Boehringer Ingelheim Indonesia
Regulatory Affairs

Trajenta®
Linagliptin

Composition

1 film-coated tablet contains 5 mg
1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]- (= linagliptin)

Excipients: mannitol, starch pregelatinised, maize starch, copovidone, magnesium stearate, Opadry Pink (02F34337)

Indications

Linagliptin is indicated in adult patients with type 2 diabetes mellitus (T2DM) to improve glycaemic control in conjunction with diet and exercise, as add on to metformin, sulphonylureas, or metformin plus sulphonylureas or metformin (>= 1500mg/day) plus empagliflozin

Dosage and administration

Adults
The recommended dose is 5 mg once daily. TRAJENTA can be taken with or without a meal at any time of the day.

Renal impairment
No dose adjustment is required for patients with renal impairment.

Hepatic Impairment
No dose adjustment is required for patients with hepatic impairment.

Elderly
No dose adjustment is necessary.

Children and adolescents
TRAJENTA is not recommended for use in children below 18 years due to lack of data on safety and efficacy.

Missed dose
If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken at the same day.

Contraindications
Hypersensitivity to the active ingredient or any of the excipients.

Special Warnings and Precautions

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

Pancreatitis
Acute pancreatitis has been observed in patients taking linagliptin. If pancreatitis is suspected, TRAJENTA should be discontinued.

Hypoglycaemia
Linagliptin alone showed a comparable incidence of hypoglycaemia to placebo.
In clinical trials of linagliptin as part of combination therapy with agents not known to cause hypoglycaemia (metformin, thiazolidinediones) rates of hypoglycaemia reported with linagliptin were similar to rates in patients taking placebo.
Sulphonylureas are known to cause hypoglycaemia. Therefore, caution is advised when linagliptin is used in combination with a sulphonylurea. A dose reduction of the sulphonylurea may be considered.

Bullous pemphigoid
Bullous pemphigoid has been observed in patients taking linagliptin. If bullous pemphigoid is suspected, TRAJENTA should be discontinued.

Interactions

Pharmacokinetic Interactions

In vitro assessment of drug interactions:
Linagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes. It is not an inducer of CYP isozymes.
Linagliptin is a P-glycoprotein substrate, and inhibits P-glycoprotein mediated transport of digoxin with low potency. Based on these results and *in vivo* drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates.

In vivo assessment of drug interactions:
Clinical data described below suggest that the risk for clinically meaningful interactions by coadministered medicinal products is low. No clinically significant interactions requiring dose adjustment were observed. Linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glibenclamide, simvastatin, warfarin, digoxin or oral contraceptives providing in vivo evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-glycoprotein, and organic cationic transporter (OCT).

Metformin: Co-administration of multiple three-times-daily doses of 850 mg metformin with a supratherapeutic dose of 10 mg linagliptin once daily did not clinical meaningfully alter the pharmacokinetics of linagliptin or metformin in healthy volunteers. Therefore, linagliptin is not an inhibitor of OCT-mediated transport.

Sulphonylureas: The steady-state pharmacokinetics of 5 mg linagliptin were not changed by co-administration of a single 1.75 mg dose glibenclamide (glyburide) and multiple oral doses of 5 mg linagliptin. However there was a clinically not relevant reduction of 14% of both AUC and C_{max} of glibenclamide. Because glibenclamide is primarily metabolized by CYP2C9, these data also support the conclusion that linagliptin is not a CYP2C9 inhibitor. Clinically meaningful interactions would not be expected with other sulphonylureas (e.g. glipizide, tolbutamide and glimepiride) which, like glibenclamide, are primarily eliminated by CYP2C9.

Ritonavir: A study was conducted to assess the effect of ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, on the pharmacokinetics of linagliptin. Co-administration of a single 5 mg oral dose of linagliptin and multiple 200 mg oral doses of ritonavir increased the AUC and C_{max} of linagliptin approximately twofold and threefold, respectively. Simulations of steady-state

plasma concentrations of linagliptin with and without ritonavir indicated that the increase in exposure will be not associated with an increased accumulation. These changes in linagliptin pharmacokinetics were not considered to be clinically relevant. Therefore, clinically relevant interactions would not be expected with other P-glycoprotein/CYP3A4 inhibitors and dose adjustment is not required.

Rifampicin: A study was conducted to assess the effect of rifampicin, a potent inductor of P-glycoprotein and CYP3A4, on the pharmacokinetics of 5 mg linagliptin. Multiple co-administration of linagliptin with rifampicin, resulted in a 39.6% and 43.8% decreased linagliptin steady-state AUC and C_{max} and about 30% decreased DPP-4 inhibition at trough. Thus linagliptin in combination with strong P-gp inducers is expected to be clinically efficacious, although full efficacy might not be achieved.

Digoxin: Co-administration of multiple daily doses of 5 mg linagliptin with multiple doses of 0.25 mg digoxin had no effect on the pharmacokinetics of digoxin in healthy volunteers. Therefore, linagliptin is not an inhibitor of P-glycoprotein-mediated transport *in vivo*.

Warfarin: Multiple daily doses of 5 mg linagliptin did not alter the pharmacokinetics of S(-) or R(+) warfarin, a CYP2C9 substrate, showing that linagliptin is not an inhibitor of CYP2C9.

Simvastatin: Multiple daily doses of 10 mg linagliptin (supratherapeutic) had a minimal effect on the steady state pharmacokinetics of simvastatin, a sensitive CYP3A4 substrate, in healthy volunteers. Following administration of 10 mg linagliptin concomitantly with 40 mg of simvastatin daily for 6 days, the plasma AUC of simvastatin was increased by 34%, and the plasma C_{max} by 10%. Therefore, linagliptin is considered to be a weak inhibitor of CYP3A4-mediated metabolism, and dosage adjustment of concomitantly administered substances metabolised by CYP3A4 is considered unnecessary.

Oral Contraceptives: Co-administration with 5 mg linagliptin did not alter the steady-state pharmacokinetics of levonorgestrel or ethinylestradiol.

The absolute bioavailability of linagliptin is approximately 30%. Because co-administration of a high-fat meal with linagliptin had no clinically relevant effect on the pharmacokinetics, linagliptin may be administered with or without food.

No studies on the effect on human fertility have been conducted for Trajenta. No adverse effects on fertility were observed in animals up to the highest dose of 240 mg/kg/day (approximately 943 times human exposure based on AUC comparisons).

