ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trajenta 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of linagliptin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

8 mm diameter round, light red film-coated tablet debossed with "D5" on one side and the Boehringer Ingelheim logo on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trajenta is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control as:
monotherapy
- when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment.

combination therapy
- in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).

4.2 Posology and method of administration

Posology
The dose of linagliptin is 5 mg once daily. When linagliptin is added to metformin, the dose of metformin should be maintained, and linagliptin administered concomitantly.
When linagliptin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin, may be considered to reduce the risk of hypoglycaemia (see section 4.4)

Special populations
Renal impairment
For patients with renal impairment, no dose adjustment for linagliptin is required.

Hepatic impairment
Pharmacokinetic studies suggest that no dose adjustment is required for patients with hepatic impairment but clinical experience in such patients is lacking.

Elderly
No dose adjustment is necessary based on age.

Paediatric population
The safety and efficacy of linagliptin in children and adolescents has not yet been established. No data are available.

Method of administration
The tablets can be taken with or without a meal at any time of the day. If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

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

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

Hypoglycaemia
Linagliptin alone showed a comparable incidence of hypoglycaemia to placebo.
In clinical trials of linagliptin as part of combination therapy with medicinal products not known to cause hypoglycaemia (metformin), rates of hypoglycaemia reported with linagliptin were similar to rates in patients taking placebo.

When linagliptin was added to a sulphonylurea (on a background of metformin), the incidence of hypoglycaemia was increased over that of placebo (see section 4.8).

Sulphonylureas and insulin are known to cause hypoglycaemia. Therefore, caution is advised when linagliptin is used in combination with a sulphonylurea and/or insulin. A dose reduction of the sulphonylurea or insulin may be considered (see section 4.2).

Acute pancreatitis
Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Acute pancreatitis has been observed in patients taking linagliptin. In a cardiovascular and renal safety study (CARMELINA) with median observation period of 2.2 years, adjudicated acute pancreatitis was reported in 0.3% of patients treated with linagliptin and in 0.1% of patients treated with placebo. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Trajenta should be discontinued; if acute pancreatitis is confirmed, Trajenta should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Bullous pemphigoid
Bullous pemphigoid has been observed in patients taking linagliptin. In the CARMELINA study, bullous pemphigoid was reported in 0.2% of patients on treatment with linagliptin and in no patient on placebo. If bullous pemphigoid is suspected, Trajenta should be discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro assessment of 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* interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates.

In vivo assessment of interactions
Effects of other medicinal products on linagliptin
Clinical data described below suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low.

Rifampicin: multiple co-administration of 5 mg linagliptin with rifampicin, a potent inductor of P-glycoprotein and CYP3A4, resulted in a 39.6% and 43.8% decreased linagliptin steady-state AUC and C_{max}, respectively, and about 30% decreased DPP-4 inhibition at trough. Thus, full efficacy of linagliptin in combination with strong P-gp inducers might not be achieved, particularly if these are administered long-term. Co-administration with other potent inducers of P-glycoprotein and CYP3A4, such as carbamazepine, phenobarbital and phenytoin has not been studied.

Ritonavir: co-administration of a single 5 mg oral dose of linagliptin and multiple 200 mg oral doses of ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, increased the AUC and C_{max} of linagliptin approximately twofold and threefold, respectively. The unbound concentrations, which are usually less than 1% at the therapeutic dose of linagliptin, were increased 4-5-fold after co-administration with ritonavir. 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.

Metformin: co-administration of multiple three times daily doses of 850 mg metformin with 10 mg linagliptin once daily did not clinical meaningfully alter the pharmacokinetics of linagliptin in healthy volunteers.

Sulphonylureas: the steady-state pharmacokinetics of 5 mg linagliptin was not changed by concomitant administration of a single 1.75 mg dose glibenclamide (glyburide).

Effects of linagliptin on other medicinal products
In clinical studies, as described below, linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glyburide, simvastatin, warfarin, digoxin or oral contraceptives providing *in vivo* evidence of a low propensity for causing medicinal product interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-glycoprotein, and organic cationic transporter (OCT).

