PRODUCT MONOGRAPH

Pr TRAJENTA®

linagliptin tablets
5 mg linagliptin, tablets, oral

ATC Code: A10BH05

Dipeptidyl peptidase 4 (DPP-4) inhibitors

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Pr TRAJENTA®

linagliptin tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 5 mg	Mannitol *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

Monotherapy: TRAJENTA (linagliptin tablets) is indicated for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance.

Add-on combination: TRAJENTA (linagliptin tablets) is indicated for use in adult patients with type 2 diabetes mellitus to improve glycemic control in combination with:

- metformin
- sulfonylurea (with or without metformin)
- metformin and empagliflozin
- basal insulin (with or without metformin)

when the therapy alone listed above, along with diet and exercise, does not provide adequate glycemic control (see CLINICAL TRIALS).

Geriatrics (≥65 years of age): No dosage adjustment is required based on age, however, greater sensitivity in some older individuals cannot be ruled out (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Pediatrics (<18 years of age): Safety and effectiveness of TRAJENTA in pediatric patients have not been established. Therefore, TRAJENTA should not be used in this patient population.

CONTRAINDICATIONS

TRAJENTA is contraindicated in:

- Patients with a history of hypersensitivity reaction to TRAJENTA or to any ingredient in the formulation, including any non-medicinal ingredient or component of the container (see

WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS). For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section.

- Patients with diabetic ketoacidosis or with type 1 diabetes mellitus.

WARNINGS AND PRECAUTIONS

General

TRAJENTA is contraindicated in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Cardiovascular

An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class.

Before initiating TRAJENTA, consider factors that may predispose patients to a risk of heart failure, such as a history of prior heart failure and a history of renal impairment. Monitor for signs and symptoms of heart failure after initiating therapy and discontinue TRAJENTA if this complication occurs.

Endocrine and Metabolism

Hypoglycemia: Caution is advised when linagliptin is used in combination with a sulfonylurea or insulin. The use of TRAJENTA as add-on therapy (with or without metformin) with an insulin secretagogue (e.g., sulfonylurea) was associated with a higher rate of hypoglycemia compared with placebo in clinical trials.

Sulphonylureas and insulin are known to cause hypoglycemia. Therefore, to reduce the risk of hypoglycemia associated with these indications, a lower dose of sulfonylurea or insulin may be considered (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

When TRAJENTA was used in combination with a sulfonylurea plus metformin, the incidence of hypoglycemia was increased over the placebo in combination with a sulfonylurea plus metformin (see ADVERSE REACTIONS).

Loss of Control of Blood Glucose: When a patient stabilized on TRAJENTA is exposed to stress such as fever, trauma, infection, or surgery, a loss of control of blood glucose may occur. At such times, it may be necessary to temporarily discontinue TRAJENTA and administer insulin.

Use with P-gp/Cytochrome P450 (CYP) 3A4 Inducers: Glycemic control should be carefully assessed when TRAJENTA is used concomitantly with a potent P-gp inducer or a potent CYP3A4 inducer. The concomitant administration of potent inducers of P-gp or CYP3A4 (e.g., rifampicin) may decrease exposure to linagliptin, which may reduce the glycemic lowering effect of TRAJENTA (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and DRUG INTERACTIONS).

Hepatic/Biliary/Pancreatic

Hepatic: Use in patients with severe hepatic impairment is not recommended (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY). The number of patients with hepatic impairment was limited in clinical trials.

Pancreatitis: There have been reports of acute and chronic pancreatitis in patients taking TRAJENTA during the clinical trials. In a long-term cardiovascular outcome trial, there were 2 (0.1%) adjudication-confirmed fatal cases due to acute pancreatitis in patients treated with TRAJENTA (see ADVERSE REACTIONS) compared to none in the placebo group. There have also been post-marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients receiving DPP-4 inhibitors. After initiation of TRAJENTA, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, TRAJENTA should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using TRAJENTA. Risk factors for pancreatitis include a history of: pancreatitis, gallstones, alcoholism, or hypertriglyceridemia.

Immune

Hypersensitivity Reactions: Serious hypersensitivity reactions, including anaphylaxis, angioedema, bronchial reactivity, rash, urticaria, and exfoliative skin conditions were observed with TRAJENTA in clinical trials and/or post-marketing reports. With other members of this class, there have been post-marketing reports of exfoliative skin conditions, including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue TRAJENTA, assess for other potential causes for the event, and institute alternative treatment for diabetes (see CONTRAINDICATIONS and ADVERSE REACTIONS).

Immunocompromised Patients: A dose-related mean decrease in absolute lymphocyte count was observed with other members of this class. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of TRAJENTA on lymphocyte counts in patients with lymphocyte abnormalities (e.g. human immunodeficiency virus) is unknown. Immunocompromised patients, such as patients who have undergone organ transplantation or patients diagnosed with human immunodeficiency syndrome have not been studied in the TRAJENTA clinical program. Therefore, the efficacy and safety profile of TRAJENTA in these patients has not been established.

Monitoring and Laboratory Tests

Blood Glucose and HbA_{1c}: Response to TRAJENTA treatment should be monitored by periodic measurements of blood glucose and HbA_{1c} levels.