Fertility, Pregnancy and Lactation

Pregnancy
There are limited data from the use of linagliptin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
As a precautionary measure, it is preferable to avoid the use of TRAJENTA during pregnancy.

Lactation
Available pharmacodynamic/toxicological data in animals have shown excretion of linagliptin/metabolites in milk. A risk to the newborns/infants cannot be excluded. TRAJENTA should not be used during breast-feeding.

Fertility

No studies on the effect on human fertility have been conducted for TRAJENTA. No adverse effects on fertility were observed in animals up to the highest dose of 240 mg/kg/day (approximately 943 times human exposure based on AUC comparisons).

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

However, patients should be advised that dizziness has been reported in clinical trials. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience dizziness, they should avoid potentially hazardous tasks such as driving or operating machinery.

Side effects

The safety of TRAJENTA has been evaluated in patients with T2DM which in most cases received the target dose of 5 mg.
In the pooled analysis of the placebo-controlled trials, the overall incidence of AEs in patients treated with placebo was similar to linagliptin 5 mg (63.4% versus 59.1%).
Discontinuation of therapy due to AEs was higher in patients who received placebo as compared to linagliptin 5 mg (4.3 % versus 3.4 %).
Due to the impact of the background therapy on adverse events (e.g. on hypoglycaemias), adverse events were analysed and displayed based on the respective treatment regimens (add on to metformin, add on to sulphonylurea, and add on to metformin plus sulphonylurea, and add on to metformin and empagliflozin.
The placebo-controlled studies included 28 studies where linagliptin was given either as

- add on to metformin
- add on to sulphonylurea
- add on to metformin + sulphonylurea
- add on to metformin and empagliflozin

The most frequently reported adverse event was hypoglycaemia observed under the triple combination, linagliptin plus metformin plus sulphonylurea 22.9% vs 14.8% in placebo.
Hypoglycaemias in the placebo-controlled studies (10.9%; N=471) were mild (80%; N=384) or moderate (16.6%; N=78) or severe (1.9%; N=9) in intensity.

Adverse reactions classified by SOC and MedDRA preferred terms reported in patients who received 5 mg TRAJENTA in the 18 double-blind studies as initial combination therapy or as add-on therapy are presented in clinical trials and adverse reactions identified from post-marketing experience in the table below (see table 1).

The adverse reactions are listed by system organ class and absolute frequency. Frequencies are defined as 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), or Very rare (<1/10,000), not known (cannot be estimated from the available data).

Tabulated summary of adverse reactions
Adverse reactions reported in patients who received TRAJENTA® 5 mg daily as mono- or add-on therapy in clinical trials and adverse reactions identified from post-marketing experience
Table 1 :

MedDRA System Organ Class terminology-	***Linagliptin adverse reactions using CCDS verbatim term MedDRA (version 18.1) term PTs***	***Frequency categories according to EU SmPC Guideline***
Infections and infestations	Nasopharyngitis	Uncommon
Immune system disorders	Hypersensitivity	Uncommon
	Angioedema[1]	Rare †
	Urticaria[1]	Rare $
Metabolism and nutrition disorders	Hypoglycaemia (when used in combination with metformin plus sulphonylurea)	Very common
	Hypertriglyceridaemia (when used in combination with sulphonylurea)	Not known #
	Hyperlipidaemia (when used in combination with pioglitazone)	Not known #
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon
Gastrointestinal disorders	Pancreatitis	Rare
	Constipation (when used in combination with insulin)	Uncommon
	Mouth ulceration [1]	Rare †
Skin and subcutaneous tissue disorders	Rash [1]	Uncommon †
	Angioderma	Rare
	Urticaria	Rare
	Bullous pemphigoid [1]	Rare $
Investigations	Weight increased (when used in combination with pioglitazone)	Common
	Lipase increased	Common [2]
	Amylase increased	Uncommon [3]

[1] ADR identified based on post-marketing experience.

[2] Based on lipase increase > 3xULN in linagliptin treated patients in MARLINA (1218.89) study.

[3] ADR identified based on laboratory analysis of amylase increase to > 3xULN in the CAROLINA (1218.74) study comparing linagliptin with active comparator glimepiride.

† ADR based on post-marketing experience, for which drug-related AEs were reported in the reference dataset (SAF-2).

$ ADR based on post-marketing experience, for which no drug-related AEs were reported in the reference dataset (SAF-2). As stated in the European SmPC Guideline "*the upper limit of the 95% confidence interval is not higher than 3/X, with X representing the total sample size summed up across all relevant clinical trials (SAF-2). For example, if a particular adverse reaction has not been observed among 3600 subjects exposed to the product in clinical trials and studies, then the upper limit of the 95% confidence interval for the point estimate is 1/1200 or less and the frequency category should be "rare", based on worst value of the point estimate.*"

ADR based on signal from clinical trial(s), but event is not reported in clinical trials as drug-related AE; therefore, a frequency could not be calculated. In line with the European SmPC Guideline the frequency "not known" was assigned.

Linagliptin cardiovascular outcome and renal safety study (CARMELINA)
The CARMELINA study evaluated the cardiovascular and renal safety of linagliptin versus placebo in patients with type 2 diabetes and with increased CV risk evidenced by a history of established macrovascular or renal disease (see section Clinical Trials). The study included 3494 patients treated with linagliptin (5 mg) and 3485 patients treated with placebo. Both treatments were added to standard of care targeting regional standards for HbA_{1c} and CV risk factors; with 54% on metformin. The overall incidence of adverse events and serious adverse events in patients receiving linagliptin was similar to that in patients receiving placebo. Safety data from this study was in line with previous known safety profile of linagliptin.

In the treated population, severe hypoglycaemic events (requiring assistance) were reported in 3.0% of patients on linagliptin and in 3.1% on placebo. Among patients who were using sulfonylurea at baseline, the incidence of severe hypoglycaemia was 2.0% in linagliptin-treated patients and 1.7% in placebo treated patients. Among patients who were using insulin at baseline, the incidence of severe hypoglycaemia was 4.4% in linagliptin-treated patients and 4.9% in placebo treated patients.

In the overall study observation period adjudicated acute pancreatitis was reported in 0.3% of patients treated with linagliptin and in 0.1% of patients treated with placebo.
In the CARMELINA study, bullous pemphigoid was reported in 0.2% patients treated with linagliptin and in no patient treated with placebo.