Metformin: co-administration of multiple daily doses of 10 mg linagliptin with 850 mg metformin, an OCT substrate, had no relevant effect on the pharmacokinetics of metformin in healthy volunteers. Therefore, linagliptin is not an inhibitor of OCT-mediated transport.

Sulphonylureas: co-administration of multiple oral doses of 5 mg linagliptin and a single oral dose of 1.75 mg glibenclamide (glyburide) resulted in clinically not relevant reduction of 14% of both AUC and C_{max} of glibenclamide. Because glibenclamide is primarily metabolised 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.

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, administered in a single dose.

Simvastatin: multiple daily doses of linagliptin had a minimal effect on the steady-state pharmacokinetics of simvastatin, a sensitive CYP3A4 substrate, in healthy volunteers. Following administration of a supratherapeutic dose 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%.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
The use of linagliptin has not been studied in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of linagliptin during pregnancy.

Breast-feeding
Available pharmacokinetic data in animals have shown excretion of linagliptin/metabolites in milk. A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from linagliptin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
No studies on the effect on human fertility have been conducted for linagliptin. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Linagliptin has no or negligible influence on the ability to drive and use machines. However patients should be alerted to the risk of hypoglycaemia especially when combined with sulphonylurea and/or insulin.

4.8 Undesirable effects

Summary of the safety profile
In the pooled analysis of the placebo-controlled trials, the overall incidence of adverse events in patients treated with placebo was similar to linagliptin 5 mg (63.4% versus 59.1%). Discontinuation of therapy due to adverse events was higher in patients who received placebo as compared to linagliptin 5 mg (4.3% versus 3.4%).

The most frequently reported adverse reaction was “hypoglycaemia” observed under the triple combination, linagliptin plus metformin plus sulphonylurea 14.8% versus 7.6% in placebo.

In the placebo-controlled studies 4.9% of patients experienced “hypoglycaemia” as an adverse reaction under linagliptin. Of these, 4.0% were mild and 0.9% were moderate and 0.1% were classified as severe in intensity. Pancreatitis was reported more often in patients randomized to linagliptin (7 events in 6,580 patients receiving linagliptin versus 2 events in 4,383 patients receiving placebo).

Tabulated list of adverse reactions
Due to the impact of the background therapy on adverse reactions (e.g. on hypoglycaemias), adverse reactions were analysed based on the respective treatment regimens (monotherapy, add-on to metformin, add-on to meformin plus sulphonylurea, and add-on to insulin).

The placebo-controlled studies included studies where linagliptin was given as

- monotherapy with short-term duration of up to 4 weeks
- monotherapy with ≥ 12 week duration
- add-on to metformin
- add-on to metformin + sulphonylurea
- add on to metformin and empagliflozin
- add-on to insulin with or without metformin

Adverse reactions classified by system organ class and MedDRA preferred terms reported in patients who received 5 mg linagliptin in double-blind studies as monotherapy or as add-on therapy are presented in the table below (see table 1).

The adverse reactions are listed by 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), very rare (<1/10,000) or not known (cannot be estimated from the available data).

Table 1 Adverse reactions reported in patients who received linagliptin 5 mg daily as monotherapy or as add-on therapies in clinical trial and from post-marketing experience

System organ class Adverse reaction	**Frequency of adverse reaction**
Infections and infestations	
Nasopharyngitis	uncommon
Immune system disorders	
Hypersensitivity (e.g. bronchial hyperreactivity)	uncommon
Metabolism and nutrition disorders	
Hypoglycaemia [1]	very common
Respiratory, thoracic and mediastinal disorders	
Cough	uncommon
Gastrointestinal disorders	
Pancreatitis	rare #
Constipation [2]	uncommon
Skin and subcutaneous tissue disorders	
Angioedema*	rare
Urticaria*	rare
Rash*	uncommon
Bullous pemphigoid	rare #
Investigations	
Amylase increased	uncommon
Lipase increased**	common