When TRAJENTA is co-administered with strong inducers of P-gp or CYP3A4, blood glucose should be monitored more closely. In cases of insufficient glycemic control, a change of the P-gp/CYP3A4 inducer to a non P-gp/CYP3A4 inducing compound or a change of TRAJENTA to another oral antidiabetic agent should be considered (see DRUG INTERACTIONS).

Hepatic Function: Hepatic function should be assessed before starting treatment and periodically thereafter.

Peri-Operative Considerations

See WARNINGS AND PRECAUTIONS, Endocrine and Metabolism section.

Renal

Clinical study experience with TRAJENTA in patients with end-stage renal disease (ESRD) and those on dialysis is limited. TRAJENTA should be used with caution in these patients (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Sexual Health

Fertility: No studies on the effect on human fertility have been conducted for TRAJENTA. No adverse effects on fertility were observed in rats up to the highest dose of 240 mg/kg/day (approximately 900 times human exposure based on AUC comparisons).

Skin

Ulcerative and necrotic skin lesions have been reported with members of the DPP-4 inhibitor class. Although skin lesions were not observed at an increased incidence in clinical trials, there is limited experience in patients with diabetic skin complications. In keeping with routine care of the diabetic patient, monitoring for skin disorders is recommended.

Bullous Pemphigoid: Cases of bullous pemphigoid have been reported with the use of TRAJENTA. In a long-term cardiovascular outcome trial, there have been reports of bullous pemphigoid in 7 (0.2%) in patients treated with TRAJENTA compared to none in patients treated with placebo, and 3 of these patients were hospitalized due to bullous pemphigoid (see ADVERSE REACTIONS). Post-marketing cases of bullous pemphigoid requiring hospitalization have been reported with the use of DPP-4 inhibitors including TRAJENTA. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving TRAJENTA. If bullous pemphigoid is suspected, TRAJENTA should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Special Populations

Pregnant Women: TRAJENTA is not recommended for use in pregnancy. There are no adequate and well controlled studies of TRAJENTA in pregnant women; therefore the safety of TRAJENTA in pregnant women is not known (see TOXICOLOGY).

Nursing Women: TRAJENTA should not be used during breast-feeding. There are no data in nursing women. Linagliptin is excreted in the milk of lactating rats. It is not known whether linagliptin is excreted in human milk. A risk to the newborns/infants cannot be excluded.

Pediatrics (<18 years of age): Safety and effectiveness of TRAJENTA in pediatric patients have not been established. Therefore, TRAJENTA should not be used in this patient population.

Geriatrics (≥65 years of age): In clinical studies, there were 12278 type 2 diabetes patients treated with linagliptin; 3276 (27%) were 65 years and over, while 535 (4%) were 75 years and over. In a placebo-controlled long-term cardiovascular outcome trial (CARMELINA), there were 2027 (58%) patients 65 years and older, 622 patients (18%) 75 years and older exposed to TRAJENTA.

No overall treatment differences in safety or effectiveness were observed for patients 65 years and over and younger patients. Although clinical studies of linagliptin have not identified differences in response across age groups, greater sensitivity of some older individuals cannot be ruled out (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

TRAJENTA (linagliptin) was generally well tolerated in controlled clinical studies with an overall incidence of adverse events in patients treated with linagliptin 5 mg comparable to placebo (63.1% vs. 60.3%, respectively). The most frequently reported adverse event was hypoglycemia observed under the triple combination, linagliptin plus metformin plus sulfonylurea 22.9% vs. 14.8% in placebo plus metformin plus sulfonylurea (see WARNINGS AND PRECAUTIONS). In the pooled placebo-controlled trials, nasopharyngitis was observed more frequently with linagliptin compared to placebo (5.9% vs. 4.7%, respectively).

The incidence of serious adverse events was low in both treatment groups (4.8% linagliptin vs. 5.9% placebo). The main causes for discontinuation for TRAJENTA were diarrhea (0.2% linagliptin vs. 0.1% placebo), glomerular filtration rate decreased (0.3% linagliptin vs. 0.2% placebo), hyperglycemia (0.2% linagliptin vs. 0.8% placebo) and hypoglycemia (0.2% linagliptin vs. 0.0% placebo).

An adverse reaction reported in ≥1% in patients treated with TRAJENTA (n=4302) and more commonly than in patients treated with placebo (n=2364) was hypoglycemia (6.2% linagliptin vs. 5.9% placebo), occurring predominantly under the triple combination, linagliptin plus metformin plus sulfonylurea.

In the pooled clinical trial program, pancreatitis was reported in 8 (0.18%) of 4302 patients (2284 patient years of exposure) treated with TRAJENTA (including 3 patients reported following the last administered dose of linagliptin) compared with 1 (0.04%) of 2364 patients (1356 patient years of exposure) treated with placebo.

In an active-controlled cardiovascular safety study (CAROLINA) with TRAJENTA with median time on treatment of 5.9 years, the incidence of severe hypoglycemia was 0.3% in the linagliptin-treated patients (n=3014) and 2.2% in glimepiride-treated patients (n=3000).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of TRAJENTA has been evaluated in over 6600 patients with type 2 diabetes mellitus (T2DM), most of whom received the target dose of 5 mg.

