 0.5 ml of solution.
Pack 4 Single-Dose Pens

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 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 coloured.
Trulicity that has been frozen must not be used.

Manufactured By:
Eli Lilly and Company
Indianapolis, IN 46285,
USA

(یہ ایک دوا ہے)

- دوا آپ کی صحت پر اثر انداز ہوتی ہے اس کا ہدایت کے خلاف استعمال آپ کے لیے نقصان دہ ہے۔
- ڈاکٹر کے نسخے، طریقہء استعمال اور فروخت کنندہ فارماسسٹ کی ہدایت پر سختی سے عمل کریں۔
- ڈاکٹر اور فارماسسٹ دواؤں کے ماہر ہیں اور ان کے فوائد اور نقصانات کو بہتر سمجھتے ہیں۔
- مجوزہ مدت استعمال میں کوئی تبدیلی نہ کریں۔
- ڈاکٹر کے مشورے کے بغیر دوا دوبارہ استعمال نہ کریں۔

دوائیں بچوں کی پہنچ سے دور رکھیں۔