* Based on post-marketing experience
** Based on lipase elevations >3xULN observed in clinical trials
# Based on *Linagliptin cardiovascular and renal safety study (CARMELINA)*, see also below
1 Adverse reaction observed in combination with metformin plus sulphonylurea
2 Adverse reaction observed in combination with insulin

Linagliptin cardiovascular 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 5.1). 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. 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% of patients treated with linagliptin and in no patient treated with placebo.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
During controlled clinical trials in healthy subjects, single doses of up to 600 mg linagliptin (equivalent to 120 times the recommended dose) were generally 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 if required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, dipeptidyl peptidase 4 (DPP-4) inhibitors, ATC code: A10BH05

Mechanism of action
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 peptide1, 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

binds very effectively to DPP-4 in a reversible manner and thus leads to a sustained increase and a prolongation of active incretin levels. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion thus resulting in an overall improvement in the glucose homeostasis. Linagliptin binds selectively to DPP-4 and exhibits a > 10,000 fold selectivity versus DPP-8 or DPP-9 activity *in vitro*.

Clinical efficacy and safety

8 phase III randomised controlled trials involving 5,239 patients with type 2 diabetes, of which 3,319 were treated with linagliptin were conducted to evaluate efficacy and safety. These studies had 929 patients of 65 years and over who were on linagliptin. There were also 1,238 patients with mild renal impairment, and 143 patients with moderate renal impairment on linagliptin. Linagliptin once daily produced clinically significant improvements in glycaemic control, with no clinically relevant change in body weight. The reductions in glycosylated haemoglobin A_{1c} (HbA_{1c}) were similar across different subgroups including gender, age, renal impairment and body mass index (BMI). Higher baseline HbA_{1c} was associated with a greater reduction in HbA_{1c}. There was a significant difference in reduction in HbA_{1c} between Asian patients (0.8%) and White patients (0.5%) in the pooled studies.

Linagliptin as monotherapy in patients ineligible for metformin

The efficacy and safety of linagliptin monotherapy was evaluated in a double-blind placebo-controlled study of 24 weeks duration. Treatment with once daily linagliptin at 5 mg provided a significant improvement in HbA_{1c} (-0.69% change compared to placebo), in patients with baseline HbA_{1c} of approximately 8%. Linagliptin also showed significant improvements in fasting plasma glucose (FPG), and 2-hour post-prandial glucose (PPG) compared to placebo. The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo.

The efficacy and safety of linagliptin monotherapy was also evaluated in patients for whom metformin therapy is inappropriate, due to intolerability or contraindicated due to renal impairment, in a double-blind placebo-controlled study of 18 weeks duration. Linagliptin provided significant improvements in HbA_{1c}, (-0.57% change compared to placebo), from a mean baseline HbA_{1c} of 8.09%. Linagliptin also showed significant improvements in fasting plasma glucose (FPG) compared to placebo. The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo.

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 HbA_{1c}, (-0.64% change compared to placebo), from a mean baseline HbA_{1c} of 8%. Linagliptin also showed significant improvements in fasting plasma glucose (FPG), and 2-hour post-prandial glucose (PPG) compared to placebo. The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo.

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 HbA_{1c} (-0.62% change compared to placebo), from a mean baseline HbA_{1c} of 8.14%. Linagliptin also showed significant improvements in patients fasting plasma glucose (FPG), and 2-hour post-prandial glucose (PPG), compared to placebo.

Linagliptin as add-on to a combination of metformin and empagliflozin therapy

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 HbA_{1c} reductions from baseline by -0.53% (significant difference to add-on placebo -0.32% (95% CI -0.52, -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 HbA_{1c} ≥7.0% and treated with linagliptin 5 mg achieved a target HbA_{1c} of <7% compared to placebo.

Linagliptin as add-on to insulin therapy
The efficacy and safety of the addition of linagliptin 5 mg to insulin alone or in combination with metformin and/or pioglitazone has been evaluated in a double-blind placebo-controlled study of 24 weeks duration. Linagliptin provided significant improvements in HbA_{1c} (-0.65% compared to placebo) from a mean baseline HbA_{1c} of 8.3%. Linagliptin also provided significant improvements in fasting plasma glucose (FPG), and a greater proportion of patients achieved a target HbA_{1c} of < 7.0%, compared to placebo. This was achieved with a stable insulin dose (40.1 IU). Body weight did not differ significantly between the groups. Effects on plasma lipids were negligible. The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo (22.2% linagliptin; 21.2% placebo).