In placebo-controlled studies, over 6600 patients were included and over 4300 patients were treated with the therapeutic dose of 5 mg linagliptin. More than 4000 patients were exposed to linagliptin 5 mg once daily for ≥12 weeks.

Adverse events were analysed based on the respective treatment regimens (monotherapy, add-on to metformin, add-on to sulfonylurea, add-on to meformin plus sulfonylurea, add-on to metformin plus empagliflozin, and add-on to insulin (with or without metformin).

Adverse reactions classified by SOC and MedDRA preferred terms reported in ≥2% of patients treated with TRAJENTA 5 mg daily as monotherapy or in combination with sulfonylurea, empagliflozin, insulin or metformin and at least 2-fold more commonly than in patients treated with placebo are shown in Table 1 below.

Table 1 Adverse Reactions Reported in ≥2% of Patients Treated with TRAJENTA and at Least 2-fold Greater than with Placebo in Placebo-Controlled Clinical Studies of TRAJENTA Monotherapy or Combination Therapy

System Organ Class/ Adverse Reaction	**Linagliptin monotherapy ***		**Linagliptin + Metformin #**		**Linagliptin + Sulphonylurea**		**Linagliptin + Metformin + Sulphonylurea**		**Linagliptin + Metformin + Empagliflozin**		**Linagliptin + Insulin §**	
	TRA-JENTA n=766 (%)	Placebo n=458 (%)	TRA-JENTA n=1322 (%)	Placebo n=583 (%)	TRA-JENTA n=161 (%)	Placebo n=84 (%)	TRA-JENTA n=791 (%)	Placebo n=263 (%)	TRA-JENTA n=238 (%)	Placebo n=240 (%)	TRA-JENTA n=720 (%)	Placebo n=700 (%)
Infections & infestations												
Nasopharyngitis	--	--	--	--	7 (4.3)	1 (1.2)	--	--	--	--	--	--
Respiratory, thoracic & mediastinal disorders												
Cough	--	--	--	--	--	--	19 (2.4)	3 (1.1)	--	--	--	--
Metabolism & nutrition disorders												
Hypertriglyceri-demia†	--	--	--	--	4 (2.4)	0 (0.0)	--	--	--	--	--	--
Gastrointestinal disorders												
Constipation	--	--	--	--	--	--	--	--	--	--	20 (2.8)	9 (1.3)

* Pooled data from 7 studies
# Pooled data from 5 studies
† Includes reports of hypertriglyceridemia (n=2; 1.2%) and blood triglycerides increased (n=2; 1.2%)
§ Includes patients with insulin only as well as patients with insulin in combination with oral antidiabetics as background

The incidence of adverse events, reported regardless of causality assessment, in ≥2% of patients and occurring more frequently in patients treated with TRAJENTA 5 mg over placebo, as add-on to

metformin, add-on to sulfonylurea, add-on to metformin plus sulfonylurea, add-on to metformin plus empagliflozin or as add-on to insulin (with or without metformin) are shown in Table 2 to Table 8.

Table 2 Linagliptin Monotherapy (pivotal trial, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study of linagliptin over 24 weeks in T2DM patients): Frequency of Adverse Events ≥2% and for Linagliptin in Excess over Placebo, Irrespective of Causality by System Organ Class and Preferred Term

System Organ Class/ Preferred term	**Placebo N (%)**	**Linagliptin N (%)**
Number of patients	167 (100.0)	336 (100.0)
Investigations	11 (6.6)	21 (6.3)
Blood glucose increased	3 (1.8)	7 (2.1)
Musculoskeletal and connective tissue disorders	10 (6.0)	32 (9.5)
Back pain	3 (1.8)	9 (2.7)
Nervous system disorders	4 (2.4)	15 (4.5)
Headache	2 (1.2)	9 (2.7)
Vascular disorders	2 (1.2)	17 (5.1)
Hypertension	2 (1.2)	12 (3.6)

Table 3 Linagliptin in Combination with Metformin (pivotal trial, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study of linagliptin over 24 weeks in T2DM patients): Frequency of Adverse Events ≥2% and for Linagliptin in Excess over Placebo, Irrespective of Causality by System Organ Class and Preferred Term

System Organ Class/ Preferred term	**Placebo N (%)**	**Linagliptin N (%)**
Number of patients	177 (100.0)	523 (100.0)
Infections and infestations	38 (21.5)	112 (21.4)
Nasopharyngitis	9 (5.1)	27 (5.2)
Influenza	5 (2.8)	18 (3.4)
Upper respiratory tract infection	4 (2.3)	15 (2.9)
Gastrointestinal disorders	20 (11.3)	58 (11.1)
Diarrhoea	4 (2.3)	15 (2.9)
Musculoskeletal and connective tissue disorders	14 (7.9)	58 (11.1)
Arthralgia	3 (1.7)	11 (2.1)
Respiratory, thoracic and mediastinal disorders	5 (2.8)	25 (4.8)
Cough	3 (1.7)	11 (2.1)