Overdose

Symptoms
During controlled clinical trials in healthy subjects, single doses of up to 600 mg linagliptin (equivalent to 120 times the recommended dose) were well tolerated. There is no experience with doses above 600 mg in humans.

Therapy
In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring and institute clinical measures as required.

Pharmacological Properties

Pharmacotherapeutic group: DPP-4 inhibitor, ATC code: A10BH05

Linagliptin is an inhibitor of the enzyme DPP-4 (Dipeptidyl peptidase 4, EC 3.4.14.5) an enzyme which is involved in the inactivation of the incretin hormones GLP-1 and GIP (glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide). These hormones are rapidly degraded by the enzyme DPP-4. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretins are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in

hepatic glucose output. Linagliptin (TRAJENTA) binds very effectively to DPP-4 in a reversible manner and thus leads to a sustained increase and a prolongation of active incretin levels. TRAJENTA glucose-dependently increases insulin secretion and lowers glucagon secretion thus resulting in an overall improvement in the glucose homoeostasis. Linagliptin binds selectively to DPP-4 and exhibits a >10000 fold selectivity versus DPP-8 or DPP-9 activity in vitro.

Clinical trials

Linagliptin as add on to metformin therapy
The efficacy and safety of linagliptin in combination with metformin was evaluated in a double blind placebo controlled study of 24 weeks duration. Linagliptin provided significant improvements in HbA1c, (-0.64 % change compared to placebo), from a mean baseline HbA1c of 8 %. Linagliptin also showed significant improvements in fasting plasma glucose (FPG) (-21.1 mg/dL/-1.2 mmol/L), 2-hour post-prandial glucose (PPG) by -67.1 mg/dl (-3.7 mmol/L) compared to placebo and a greater portion of patients achieved a target HbA1c of < 7.0% (28.3% on linagliptin vs. 11.4% on placebo). The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo. Body weight did not differ significantly between the groups.

The efficacy and safety of linagliptin in combination with metformin was evaluated in a 24-week placebo-controlled factorial study of initial therapy. Linagliptin 2.5 mg twice daily in combination with metformin (500 mg or 1000 mg twice daily) provided significant improvements in glycaemic parameters compared with either monotherapy (mean baseline HbA1c 8.65%). The mean treatment difference in HbA1c between linagliptin+metformin combination therapy versus metformin monotherapy from baseline to Week 24 (LOCF) was -0.51% (95% CI -0.73, -0.30; p<0.0001) for linagliptin 2.5 mg+metformin 1000 mg twice daily compared to metformin 1000 mg twice daily, -0.58% (95% CI -0.79, -0.36; p<0.0001) for linagliptin 2.5 mg+metformin 500 mg twice daily compared to metformin 500 mg twice daily. The placebo-corrected mean HbA1c change from baseline for linagliptin 2.5/metformin 1000 mg twice daily were 1.71% which led to HbA1c control (<7.0%) in 53.6% of patients (compared to 30.7% on monotherapy with metformin 1000 mg twice daily). Mean reductions from baseline in HbA1c were generally greater for patients with higher baseline HbA1c values. Effects on plasma lipids were generally neutral. The decrease in body weight with the combination of linagliptin and metformin was similar to that observed for metformin alone or placebo; there was no change from baseline for patients on linagliptin alone. The incidence of hypoglycaemia was similar across treatment groups (placebo 1.4%, linagliptin 5 mg 0%, metformin 2.1%, and linagliptin 2.5mg plus metformin twice daily 1.4%). In addition, this study included patients (n=66) with more severe hyperglycaemia (HbA1c at baseline >/=11%) who were treated with twice daily open-label linagliptin 2.5 mg and metformin 1000 mg. In this group of patients, the mean baseline HbA1c value was 11.8% and mean FPG was 261.8 mg/dL. A mean decrease from baseline of -3.74% in HbA1c (n=48) and -81.2 mg/dL for FPG (n=41) was observed for patients completing the 24 week trial period without rescue therapy. In the LOCF analysis including all patients with primary endpoint measurements (n=65) at last observation without rescue therapy changes from baseline were -3.19% for HbA1c and -73.6 mg/dL for FPG.

The efficacy and safety of linagliptin 2.5 mg twice daily versus 5 mg once daily in combination with metformin in patients with insufficient glycaemic control on metformin monotherapy was evaluated in a double blind placebo controlled study of 12 weeks duration. Linagliptin (2.5 mg twice daily and 5 mg once daily) added to metformin provided significant improvements in glycemic parameters compared with placebo. Linagliptin 5 mg once daily and 2.5 mg twice daily provided comparable (CI: -0.07; 0.19) significant HbA1c reductions of -0.80 % (from baseline 7.98%), and -0.74 (from baseline 7.96%) compared to placebo. The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo. Body weight did not differ significantly between the groups.

Linagliptin as add on to sulphonylurea therapy
The efficacy and safety of linagliptin in combination with sulphonylurea was evaluated in a double blind placebo controlled study of 18 weeks duration. Linagliptin provided significant improvements in HbA1c, (-0.47 % change compared to placebo), from a mean baseline HbA1c of 8.6%. Linagliptin also showed significant improvements in patients achieving a target HbA1c of < 7.0%. Body weight did not differ significantly between the groups.

Linagliptin as add on to a combination of metformin and sulphonylurea therapy
A placebo controlled study of 24 weeks in duration was conducted to evaluate the efficacy and safety of linagliptin 5 mg to placebo, in patients not sufficiently treated with a combination with metformin and a sulphonylurea. Linagliptin provided significant improvements in HbA1c (-0.62 % change compared to placebo), from a mean baseline HbA1c of 8.14%. Linagliptin also showed significant improvements in patients achieving a target HbA1c of < 7.0%, and also for fasting plasma glucose (FPG) (-12.7 mg/dL/-0.7 mmol/L), compared to placebo. Body weight did not differ significantly between the groups.

Linagliptin as add on to a combination of metformin and empagliflozin
In patients inadequately controlled with metformin and empagliflozin (10 mg (n=247) or 25 mg (n=217)), 24-weeks treatment with add-on therapy of linagliptin 5 mg provided adjusted mean HbA1c reductions from baseline by -0.53% (significant difference to add-on placebo -0.32% (95% CI -0.25, -0.13) and -0.58% (significant difference to add-on placebo -0.47% (95% CI -0.66; -0.28), respectively. A statistically significant greater proportion of patients with a baseline HbA1c ≥7.0% and treated with linagliptin 5 mg achieved a target HbA1c of <7% compared to placebo.
In prespecified subgroups of patients with baseline HbA1c greater or equal than 8.5% (n=66 and n=42 patients on metformin plus empagliflozin 10 mg or 25 mg, respectively), the adjusted mean HbA1c reductions from baseline to 24 weeks on add-on therapy with linagliptin 5 mg were -0.97% (p=0.0875, for difference to add-on placebo) and -1.16% (p=0.0046, for difference to add-on placebo), respectively.