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 (mean dose 3 mg) in patients with inadequate glycaemic control on metformin monotherapy, mean reductions in HbA_{1c} were -0.16% with linagliptin (mean baseline HbA_{1c} 7.69%) and -0.36% with glimepiride (mean baseline HbA_{1c} 7.69%.) with a mean treatment difference of 0.20% (97.5% CI: 0.09, 0.299). The incidence of hypoglycaemia in the linagliptin group (7.5%) 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. Most patients (80.5%) received insulin as background therapy, alone or in combination with other oral anti-diabetics such as sulphonylurea, glinide and pioglitazone. There was a further follow up 40 week treatment period during which dose adjustments in antidiabetes background therapies were allowed.

Linagliptin provided significant improvements in HbA_{1c} (-0.59 % change compared to placebo after 12 weeks), from a mean baseline HbA_{1c} of 8.2%. The observed difference in HbA_{1c} 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. There was no difference between groups in severe hypoglycaemic events.

Linagliptin as add-on therapy in elderly (age ≥ 70 years) with type 2 diabetes
The efficacy and safety of linagliptin in elderly (age ≥ 70years) with type 2 diabetes was evaluated in a double-blind study of 24 weeks duration. Patients received metformin and/or sulphonylurea and/or insulin as background therapy. Doses of background antidiabetic medicinal products were kept stable during the first 12 weeks, after which adjustments were permitted. Linagliptin provided significant improvements in HbA_{1c} (-0.64 % change compared to placebo after 24 weeks), from a mean baseline HbA_{1c} of 7.8%. Linagliptin also showed significant improvements in fasting plasma glucose (FPG) compared to placebo. Body weight did not differ significantly between the groups.

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 1211 (17.4%) patients ≥ 75 years of age and 4348 (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 usual care, did not increase the risk of major adverse cardiovascular events or renal outcome events. There was no increased risk in hospitalization for heart failure which was an additional adjudicated endpoint observed compared to usual care without linagliptin in patients with type 2 diabetes (see table 2).

Table 2 Cardiovascular and renal outcomes 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)
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

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

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.

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 1-4mg (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 (see table 3) as compared to glimepiride. Results were consistent for patients treated with or without metformin.

Table 3 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)**
All-cause mortality	308 (10.2)	16.8	336 (11.2)	18.4	0.91 (0.78,1.06)
CV death	169 (5.6)	9.2	168 (5.6)	9.2	1.00 (0.81, 1.24)
Hospitalization for heart failure (HHF)	112 (3.7)	6.4	92 (3.1)	5.3	1.21 (0.92, 1.59)

* 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

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.

Paediatric population

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

5.2 Pharmacokinetic properties

The pharmacokinetics of linagliptin has been extensively characterised in healthy subjects and patients with type 2 diabetes. After oral administration of a 5 mg dose to healthy volunteers or patients, linagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1.5 hours post-dose.

Plasma concentrations of linagliptin decline in a triphasic 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 medicinal product. 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 of 5 mg linagliptin, steady-state plasma concentrations 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). Due to the concentration dependent binding of linagliptin to DPP-4, the pharmacokinetics of linagliptin based on total exposure is not linear; indeed total plasma AUC of linagliptin increased in a less than dose-proportional manner while unbound AUC increases in a roughly 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%. Co-administration of a high-fat meal with linagliptin prolonged the time to reach C_{max} by 2 hours and lowered C_{max} by 15% but no influence on AUC $_{0\text{-}72h}$ was observed. No clinically relevant effect of C_{max} and T_{max} changes is expected; therefore linagliptin may be administered with or without food.

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 1,110 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 30-20% 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 a 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 insufficiency compared to normal healthy control subjects. The study included patients with renal insufficiency 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) x weight/72 x serum creatinine [x 0.85 for females], where age is in years, weight in kg, and serum creatinine is in 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 insufficiency.