Table 4 Linagliptin in Combination with Sulfonylurea (pivotal trial, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study of linagliptin over 18 weeks in T2DM patients): Frequency of Adverse Events ≥2% and for Linagliptin in Excess over Placebo, Irrespective of Causality by System Organ Class and Preferred Term

System Organ Class/ Preferred term	**Placebo N (%)**	**Linagliptin N (%)**
Number of patients	84 (100.0)	161 (100.0)
Infections and infestations	4 (4.8)	20 (12.4)
Nasopharyngitis	1 (1.2)	7 (4.3)
Urinary tract infection	0 (0.0)	5 (3.1)

Table 5 Linagliptin in Combination with Metformin and Sulfonylurea (pivotal trial, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study of linagliptin over 24 weeks in T2DM patients): Frequency of Adverse Events ≥2% and for Linagliptin in Excess over Placebo, Irrespective of Causality by System Organ Class and Preferred Term

System Organ Class/ Preferred term	**Placebo N (%)**	**Linagliptin N (%)**
Number of patients	263 (100.0)	791 (100.0)
General disorders and administration site conditions	18 (6.8)	61 (7.7)
Asthenia	5 (1.9)	19 (2.4)
Infections and infestations	76 (28.9)	169 (21.4)
Nasopharyngitis	12 (4.6)	40 (5.1)
Metabolism and nutrition disorders	68 (25.9)	246 (31.1)
Hypoglycemia	39 (14.8)	180 (22.8)
Musculoskeletal and connective tissue disorders	24 (9.1)	98 (12.4)
Arthralgia	4 (1.5)	21 (2.7)
Respiratory, thoracic and mediastinal disorders	7 (2.7)	33 (4.2)
Cough	3 (1.1)	19 (2.4)
Vascular disorders	6 (2.3)	34 (4.3)
Hypertension	5 (1.9)	19 (2.4)

Table 6 Linagliptin in Combination with Metformin (randomized, double-blind, active-controlled, parallel-group efficacy and safety study of linagliptin as add-on combination use with metformin compared to a sulfonylurea agent (glimepiride) over 2 years in T2DM patients): Frequency of Adverse Events ≥2% and for Linagliptin in Excess over Placebo, Irrespective of Causality by System Organ Class and Preferred Term

System Organ Class/ Preferred term	**Linagliptin + Metformin N (%)**	**Glimepiride + Metformin N (%)**
Number of patients	776 (100.0)	775 (100.0)
Infections and infestations	378 (48.7)	393 (50.7)
Upper respiratory tract infections	62 (8.0)	59 (7.6)
Cystitis	19 (2.4)	13 (1.7)
Blood and lymphatic system disorders	36 (4.6)	30 (3.9)
Anaemia	25 (3.2)	17 (2.2)
Psychiatric disorders	68 (8.8)	61 (7.9)
Depression	24 (3.1)	22 (2.8)
Nervous system disorders	149 (19.2)	181 (23.4)
Headache	50 (6.4)	40 (5.2)
Vascular disorders	89 (11.5)	110 (14.2)
Arteriosclerosis	20 (2.6)	11 (1.4)
Respiratory, thoracic and mediastinal disorders	108 (13.9)	102 (13.2)
Cough	47 (6.1)	28 (4.9)
Gastrointestinal disorders	215 (27.7)	220 (28.4)
Constipation	33 (4.3)	16 (2.1)
Dyspepsia	23 (3.0)	17 (2.2)
Abdominal pain upper	18 (2.3)	17 (2.2)
Vomiting	17 (2.2)	12 (1.5)
Skin and subcutaneous tissue disorders	119 (15.3)	95 (12.3)
Eczema	18 (2.3)	15 (1.9)
Musculoskeletal and connective tissue disorders	257 (33.1)	244 (31.5)
Back pain	71 (9.1)	65 (8.4)
Arthralgia	63 (8.1)	47 (6.1)
Pain in extremity	41 (5.3)	30 (3.9)
Osteoarthritis	33 (4.3)	32 (4.1)
General disorders and administration site conditions	114 (14.7)	120 (15.5)
Fatigue	23 (3.0)	20 (2.6)
Injury, poisoning and procedural complications	127 (16.4)	107 (13.8)
Fall	22 (2.8)	11 (1.4)

Table 7 Linagliptin in Combination with Metformin plus Empagliflozin (pivotal trial, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study of linagliptin over 24 weeks in T2DM patients): Frequency of Adverse Events ≥2% and for Linagliptin in Excess over Placebo, Irrespective of Causality by System Organ Class and Preferred Term

System Organ Class/ Preferred term	**Placebo N (%)**	**Linagliptin N (%)**
Number of patients	240 (100.0)	238 (100.0)
Infections and infestations	60 (25.0)	61 (25.6)
Urinary tract infections	13 (5.4)	21 (8.8)
Bronchitis	2 (0.8)	5 (2.1)
Nervous System disorders	11 (4.6)	9 (3.8)
Headache	4 (1.7)	5 (2.1)
Vascular disorders	8 (3.3)	7 (2.9)
Hypertension	5 (2.1)	6 (2.5)
Investigations	19 (7.9)	14 (5.9)
Lipase increased	8 (3.3)	11 (4.6)