Linagliptin 24 month data, as add on to metformin in comparison with glimepiride
In a study comparing the efficacy and safety of the addition of linagliptin 5 mg or glimepiride (a sulphonylurea agent) in patients with inadequate glycaemic control on metformin monotherapy, linagliptin was similar to glimepiride in reducing HbA1c, with a mean treatment difference in HbA1c from baseline to 104 weeks for linagliptin compared to glimepiride of +0.20%. In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, showed a statistically significant improvement with linagliptin compared with glimepiride treatment. The incidence of hypoglycaemia in the linagliptin group (5.3 %) was significantly lower than that in the glimepiride group (36.1 %). Patients treated with linagliptin exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glimepiride (-1.39 vs +1.29 kg).

Linagliptin as add on therapy in patients with severe renal impairment, 12 week placebo controlled data (stable background) and 40 week placebo controlled extension (adjustable background)
The efficacy and safety of linagliptin was also evaluated in type 2 diabetes patients with severe renal impairment in a double blind study versus placebo for 12 weeks duration, during which background glycaemic therapies were kept stable. Patients were on a variety on background therapies including insulin, sulphonylurea, glinides and pioglitazone. There was a follow up 40 week period during which dose adjustments in antidiabetes background therapies were allowed

Linagliptin provided significant improvements in HbA1c (-0.59 % change compared to placebo), from a mean baseline HbA1c of 8.2%. A greater portion of patients achieved a target HbA1c of <

7.0%, compared to placebo. The observed difference in HbA1c over placebo was -0.72% after 52 weeks.

Body weight did not differ significantly between the groups. The observed incidence of hypoglycaemia in patients treated with linagliptin was higher than placebo, due to an increase in asymptomatic hypoglycaemic events. This can be attributed to the antidiabetes background therapies (insulin and sulphonylurea or glinides). There was no difference between groups in severe hypoglycaemic events.

Linagliptin as add on therapy in elderly patients (age ≥ 70 years) with type 2 diabetes
The efficacy and safety of linagliptin in elderly (age ≥ 70years) type 2 diabetes patients has been evaluated in a double blind study versus placebo for 24 weeks duration. Patients received metformin and/or sulphonylurea and/or insulin as background therapy. Doses of background antidiabetic medications were kept stable during the first 12 weeks, after which adjustments were permitted. Linagliptin provided significant improvements in HbA1c of -0.64 % (95% CI -0.81, -0.48; p<0.0001) compared to placebo after 24 weeks, from a mean baseline HbA1c of 7.8%. Linagliptin also showed significant improvements in fasting plasma glucose (FPG) of -20.7mg/dL (95% CI -30.2, -11.2; p<0.0001) compared to placebo (-1.1 mmol/L). Body weight did not differ significantly between the groups. However, on a background of sulphonylurea with or without metformin, hypoglycaemia was reported in a higher proportion of patients treated with linagliptin (24 of 82 patients, 29.3%) compared to placebo (7 of 42 patients, 16.7%). There was no difference between groups in severe hypoglycaemic events.

Linagliptin cardiovascular and renal safety study (CARMELINA)

CARMELINA was a randomized study in 6979 patients with type 2 diabetes with increased CV risk evidenced by a history of established macrovascular or renal disease who were treated with linagliptin 5 mg (3494) or placebo (3485) added to standard of care targeting regional standards for HbA_{1c}, CV risk factors and renal disease. The study population included 1,211 (17.4%) patients ≥ 75 years of age and 4,348 (62.3%) patients with renal impairment. Approximately 19% of the population had eGFR ≥45 to <60 mL/min/1.73 m^2, 28% of the population had eGFR ≥30 to <45 mL/min/1.73 m^2 and 15% had eGFR < 30 mL/min/1.73 m^2.

The mean HbA_{1c} at baseline was 8.0%.

The study was designed to demonstrate non-inferiority for the primary cardiovascular endpoint which was a composite of the first occurrence of cardiovascular death or a non-fatal myocardial infarction (MI) or a non-fatal stroke (3P-MACE). The renal composite endpoint was defined as renal death or sustained end stage renal disease or sustained decrease of 40% or more in eGFR.

After a median follow up of 2.2 years, linagliptin, when added to standard of care, did not increase the risk of major adverse cardiovascular events or renal outcome events (Table 2 and Figure 1). There was no increased risk in hospitalization for heart failure which was an additional adjudicated endpoint observed compared to standard of care without linagliptin in patients with type 2 diabetes (Table 3).

Table 2 Major adverse cardiovascular events (MACE) and renal outcome events by treatment group in the CARMELINA study

	Linagliptin 5mg		**Placebo**		**Hazard Ratio**
	Number of Subjects (%)	Incidence Rate per 1000 PY*	Number of Subjects (%)	Incidence Rate per 1000 PY*	(95% CI)
Number of patients	3494		3485		
Primary CV composite (Cardiovascular death, non-fatal MI, non-fatal stroke)	434 (12.4)	57.7	420 (12.1)	56.3	1.02 (0.89, 1.17)**
Secondary renal composite (renal death, ESRD, 40% sustained decrease in eGFR)	327 (9.4)	48.9	306 (8.8)	46.6	1.04 (0.89, 1.22)

* PY=patient years
** Test on non-inferiority to demonstrate that the upper bound of the 95% CI for the hazard ratio is less than 1.3