Hepatic impairment
In non-diabetic patients with mild moderate and severe hepatic insufficiency (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 proposed for diabetic patients with mild, moderate or severe hepatic impairment.

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

II data. The clinical trials before marketing authorisation have been performed up to a BMI equal to 40 kg/m^2.

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.

Elderly
No dosage adjustment is required based on age up to 80 years, 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. Older subjects (65 to 80, oldest patient was 78 years) had comparable plasma concentrations of linagliptin compared to younger subjects.

Paediatric population
A paediatric Phase 2 study examined the pharmacokinetics and pharmacodynamics of 1 mg and 5 mg linagliptin in children and adolescents ≥10 to <18 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects. Linagliptin 5 mg showed superiority over 1 mg with regard to trough DPP-4 inhibition (72% vs 32%, p=0.0050) and a numerically larger reduction with regard to adjusted mean change from baseline in HbA_{1c} (-0.63% vs -0.48%, n.s.). Due to the limited nature of the data set the results should be interpreted cautiously.

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, 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.

5.3 Preclinical safety data

Liver, kidneys and gastrointestinal tract are the principal target organs of toxicity in mice and rats at repeat doses of linagliptin of more than 300 times the human exposure.
In rats effects on reproductive organs, thyroid and the lymphoid organs were seen at more than 1,500 times human exposure. Strong pseudo-allergic reactions were observed in dogs at medium doses, secondarily causing cardiovascular changes, which were considered dog-specific. Liver, kidneys, stomach, reproductive organs, thymus, spleen, and lymph nodes were target organs of toxicity in Cynomolgus monkeys at more than 450 times human exposure. At more than 100 times human exposure, irritation of the stomach was the major finding in these monkeys.

Linagliptin and its main metabolite did not show a genotoxic potential.
Oral 2 year carcinogenicity studies in rats and mice revealed no evidence of carcinogenicity in rats or male mice. A significantly higher incidence of malignant lymphomas only in female mice at the highest dose (> 200 times human exposure) is not considered relevant for humans (explanation: non-treatment related but due to highly variable background incidence). Based on these studies there is no concern for carcinogenicity in humans.

The NOAEL for fertility, early embryonic development and teratogenicity in rats was set at >900 times the human exposure. The NOAEL for maternal-, embryo-fetal-, and offspring toxicity in rats was 49 times human exposure. No teratogenic effects were observed in rabbits at >1,000 times human exposure. A NOAEL of 78 times human exposure was derived for embryo-fetal toxicity in rabbits, and for maternal toxicity the NOAEL was 2.1 times human exposure. Therefore, it is considered unlikely that linagliptin affects reproduction at therapeutic exposures in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Mannitol
Pregelatinised starch (maize)
Maize starch
Copovidone
Magnesium stearate

Film coating
Hypromellose
Titanium dioxide (E171)
Talc
Macrogol (6000)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Perforated alu/alu unit dose blisters in cartons containing 10 x 1, 14 x 1, 28 x 1, 30 x 1, 56 x 1, 60 x 1, 84 x 1, 90 x 1, 98 x 1, 100 x 1 and 120 x 1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/707/001 (10 x 1 tablets)
EU/1/11/707/002 (14 x 1 tablets)
EU/1/11/707/003 (28 x 1 tablets)
EU/1/11/707/004 (30 x 1 tablets)
EU/1/11/707/005 (56 x 1 tablets)

EU/1/11/707/006 (60 x 1 tablets)
EU/1/11/707/007 (84 x 1 tablets)
EU/1/11/707/008 (90 x 1 tablets)
EU/1/11/707/009 (98 x 1 tablets)
EU/1/11/707/010 (100 x 1 tablets)
EU/1/11/707/011 (120 x 1 tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 August 2011
Date of latest renewal: 22 March 2016

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

Boehringer Ingelheim Hellas Single Member S.A.
5th km Paiania – Markopoulo
Koropi Attiki, 19441
Greece

Dragenopharm Apotheker Püschl GmbH
Göllstraße 1
84529 Tittmoning
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