Table 8 Linagliptin in Combination with Basal Insulin (pivotal trial, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study of linagliptin over 52 weeks in T2DM patients): Frequency of Adverse Events ≥2% and for Linagliptin in Excess over Placebo, Irrespective of Causality by System Organ Class and Preferred Term

System Organ Class/ Preferred term	**Placebo N (%)**	**Linagliptin N (%)**
Number of patients	630	631
General disorders and administration site conditions	74 (11.7)	84 (13.3)
Oedema peripheral	15 (2.4)	20 (3.2)
Fatigue	11 (1.7)	16 (2.5)
Infections and infestations	248 (39.4)	239 (37.9)
Nasopharyngitis	62 (9.8)	71 (11.3)
Upper respiratory tract infection	30 (4.8)	31 (4.9)
Sinusitis	10 (1.6)	17 (2.7)
Pharyngitis	9 (1.4)	14 (2.2)
Blood and lymphatic system disorders	20 (3.2)	26 (4.1)
Anaemia	12 (1.9)	20 (3.2)
Nervous System disorders	112 (17.8)	106 (16.8)
Headache	27 (4.3)	35 (5.5)
Dizziness	30 (4.8)	34 (5.4)
Eye disorders	50 (7.9)	57 (9.0)
Cataract	13 (2.1)	14 (2.2)
Diabetic retinopathy	7 (1.1)	13 (2.1)
Gastrointestinal disorders	126 (20.0)	140 (22.2)
Diarrhea	30 (4.8)	33 (5.2)
Nausea	14 (2.2)	27 (4.3)
Constipation	9 (1.4)	15 (2.4)
Toothache	12 (1.9)	14 (2.2)
Musculoskeletal and connective tissue disorders	141 (22.4)	128 (20.3)

Back pain	30 (4.8)	35 (5.5)
Pain in extremity	20 (3.2)	24 (3.8)
Osteoarthritis	14 (2.2)	15 (2.4)
Investigations	62 (9.8)	65 (10.3)
Glycosylated hemoglobin increased	13 (2.1)	15 (2.4)
Injury, poisoning and procedural complications	77 (12.2)	77 (12.2)
Fall	13 (2.1)	16 (2.5)

Less Common Clinical Trial Adverse Drug Reactions (≥0.1% and <2%)[a]

Gastrointestinal Disorders: abdominal distention, dyspepsia, abdominal pain upper, diarrhea, gastritis, nausea, vomiting
General Disorders and Administration Site Conditions: asthenia, malaise
Infections and Infestations: nasopharyngitis[*]
Investigations: aspartate aminotransferase increased
Musculoskeletal and Connective Tissue Disorders: myalgia
Nervous System Disorders: tremor, headache
Respiratory and Thoracic: cough[*]
Skin and Subcutaneous Tissue Disorders: pruritis[*]

[a] Adverse events that occurred with an incidence between 0.1 and 2.0% in the dataset of pooled placebo-controlled clinical trials and were greater than placebo. Inclusion does not necessarily represent a causal relationship to TRAJENTA.
[*] BI assessed ADRs

Adverse Reactions in Specific Populations

Linagliptin Cardiovascular and Renal Safety Study (CARMELINA): For details pertaining to study design and patient population, see CLINICAL TRIALS.

In the overall study observation period, numerical imbalances for pemphigoid events, skin lesions and adjudication-confirmed acute pancreatitis events were observed.

Skin: Bullous pemphigoid was reported in 7 (0.2%) patients treated with TRAJENTA compared to none in patients treated with placebo. Skin lesions were reported in 0.2% of patients treated with TRAJENTA compared to less than 0.1% in the placebo group.

Pancreatitis: The incidence of adjudication-confirmed pancreatitis events was higher in the TRAJENTA group (n=9 [0.3%]) compared to placebo group (n=5 [0.1%]). The TRAJENTA group experienced a greater number of severe cases of pancreatitis including two fatal outcomes due to pancreatitis, compared to none in the placebo group. Cases of adjudication-confirmed pancreatic cancers were rare but were numerically higher in the linagliptin group (n=11 [0.3%]) than in the placebo group (n=4 [0.1%]).

Hypoglycemia: A numerically higher rate of hypoglycemia was observed with TRAJENTA compared with placebo in patients taking sulfonylurea at baseline. Among patients who were using sulfonylurea at baseline, the incidence of severe hypoglycemia 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 hypoglycemia was 4.4% in linagliptin-treated patients and 4.9% in placebo-treated patients.

Elderly patients: In a study of linagliptin as add-on therapy in elderly T2DM patients (age ≥70 years), the AE profile between linagliptin and placebo arms showed a similar incidence of AE's between treatment arms, but higher levels of treatment-related AEs, AEs resulting in discontinuation, severe AEs and serious AEs in the linagliptin arm. The most common events that were proportionally greater in the linagliptin arm were hypoglycemia and nasopharyngitis. The most common treatment-related AEs that were more common in the linagliptin arm were hypoglycemia and diarrhea. There was one episode of hypoglycemia requiring external assistance in the linagliptin arm, which was not considered a serious AE; and none in the placebo arm. The imbalance in hypoglycemic events can be attributed primarily to patients on a background of sulfonylurea.