Figure 1 Time to first occurrence of 3P-MACE in CARMELINA

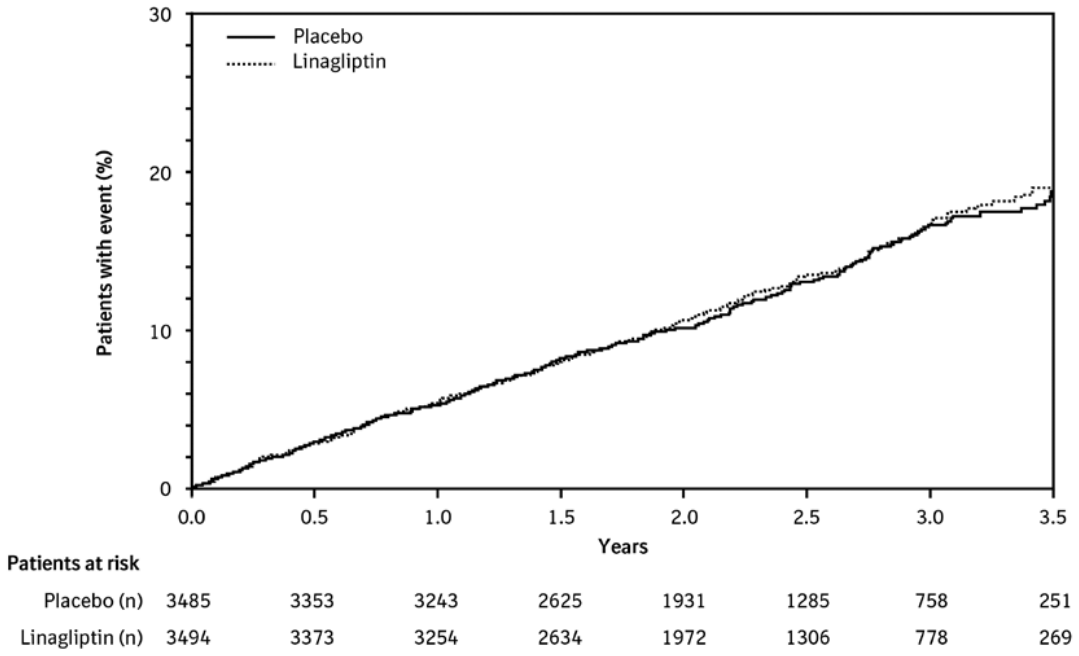

Table 3 Hospitalization for heart failure and mortality by treatment group in the CARMELINA study

	Linagliptin 5mg		**Placebo**		**Hazard Ratio**
	Number of Subjects (%)	Incidence Rate per 1000 PY*	Number of Subjects (%)	Incidence Rate per 1000 PY*	(95% CI)
Number of patients	3494		3485		
All-cause mortality	367 (10.5)	46.9	373 (10.7)	48.0	0.98 (0.84, 1.13)
CV death	255 (7.3)	32.6	264 (7.6)	34	0.96 (0.81, 1.14)
Hospitalization for heart failure	209 (6.0)	27.7	226 (6.5)	30.4	0.90 (0.74, 1.08)

* PY=patient years

In analyses for albuminuria progression (change from normoalbuminuria to micro- or macroalbuminuria, or from microalbuminuria to macroalbuminuria) the estimated hazard ratio was 0.86 (95% CI 0.78, 0.95) for linagliptin versus placebo. The microvascular endpoint was defined as the composite of renal death, sustained ESRD, sustained decrease of ≥50% in eGFR, albuminuria progression, use of retinal photocoagulation or intravitreal injections of an anti-VEGF therapy for diabetic retinopathy or vitreous haemorrhage or diabetes-related-blindness. The estimated hazard ratio for time to first occurrence for the composite microvascular endpoint was 0.86 (95% CI 0.78, 0.95) for linagliptin versus placebo, mainly driven by albuminuria progression.

Linagliptin cardiovascular safety study (CAROLINA)

CAROLINA was a randomized study in 6033 patients with early type 2 diabetes and increased CV risk or established complications who were treated with linagliptin 5 mg (3023) or glimepiride 1- 4 mg (3010) added to standard of care (including background therapy with metformin in 83% of patients) targeting regional standards for HbA_{1c} and CV risk factors. The mean age for study population was 64 years and included 2030 (34%) patients ≥ 70 years of age. The study population included 2089 (35%) patients with cardiovascular disease and 1130 (19%) patients with renal impairment with an eGFR < 60ml/min/1.73m^2 at baseline. The mean HbA_{1c} at baseline was 7.15%.

The study was designed to demonstrate non-inferiority for the primary cardiovascular endpoint which was a composite of the first occurrence of cardiovascular death or a non-fatal myocardial infarction (MI) or a non-fatal stroke (3P-MACE).

After a median follow up of 6.25 years, linagliptin did not increase the risk of major adverse cardiovascular events (Table 4) as compared to glimepiride. Results were consistent for patients treated with or without metformin.

Table 4 Major adverse cardiovascular events (MACE) and mortality by treatment group in the CAROLINA study

	Linagliptin 5mg		**Glimepiride (1-4mg)**		**Hazard Ratio**
	Number of Subjects (%)	Incidence Rate per 1000 PY*	Number of Subjects (%)	Incidence Rate per 1000 PY*	(95% CI)
Number of patients	3023		3010		
Primary CV composite (Cardiovascular death, non-fatal MI, non-fatal stroke)	356 (11.8)	20.7	362 (12.0)	21.2	0.98 (0.84, 1.14)**

* PY=patient years
** Test on non-inferiority to demonstrate that the upper bound of the 95% CI for the hazard ratio is less than 1.3

The composite of treatment sustainability, a key secondary endpoint, was defined as the proportion of patients on study treatment following initial titration period (16 weeks) that maintain glycaemic control ($HbA_{1c} \leq 7.0\%$) at final visit without need for additional antidiabetic drug therapy (rescue medication) without any moderate (symptomatic with glucose value ≤ 70mg/dL) or severe (requiring assistance) hypoglycaemic episodes and without > 2% weight gain. A higher number of patients on linagliptin (481, 16.0%) achieved this key secondary endpoint compared to glimepiride (305, 10.2%).

For the entire treatment period (median time on treatment 5.9 years) the rate of patients with moderate or severe hypoglycaemia was 6.5% on linagliptin versus 30.9% on glimepiride, severe hypoglycaemia occurred in 0.3% of patients on linagliptin versus 2.2% on glimepiride.

Pharmacokinetics

The pharmacokinetics of linagliptin has been extensively characterized in healthy subjects and patients with type 2 diabetes. After oral administration of a 5 mg dose to healthy volunteers patients, linagliptin was rapidly absorbed, with peak plasma concentrations (median Tmax) occurring 1.5 hours postdose.