The MAH shall perform the pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Trajenta 5 mg film-coated tablets
linagliptin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg of linagliptin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 x 1 film-coated tablets
14 x 1 film-coated tablets
28 x 1 film-coated tablets
30 x 1 film-coated tablets
56 x 1 film-coated tablets
60 x 1 film-coated tablets
84 x 1 film-coated tablets
90 x 1 film-coated tablets
98 x 1 film-coated tablets
100 x 1 film-coated tablets
120 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/707/001 10 x 1 tablets
EU/1/11/707/002 14 x 1 tablets
EU/1/11/707/003 28 x 1 tablets
EU/1/11/707/004 30 x 1 tablets
EU/1/11/707/005 56 x 1 tablets
EU/1/11/707/006 60 x 1 tablets
EU/1/11/707/007 84 x 1 tablets
EU/1/11/707/008 90 x 1 tablets
EU/1/11/707/009 98 x 1 tablets
EU/1/11/707/010 100 x 1 tablets
EU/1/11/707/011 120 x 1 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Trajenta 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PERFORATED)

1. NAME OF THE MEDICINAL PRODUCT

Trajenta 5 mg tablets
Linagliptin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Trajenta 5 mg film-coated tablets
Linagliptin

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

What is in this leaflet:

1. What Trajenta is and what it is used for

Trajenta contains the active substance linagliptin which belongs to a group of medicines called "oral anti-diabetics". Oral anti-diabetics are used to treat high blood sugar levels. They work by helping the body reduce the level of sugar in your blood.

Trajenta is used for 'type 2 diabetes' in adults, if the disease cannot be adequately controlled with one oral anti-diabetic medicine (metformin or sulphonylureas) or diet and exercise alone. Trajenta may be used together with other anti-diabetic medicines e.g. metformin, sulphonylureas (e.g. glimepiride, glipizide), empagliflozin, or insulin.

It is important to keep following the advice about diet and exercise that you have been given by your doctor or nurse.

2. What you need to know before you take Trajenta

Do not take Trajenta
- if you are allergic to linagliptin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Trajenta if you:
- have type 1 diabetes (your body does not produce any insulin) or diabetic ketoacidosis (a complication of diabetes with high blood sugar, rapid weight loss, nausea or vomiting). Trajenta should not be used to treat these conditions.
- are taking an anti-diabetic medicine known as a 'sulphonylurea'(e.g. glimepiride, glipizide), your doctor may want to reduce your dose of sulphonylurea when you take it together with Trajenta in order to avoid your blood sugar going too low.
- have had allergic reactions to any other medicines that you take to control the amount of sugar in your blood.
- have or have had a disease of the pancreas.

If you have symptoms of acute pancreatitis, like persistent, severe stomach ache (abdominal pain), you should consult your doctor.

If you encounter blistering of the skin it may be a sign for a condition called bullous pemphigoid. Your doctor may ask you to stop Trajenta.

Diabetic skin lesions are a common complication of diabetes. You are advised to follow the recommendations for skin and foot care that you are given by your doctor or nurse.

Children and adolescents
Trajenta is not recommended for children and adolescents under 18 years.

Other medicines and Trajenta
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, you should tell your doctor if you are using medicines containing any of the following active substances:
- Carbamazepine, phenobarbital or phenytoin. These may be used to control fits (seizures) or chronic pain.
- Rifampicin. This is an antibiotic used to treat infections such as tuberculosis.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is unknown if Trajenta is harmful to the unborn child. Therefore, it is preferable to avoid using Trajenta if you are pregnant.
It is not known if Trajenta passes into human breast milk. A decision must be made by your doctor whether to discontinue breast-feeding or to discontinue/abstain from Trajenta therapy.

Driving and using machines
Trajenta has no or negligible influence on the ability to drive and use machines.

Taking Trajenta in combination with medicines called sulphonylureas and/or insulin can cause too low blood sugar levels (hypoglycaemia), which may affect your ability to drive and use machines or work without safe foothold. However, more frequent blood glucose testing might be recommended to minimise the risk for hypoglycaemia, especially when Trajenta is combined with sulphonylurea and/or insulin.