In the long-term clinical trial, CARMELINA, involving 2027 (58%) patients ≥65 years exposed to TRAJENTA, there were no clinically meaningful differences in the safety profile of elderly patients on linagliptin vs. placebo. This includes adjudication-confirmed CV outcome events and hypoglycemia adverse events.

Patients with severe renal impairment: In a study of linagliptin as add-on therapy in T2DM patients with severe renal impairment (eGFR <30 mL/min), the reported safety and laboratory results were comparable between linagliptin and placebo except for the AEs belonging to 'renal impairment' which were more frequent in linagliptin (16.2% in linagliptin vs. 6.2% in placebo). Since severe renal impairment was an inclusion criterion for the study, these AEs were considered a worsening of the concomitant diagnosis at study entry. Renal function as measured by means eGFR and creatinine clearance did not change over 52 weeks treatment with linagliptin compared to placebo.

The observed incidence of hypoglycemia in patients treated with linagliptin (63%) was higher than placebo (49%), due to an increase in asymptomatic hypoglycemia events. There was no difference between groups in severe hypoglycemic events, defined as an event requiring assistance. Events that were considered life-threatening or required hospitalization were reported in 2 (2.9%) patients on TRAJENTA and 1 (1.5%) patient on placebo.

In the long-term clinical trial, CARMELINA, approximately 15% of the population had severe renal impairment (eGFR <30 mL/min/1.73 m^2). In these patients, the overall reported safety and laboratory results were generally similar between TRAJENTA and placebo treatment arms, including those for renal adverse events (18.2% in linagliptin and 19.2% in placebo) and hypoglycemia (40.3% in linagliptin and 39.6% in placebo). Renal function (eGFR) did not change over the duration of the study with linagliptin compared to placebo

Abnormal Hematologic and Clinical Chemistry Findings

Changes in laboratory values that occurred more frequently in the TRAJENTA group (≥1% more than in the placebo or active-control group) were:

- *Lipase:* Increases in blood lipase levels (in a 24-week clinical trial, 2.3% in placebo group and 9.9% in the TRAJENTA group experienced lipase levels >3 times upper limit of normal (ULN), during treatment or post-treatment period (approximately 4 weeks); the ULN for lipase level in blood was 60 U/L);

- *Hemoglobin:* Decreases in hemoglobin (4.0% in the placebo group, 7.4% in the TRAJENTA group; based on pooled placebo-controlled trials with insulin +/- antihyperglycemic agents background);
- *Amylase:* Increases in amylase (3.3% in the placebo group, 5.9% in the TRAJENTA group; based on pooled placebo-controlled trials with insulin +/- antihyperglycemic agents background). In an active-controlled cardiovascular safety study with TRAJENTA, 0.6% in the active-control (glimepiride) group and 1.0% in TRAJENTA group experienced amylase levels above 3 times ULN.

Post-Marketing Adverse Drug Reactions

Additional adverse reactions have been identified during post-marketing use of TRAJENTA. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatic/Biliary/Pancreatic: acute pancreatitis
Immune System Disorders: hypersensitivity reactions including anaphylaxis, angioedema, rash, and exfoliative skin conditions, urticaria, mouth ulceration
Musculoskeletal and Connective Tissue Disorders: arthralgia, rhabdomyolysis
Skin and Subcutaneous Tissue Disorders: bullous pemphigoid

DRUG INTERACTIONS

Overview

The propensity of linagliptin to be involved in clinically meaningful drug interactions mediated by plasma protein binding displacement is low, considering that linagliptin is only moderately bound to serum albumin and alpha-1-acid-glycoprotein.

Pharmacokinetic Interactions

In Vitro Assessment of Drug Interactions: Linagliptin is metabolized by the CYP isozyme CYP3A4 to one pharmacologically inactive metabolite. In *in vitro* studies, linagliptin is a weak competitive and a weak to moderate inhibitor of CYP3A4. Linagliptin is not an inhibitor of CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 4A11 and is not an inducer of CYP 1A2, CYP 2B6 or CYP 3A4.

Linagliptin is a P-glycoprotein substrate, and inhibits P-glycoprotein mediated transport of digoxin with low potency *in vitro*. Based on these results and *in vivo* drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates.

In the case of long term co-treatment with strong inducers of P-gp or CYP3A4, full-efficacy may not be achieved. Therefore, blood glucose should be closely monitored. In cases of insufficient efficacy, the physician should consider either a change of the P-gp/CYP3A4 inducer to a non P-gp/CYP3A4 inducing compound or a change of linagliptin to another oral antidiabetic (see WARNINGS AND PRECAUTIONS).

Drug-Drug Interactions

In Vivo Assessment of Drug Interactions: Linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glibenclamide, simvastatin, pioglitazone, 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). No dose adjustment of TRAJENTA is recommended based on results of the described pharmacokinetic studies.