Plasma concentrations of linagliptin decline in a at least biphasic manner with a long terminal half-life (terminal half-life for linagliptin more than 100 hours), that is mostly related to the saturable, tight binding of linagliptin to DPP-4 and does not contribute to the accumulation of the drug. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of 5 mg linagliptin, is approximately 12 hours. After once-daily dosing, steady-state plasma concentrations of 5 mg linagliptin are reached by the third dose. Plasma AUC of linagliptin increased approximately 33% following 5 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for linagliptin AUC were small (12.6% and 28.5%, respectively). Plasma AUC of linagliptin increased in a less than dose-proportional manner. The pharmacokinetics of linagliptin was generally similar in healthy subjects and in patients with type 2 diabetes.

Absorption
The absolute bioavailability of linagliptin is approximately 30%. Because coadministration of a high-fat meal with linagliptin had no clinically relevant effect on the pharmacokinetics, linagliptin

may be administered with or without food. *In vitro* studies indicated that linagliptin is a substrate of P-glycoprotein and of CYP3A4. Ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, led to a twofold increase in exposure (AUC) and multiple co-administration of linagliptin with rifampicin, a potent inducer of P-gp and CYP3A, resulted in an about 40% decreased linagliptin steady-state AUC, presumably by increasing/decreasing the bioavailability of linagliptin by inhibition/induction of P-glycoprotein.

Distribution
As a result of tissue binding, the mean apparent volume of distribution at steady state following a single 5 mg intravenous dose of linagliptin to healthy subjects is approximately 1110 litres, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99% at 1 nmol/L to 75-89% at ≥30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70-80% of linagliptin was bound to other plasma proteins than DPP-4, hence 20-30% were unbound in plasma.

Biotransformation
Following a [^{14}C] linagliptin oral 10 mg dose, approximately 5% of the radioactivity was excreted in urine. Metabolism plays a subordinate role in the elimination of linagliptin. One main metabolite with an relative exposure of 13.3 % of linagliptin at steady state was detected which was found to be pharmacologically inactive and thus does not contribute to the plasma DPP-4 inhibitory activity of linagliptin.

Excretion
Following administration of an oral [^{14}C] linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated in faeces (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady state was approximately 70 mL/min.

Special Populations
Renal Impairment
A multiple-dose, open-label study was conducted to evaluate the pharmacokinetics of linagliptin (5 mg dose) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with renal impairment classified on the basis of creatinine clearance as mild (50 to <80 mL/min), moderate (30 to <50 mL/min), and severe (<30 mL/min), as well as patients with ESRD on hemodialysis. In addition patients with T2DM and severe renal impairment (<30 mL/min) were compared to T2DM patients with normal renal function. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula:
CrCl = [140 - age (years)] x weight (kg) {x 0.85 for female patients} / [72 x serum creatinine (mg/dL)].
Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects. In moderate renal impairment, a moderate increase in exposure of about 1.7 fold was observed compared with control. Exposure in T2DM patients with severe RI was increased by about 1.4 fold compared to T2DM patients with normal renal function. Steady-state predictions for AUC of linagliptin in patients with ESRD indicated comparable exposure to that of patients with moderate or severe renal impairment. In addition, linagliptin is not expected to be eliminated to a therapeutically significant degree by hemodialysis or peritoneal dialysis. Therefore, no dosage adjustment of linagliptin is necessary in patients with any degree of renal impairment. In addition, mild renal impairment had no effect on linagliptin pharmacokinetics in patients with type 2 diabetes as assessed by population pharmacokinetic analyses.

Hepatic Impairment

In patients with mild moderate and severe hepatic impairment (according to the Child-Pugh classification), mean AUC and C_{max} of linagliptin were similar to healthy matched controls following administration of multiple 5 mg doses of linagliptin. No dosage adjustment for linagliptin is necessary for patients with mild, moderate or severe hepatic impairment.

Body Mass Index (BMI)
No dosage adjustment is necessary based on BMI. Body mass index had no clinically relevant effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data.

Gender
No dosage adjustment is necessary based on gender. Gender had no clinically relevant effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data.

Geriatric
No dosage adjustment is required based on age, as age did not have a clinically relevant impact on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) had comparable plasma concentrations of linagliptin compared to younger subjects.

Paediatric
Studies characterizing the pharmacokinetics of linagliptin in paediatric patients have not been yet performed.

Race
No dosage adjustment is necessary based on race. Race had no obvious effect on the plasma concentrations of linagliptin based on a composite analysis of available pharmacokinetic data, including patients of Caucasian, Hispanic, African-American, and Asian origin. In addition the pharmacokinetic characteristics of linagliptin were found to be similar in dedicated phase I studies in Japanese, Chinese and Caucasian healthy volunteers and African American type 2 diabetes patients.

Toxicology

Carcinogenicity
A two-year carcinogenicity study was conducted in male and female rats given oral doses of linagliptin of 6, 18, and 60 mg/kg/day. There was no increase in the incidence of tumours in any organ up to 60 mg/kg/day. This dose results in exposures approximately 418 times the human exposure at the maximum recommended daily adult human dose (MRHD) of 5 mg/day based on AUC comparisons. A two-year carcinogenicity study was conducted in male and female mice given oral doses of 8, 25 and 80 mg/kg/day. There was no evidence of a carcinogenic potential up to 80 mg/kg/day, approximately 242 times human exposure at the MRHD.

Genotoxicity
Linagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in human lymphocytes, and an in vivo micronucleus assay.

Reproduction Toxicity
In rat fertility studies with oral gavage doses of 10, 30 and 240 mg/kg/day, males were treated for 4 weeks prior to mating and during mating; females were treated 2 weeks prior to mating through

gestation day 6. No adverse effect on early embryonic development, mating, fertility, and bearing live young were observed up to the highest dose of 240 mg/kg/day (approximately 943 times human exposure at the MRHD of 5 mg/day based on AUC comparisons).
In the studies on embryo-foetal development in rats and rabbits, linagliptin was shown to be not teratogenic at dosages up to and including 240 mg/kg/day (943x MRHD) in the rat and 150 mg/kg/day (1943x MRHD) in the rabbit. A NOAEL of 30 mg/kg/day (49x MRHD) and 25 mg/kg (78x MRHD) was derived for embryo-foetal toxicity in the rat and the rabbit, respectively.