3. How to take Trajenta

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

The recommended dose of Trajenta is one 5 mg tablet once a day.

You can take Trajenta with or without food.

Your doctor may prescribe Trajenta together with another oral anti-diabetic medicine. Remember to take all medicines as directed by your doctor to achieve the best results for your health.

If you take more Trajenta than you should
If you take more Trajenta than you should, talk to a doctor immediately.

If you forget to take Trajenta
- If you forget to take a dose of Trajenta, take it as soon as you remember it. However, if it is nearly time for the next dose, skip the missed dose.
- Do not take a double dose to make up for a forgotten dose. Never take two doses on the same day.

If you stop taking Trajenta
Do not stop taking Trajenta without first consulting your doctor. Your blood sugar levels may increase when you stop taking Trajenta.

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

4. Possible side effects

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

Some symptoms need immediate medical attention
You should stop taking Trajenta and see your doctor immediately if you experience the following symptoms of low blood sugar: trembling, sweating, anxiety, blurred vision, tingling lips, paleness, mood change or confusion (hypoglycaemia). Hypoglycaemia (frequency: very common, may affect more than 1 in 10 people) is an identified side effect when Trajenta is taken together with metformin and a sulphonylurea.

Some patients have experienced allergic reactions (hypersensitivity; frequency uncommon, may affect up to 1 in 100 people) while taking Trajenta alone or in combination with other medicinal products for the treatment of diabetes, which may be serious, including wheezing and shortness of breath (bronchial hyperreactivity; frequency not known, frequency cannot be estimated from the available data). Some patients experienced rash (frequency uncommon), hives (urticaria; frequency rare, may affect up to 1 in 1000 people), and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing (angioedema; frequency rare). If you experience any of the signs of illness mentioned above, stop taking Trajenta and call your doctor right away. Your doctor may prescribe a medicine to treat your allergic reaction and a different medicine for your diabetes.

Some patients have experienced inflammation of the pancreas (pancreatitis; frequency rare, may affect up to 1 in 1000 people) while taking Trajenta alone or in combination with other medicinal products for the treatment of diabetes.
STOP taking Trajenta and contact a doctor immediately if you notice any of the following serious side effects:
- Severe and persistent pain in the abdomen (stomach area) which might reach through to your back, as well as nausea and vomiting, as it could be a sign of an inflamed pancreas (pancreatitis).

Some patients have had the following side effects while taking Trajenta alone or in combination with other medicinal products for the treatment of diabetes:
- Common: level of lipase in the blood increased.
- Uncommon: inflamed nose or throat (nasopharyngitis), cough, constipation (in combination with insulin), level of amylase in the blood increased.
- Rare: blistering of skin (bullous pemphigoid).

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

5. How to store Trajenta

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

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

This medicine does not require any special storage conditions.

Do not use Trajenta if the package is damaged or shows signs of tampering.

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

6. Contents of the pack and other information

What Trajenta contains

- The active substance is linagliptin
  Each film-coated tablet (tablet) contains 5 mg of linagliptin

- The other ingredients are
  Tablet core: Mannitol, pregelatinised starch (maize), maize starch, copovidone, magnesium stearate
  Film coating: Hypromellose, titanium dioxide (E171), talc, macrogol (6000), iron oxide red (E172)

What Trajenta looks like and contents of the pack

- Trajenta 5 mg tablets are 8 mm diameter round, light red film-coated tablets debossed with "D5" on one side and the Boehringer Ingelheim logo on the other.

- Trajenta is available in perforated aluminium/aluminium unit dose blisters. The pack sizes are 10 x 1, 14 x 1, 28 x 1, 30 x 1, 56 x 1, 60 x 1, 84 x 1, 90 x 1, 98 x 1, 100 x 1 and 120 x 1 tablets.

Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

Manufacturer
Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
D-55216 Ingelheim am Rhein
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Boehringer Ingelheim Hellas Single Member S.A.
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Koropi Attiki, 19441
Greece

Dragenopharm Apotheker Püschl GmbH
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Germany

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

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