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 alter the pharmacokinetics of linagliptin or metformin in healthy volunteers in a clinically meaningful way. Therefore, linagliptin is not an inhibitor of OCT-mediated transport.

Sulfonylureas: The steady state pharmacokinetics of 5 mg linagliptin (administered once daily for 5 days) were not changed by co-administration of a single 1.75 mg dose of glibenclamide (glyburide). 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 sulfonylureas (e.g. glipizide, tolbutamide and glimepiride) which, like glibenclamide, are primarily eliminated by CYP2C9.

Pioglitazone: Co-administration of multiple daily doses of 10 mg linagliptin (supratherapeutic) with multiple daily doses of 45 mg pioglitazone, a CYP2C8 and CYP3A4 substrate, had no clinically relevant effect on the pharmacokinetics of either linagliptin or pioglitazone or the active metabolites of pioglitazone. This indicates that linagliptin is not an inhibitor of CYP2C8-mediated metabolism *in vivo* and supports the conclusion that the *in vivo* inhibition of CYP3A4 by linagliptin is negligible.

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 200 mg twice daily oral doses of ritonavir for three days 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 not be 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 inducer of P-glycoprotein and CYP3A4, on the pharmacokinetics of 5 mg linagliptin. Co-administration of linagliptin with rifampicin, 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 might not be achieved with long term co-administration of linagliptin and rifampicin (or other strong P-gp/CYP3A4 inducers). The physician should closely monitor glucose. In cases of insufficient efficacy, the physician should consider either a change of the P-gp/CYP3A4 inducer to a non P-gp/CYP3A4 inducing compound or a change of TRAJENTA to another oral antidiabetic (see WARNINGS AND PRECAUTIONS).

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 linagliptin 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 unlikely to cause clinical meaningful interactions with simvastatin (or other statins which share similar elimination pathways). 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.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
Effects on Ability to Drive and Use Machines: No formal studies have been conducted with TRAJENTA on the effects on the ability to drive and use machines. However, patients should be warned about driving a vehicle or operating machinery under conditions where a risk of hypoglycemia is present (see WARNINGS AND PRECAUTIONS). When TRAJENTA is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycemia while driving or using machinery.

DOSAGE AND ADMINISTRATION

Dosing Considerations
TRAJENTA can be taken with or without a meal.

Concomitant Use with Insulin or an Insulin Secretagogue (e.g., Sulfonylurea)
When TRAJENTA is used in combination with insulin or an insulin secretagogue (e.g., sulfonylurea), a lower dose of insulin or the insulin secretagogue may be considered to reduce the risk of hypoglycemia (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

Recommended Dose and Dosage Adjustment

Adults

The recommended dose of TRAJENTA is 5 mg once daily.

Renal Impairment: No dosage adjustment for TRAJENTA is required in patients with renal impairment. Use of TRAJENTA in patients with end-stage renal disease (ESRD) and those on dialysis should be with caution.

Hepatic Impairment: No dosage adjustment for TRAJENTA is required in patients with mild and moderate hepatic impairment. Use of TRAJENTA in patients with severe hepatic impairment is not recommended.

Geriatrics (≥65 years of age): No dosage adjustment is necessary for geriatric patients.

Pediatrics (<18 years of age): There are no data available on the use of TRAJENTA in patients younger than 18 years of age. Therefore, use of TRAJENTA in pediatric patients is not recommended.

Missed Dose

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

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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.

Linagliptin is not expected to be eliminated to a therapeutically significant degree by hemodialysis or peritoneal dialysis.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Linagliptin is a potent, reversible and selective inhibitor of the enzyme DPP-4 (Dipeptidyl peptidase 4, EC 3.4.14.5) which is involved in the inactivation of the incretin hormones (glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These incretin hormones are rapidly degraded by the enzyme DPP-4. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. GLP-1 and GIP are secreted by the intestine at a low basal level throughout the day and concentrations are increased in response to a meal. 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 production. Linagliptin binds to DPP-4 in a reversible

manner and thus leads to an 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 homoeostasis.

Pharmacodynamics

Linagliptin binds selectively to DPP-4 and exhibits a >10,000-fold selectivity versus closely related proteases DPP-8 or DPP-9 activity *in vitro*. Linagliptin treatment resulted in an inhibition of plasma DPP-4 in clinical studies. The plasma DPP-4 activity was inhibited in a dose-dependent manner after single dose administration of linagliptin. At steady state, plasma DPP-4 activity was inhibited over 24 h by more than 80% in most patients receiving 5 mg linagliptin once daily. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion.

Cardiac Electrophysiology: In a randomized, placebo-controlled crossover study, 44 healthy subjects were administered a single oral dose of linagliptin 5 mg, linagliptin 100 mg (20 times the recommended dose), and placebo. No increase in the QTc, PR, or QRS intervals was observed with either the recommended dose of 5 mg or the 100 mg dose. A small increase in heart rate was seen at the linagliptin 100 mg dose, with a peak effect of about 4 bpm at 1 h post-dosing. No significant increase in heart rate was observed after the 5 mg therapeutic dose. The mean C_{max} values were 7 nM for the single 5 mg dose and 267 nM for the single 100 mg dose.