Availability:
Box, 3 alublisters @ 10 film coated tablet Reg. No: XXXXXXXXXXXXXX

Storage conditions:
Store below 30°C, protect from light
Store in a safe place, out of the reach of children

Only on doctor's prescription
Harus dengan resep dokter

Manufactured by:
Dragenopharm
Apotheker Püschl GmbH
Tittmoning, Germany

For:
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

Imported by:
PT Tunggal Idaman Abdi
Jakarta, Indonesia

Boehringer Ingelheim Indonesia
Regulatory Affairs

Produk Informasi untuk Pasien

Trajenta 5 mg tablet salut selaput
Linagliptin

Bacalah seluruh leaflet ini dengan cermat sebelum Anda minum obat ini karena leaflet ini berisikan informasi penting bagi Anda.
- Simpanlah leaflet ini. Anda mungkin suatu saat perlu membacanya kembali.
- Bila Anda memiliki pertanyaan lebih lanjut, Anda dapat bertanya kepada dokter, apoteker atau perawat Anda.
- Obat ini diresepkan hanya untuk Anda. Jangan berikan untuk orang lain. Hal ini dapat membahayakan mereka walau tanda-tanda penyakit mereka sama dengan Anda.
- Bila Anda mengalami efek samping, bicarakan kepada dokter, apoteker atau perawat Anda termasuk kemungkinan efek samping apapun yang tidak terdapat dalam leaflet ini.

Apa saja yang terkandung dalam leaflet ini:

1. Apakah Trajenta dan digunakan untuk apakah obat ini

Trajenta mengandung substansi aktif linagliptin yang termasuk dalam kelompok obat yang disebut anti diabetes oral. Obat anti diabetes orang digunakan untuk mengobati kadar gula darah yang tinggi. Obat ini bekerja dengan cara membantu tubuh untuk mengurangi kadar gula dalam darah.

Trajenta digunakan untuk diabetes tipe 2 pada pasien dewasa, jika penyakit tidak cukup terkontrol dengan satu obat anti diabetes oral (metformin atau sulfonilurea) atau dengan diet dan olahraga saja. Trajenta digunakan bersama dengan obat anti diabetes lainnya seperti metformin, sulfonilurea, metformin dan sulfonilurea atau metformin dan empagliflozin.

Penting bagi Anda untuk melanjutkan rencana diet dan olah raga Anda seperti yang telah dianjurkan oleh dokter, atau perawat Anda.

2. Apa yang perlu Anda ketahui sebelum Anda minum Trajenta

Jangan minum Trajenta
- Bila Anda alergi terhadap linagliptin atau bahan lainnya dalam obat ini (tertulis dalam bab 6).

Peringatan dan perhatian
Bicarakan dengan dokter, apoteker, atau perawat Anda sebelum minum Trajenta:
- Bila Anda memiliki diabetes tipe 1 (tubuh Anda tidak memproduksi insulin) atau ketoasidosis diabetik (suatu komplikasi diabetes dengan kadar gula tinggi, penurunan

berat badan yang cepat, mual dan muntah). Trajenta tidak boleh digunakan untuk mengobati kondisi ini.

- Bila Anda minum obat antidiabetik yang diketahui sebagai golongan 'sulfonilurea' (contoh : glimepiride, glipizide), maka dokter Anda mungkin akan menurunkan dosis sulfonilurea ketika Anda menggunakannya bersama dengan Trajenta untuk menghindari kadar gula darah yang terlalu rendah (hipoglikemia).
- Bila Anda memiliki reaksi alergi terhadap obat lain yang dikonsumsi untuk mengontrol kadar gula di dalam darah
- Bila Anda memiliki atau pernah memiliki gangguan pankreas
- Bila Anda mengalami gejala pankreatitis akut seperti sakit perut yang terus menerus dan parah (nyeri abdomen), Anda harus berkonsultasi dengan dokter Anda
- Bila kulit Anda melepuh, itu mungkin merupakan tanda kondisi yang disebut pemfigoid bulosa. Dokter Anda mungkin akan meminta Anda untuk berhenti minum Trajenta
- Lesi kulit diabetes adalah komplikasi umum dari diabetes. Anda disarankan untuk mengikuti rekomendasi perawatan kulit dan kaki yang diberikan oleh dokter atau perawat Anda

Anak dan remaja
Trajenta tidak direkomendasikan untuk anak dan remaja usia dibawah 18 tahun.

Obat-obatan lainnya dan Trajenta
Beritahukan kepada dokter atau apoteker Anda bila Anda sedang minum, akhir-akhir ini minum, atau mungkin minum obat-obatan lainnya.

Secara khusus, Anda harus memberi tahu dokter Anda jika Anda menggunakan obat-obatan yang mengandung salah satu zat aktif berikut :

- Karbamazepin, fenobarbital, atau fenitoin. Ini mungkin digunakan untuk kejang atau nyeri kronis
- Rifampisin. Ini adalah antibiotik yang digunakan untuk mengobati infeksi seperti tuberkulosis

Kehamilan dan menyusui
Bila Anda hamil atau menyusui, berpikir bahwa kemungkinan Anda hamil atau merencanakan untuk memiliki bayi, mintalah saran kepada dokter atau apoteker Anda sebelum minum obat ini.

Belum diketahui apakah Trajenta berbahaya bagi janin. Lebih baik Anda menghindari menggunakan Trajenta bila Anda hamil.
Belum diketahui apakah Trajenta dapat masuk kedalam air susu ibu. Keputusan harus dibuat oleh dokter Anda apakah akan menghentikan menyusui atau menghentikan/abstain dari pengobatan Trajenta

Mengendarai dan mengoperasikan mesin
Trajenta tidak mempengaruhi atau dapat diabaikan pengaruhnya terhadap kemampuan mengendarai dan mengoperasikan mesin.

Meminum Trajenta yang dikombinasi dengan obat dari golongan sulfonilurea dapat mengakibatkan kadar gula darah menjadi terlalu rendah (hipoglikemia) sehingga

mempengaruhi kemampuan Anda mengendarai dan mengoperasikan mesin atau bekerja tanpa pengaman kaki. Namun disarankan unruk melakukan tes gula darah lebih sering untuk mengurangi risiko hipoglikemia, terutama saat Trajenta dikombinasikan dengan sulfonilurea

3. Bagaimana cara minum Trajenta

Selalu minum obat ini sesuai dengan instruksi dokter Anda. Tanyakan kepada dokter atau apoteker Anda bila Anda merasa tidak yakin.

Dosis Trajenta yang dianjurkan 5 mg sekali sehari.

Anda dapat meminum Trajenta dengan atau tanpa makanan.

Dokter Anda mungkin meresepkan Trajenta bersama dengan obat antidiabetik oral lainnya. Ingatlah untuk meminum semua obat sesuai dengan instruksi yang diberikan oleh dokter Anda agar dapat dicapai hasil terbaik bagi kesehatan Anda

Bila Anda minum Trajenta lebih banyak dari seharusnya

Bila Anda minum Trajenta lebih banyak dari seharusnya, Anda harus beritahukan dokter Anda

Bila Anda lupa minum Trajenta

Bila Anda lupa minum satu dosis maka Anda sebaiknya segera meminumnya begitu Anda ingat. Akan tetapi bila waktunya sudah mendekati jadwal dosis obat selanjutnya maka lompati dosis yang terlupakan tersebut.
Jangan minum dosis ganda untuk menggantikan dosis yang terlupa. Jangan pernah minum dosis ganda pada hari yang sama.

Bila Anda berhenti minum Trajenta

Jangan berhenti minum Trajenta tanpa berkonsultasi terlebih dahulu dengan dokter Anda. Kadar gula darah akan dapat meningkat ketika Anda berhenti minum Trajenta.

Bila Anda memiliki pertanyaan lebih lanjut mengenai cara minum obat ini, bertanyalah kepada dokter, apoteker atau perawat Anda.

4. Kemungkinan efek samping

Sebagaimana obat lainnya, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Beberapa gejala yang memerlukan perhatian medis segera :
Anda harus berhenti minum Trajenta dan segera berkonsultasi dengan dokter Anda bila Anda mengalami salah satu efek samping dari gula darah rendah berikut ini: gemetar, berkeringat, gelisah, penglihatan kabur, bibir kesemutan, pucat, perubahan suasana hati atau kebingungan (hipoglikemia). Hipoglikemia (frekuensi: sangat sering terjadi, dapat dialami lebih dari 1 dari 10 orang) adalah efek samping yang teridentifikasi ketika Trajenta dikonsumsi bersamaan dengan metformin dan sulfonilurea.

Beberapa pasien pernah mengalami reaksi alergi (hipersensitivitas; frekuensi tidak sering terjadi, dapat dialami 1 dari 100 orang) saat mengonsumsi Trajenta saja atau

dalam kombinasi dengan produk obat lain untuk pengobatan diabetes, yang mungkin serius, termasuk mengi dan sesak napas (hiperreaktivitas bronkial; frekuensi tidak diketahui, frekuensi tidak dapat diperkirakan dari data yang tersedia). Beberapa pasien mengalami ruam (frekuensi tidak sering terjadi), gatal-gatal (urtikaria; frekuensi jarang, dapat dialami 1 dari 1000 orang), dan pembengkakan pada wajah, bibir, lidah, dan tenggorokan yang dapat menyebabkan kesulitan bernapas atau menelan (angioedema; frekuensi jarang). Jika Anda mengalami salah satu tanda penyakit yang disebutkan di atas, hentikan penggunaan Trajenta dan segera hubungi dokter Anda. Dokter Anda mungkin meresepkan obat untuk mengobati reaksi alergi Anda dan obat lain untuk diabetes Anda.

Beberapa pasien pernah mengalami radang pankreas (pankreatitis; frekuensi jarang, dapat dialami 1 dari 1000 orang) saat mengkonsumsi Trajenta saja atau dikombinasikan dengan produk obat lain untuk pengobatan diabetes.

BERHENTI meminum Trajenta dan segera hubungi dokter jika Anda mengalami salah satu dari efek samping yang serius berikut ini:

Nyeri hebat dan terus-menerus di perut (area perut) yang bisa mencapai punggung, serta mual dan muntah, karena ini bisa menjadi tanda peradangan pankreas (pankreatitis).

Beberapa pasien mengalami efek samping berikut saat mengonsumsi Trajenta sendiri atau dalam kombinasi dengan produk obat lain untuk pengobatan diabetes:

- Umum: kadar lipase dalam darah meningkat.
- Jarang: radang hidung atau tenggorokan (nasofaringitis), batuk, kadar amilase dalam darah meningkat.
- Jarang: kulit melepuh (pemfigoid bulosa).

Pelaporan efek samping
Bila Anda mengalami efek samping apa pun, beritahukan dokter, apoteker, atau perawat Anda, termasuk efek samping yang belum tertulis dalam leaflet ini. Dengan melaporkan efek samping, Anda dapat mendukung ketersediaan informasi keamanan yang lebih banyak untuk obat ini.

5. Bagaimana cara menyimpan Trajenta

Jangan gunakan obat ini setelah tanggal kadaluarsa yang tertulis pada blister dan karton setelah tulisan ‘EXP’. Tanggal kadaluarsa merujuk kepada hari terakhir pada bulan tersebut.

Jangan gunakan Trajenta bila paket rusak atau menunjukkan tanda-tanda rusak.

Jangan membuang obat apapun melalui pembuangan limbah air atau limbah rumah tangga. Bertanyalah kepada apoteker Anda bagaimana cara membuang obat-obatan yang tidak Anda gunakan lagi. Tindakan ini akan membantu melindungi lingkungan.

6. Isi paket dan informasi lainnya

Apakah bahan yang terkandung dalam Trajenta

Zat aktifnya adalah linagliptin. Setiap tablet mengandung linagliptin 5 mg.

Bahan lainnya adalah:
inti tablet: Mannitol, pregelatinised starch (maize), maize starch, copovidone, magnesium stearate
penyalut tablet: Hypromellose, titanium dioxide (E171), talk, makrogol (6000), iron oxide red (E172)

Seperti apakah tampilan dan isi paket Trajenta

- Tablet salut selaput Trajenta 5 mg berbentuk bulat dengan diameter 8 mm, berwarna merah muda.
- Tablet ini bertuliskan "D5" pada satu sisi dan logo Boehringer Ingelheim pada sisi lainnya.
- Tablet Trajenta tersedia dalam blister *unit dose* yang terbuat dari aluminium/aluminium yang dapat dikoyak. Ukuran paket adalah 30x1, tablet salut selaput.

Trajenta 5 mg Reg. No: XXXXXXXXXXXXX

Harus dengan resep dokter

Kondisi penyimpanan :
Simpan di bawah suhu 30°C, terlindung dari cahaya
Simpan di tempat yang aman, jauhkan dari jangkauan anak-anak

Diproduksi oleh :
Dragenopharm Apotheker Püschl GmbH
Tittmoning, Jerman

Untuk :
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Jerman

Diimpor oleh :
PT Tunggal Idaman Abdi
Jakarta, Indonesia