Pharmacokinetics

The pharmacokinetics of linagliptin has been extensively characterized in healthy subjects and patients with type 2 diabetes.

Table 9 Summary of Linagliptin Pharmacokinetic Parameters in Healthy Volunteers

	C_{max} (nmol/L)	T_{max} (h)	AUC $_{0-24}$ (nmol*h/L)	Renal clearance CL_R (mL/min)
Single oral dose (5 mg) mean	8.90	1.5	139	70

Linagliptin shows non-linear pharmacokinetics in the dose range of 1 to 10 mg, which includes the therapeutic 5 mg dose. As a consequence, the pharmacokinetic parameters are concentration dependent due to the non-linearity exhibited by linagliptin.

After oral administration of a 5 mg dose to healthy subjects, linagliptin was rapidly absorbed, with maximum linagliptin plasma concentrations (C_{max}) attained at about 1.5 hours. The C_{max} and AUC values increased in a less than dose-proportional manner. Following a 5 mg single oral dose of linagliptin to healthy subjects, the mean plasma $AUC_{0-\infty}$ value for linagliptin was 139 nmol*h/L and the corresponding plasma C_{max} value was 8.90 nmol/L. The intra-subject and inter-subject coefficients of variation for linagliptin AUC were 12.6% and 28.5%, respectively. The corresponding values for linagliptin C_{max} were 25.1% and 40.3%, respectively.

Plasma concentrations of linagliptin decline in at least biphasic manner with a long terminal half-life (>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 accumulation half-life of linagliptin, as determined

from accumulation after 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 pharmacokinetics of linagliptin was consistent in healthy subjects and in patients with type 2 diabetes.

The absolute bioavailability of the 10 mg tablet was investigated versus 5 mg given intravenously. As the pharmacokinetics of linagliptin change with increasing plasma concentrations due to concentration-dependent protein binding, a modelling approach was identified as the appropriate method for bioavailability assessment. The absolute bioavailability of the 10 mg tablet was estimated to be around 30%.

Absorption: Linagliptin may be administered with or without food. Co-administration of a high-fat meal with linagliptin had no clinically relevant effect on linagliptin pharmacokinetics. *In vitro* studies indicated that linagliptin is a substrate of P-glycoprotein (see DRUG INTERACTIONS).

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 (>30 nM) the plasma protein binding of linagliptin was constant with a moderate bound fraction between 70-80%. Plasma binding was not altered in patients with renal or hepatic impairment.

Metabolism: Following oral administration, the majority (about 90%) of linagliptin was excreted unchanged, indicating that metabolism represents a minor elimination pathway. *In vitro* studies indicated that linagliptin is a substrate of CYP3A4 (see DRUG INTERACTIONS). A small fraction of absorbed linagliptin is metabolized to a pharmacologically inactive metabolite, which shows a steady state exposure of 13.3% relative to linagliptin.

Excretion: Following oral administration of 10 mg [^{14}C] linagliptin dose to healthy subjects, approximately 85% of radioactivity was recovered in faeces (80%) and urine (5.4%) within 4 days of dosing. Renal clearance at steady state ($CL_{R,ss}$) was approximately 70 mL/min.

Special Populations and Conditions

Pediatrics (<18 years of age): Studies characterizing the pharmacokinetics of linagliptin in pediatric patients have not yet been performed. Therefore, TRAJENTA should not be used in this patient population.

Geriatrics (≥65 years of age): 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. Elderly subjects (65 to 80 years) had comparable plasma concentrations of linagliptin compared to younger subjects.

Gender: No dosage adjustment is required based on gender. Gender had no clinically relevant effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis.

Race: No dosage adjustment is required based on race. Race had no obvious effect on the plasma concentrations of linagliptin based on a composite analysis of available pharmacokinetic data.

Body Mass Index (BMI): No dosage adjustment is required based on BMI.

Renal Impairment: A multiple-dose, open-label study was conducted to evaluate the pharmacokinetics of linagliptin (5 mg dose) in patients (n=6 in each group) with mild and moderate renal impairment compared to subjects with normal renal function. A single-dose pharmacokinetic study of linagliptin was conducted in patients with severe renal impairment (n=6) and ESRD (n=6). The studies 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 end-stage renal disease on hemodialysis. In addition, patients with T2DM and severe renal impairment (n=10) were compared to T2DM patients with normal renal function (n=11) in a multiple-dose study. After a single oral dose of linagliptin, exposure was 1.2 to 1.6-fold higher for patients with renal impairment (with or without T2DM) than for subjects with normal renal function (with or without T2DM).

Under steady state conditions, (oral administration of multiple 5 mg doses), pharmacokinetic characteristics in patients with mild renal impairment were comparable to those of subjects with normal renal function. An overall increase in $AUC_{\tau,ss}$ exposure of approximately 1.1 to 1.7-fold was observed for patients with mild or moderate renal impairment (without T2DM) or severe renal impairment (with T2DM) relative to controls with normal renal function (with or without T2DM). Because increases of this magnitude are not clinically relevant, dosage adjustment in patients with renal impairment is not required. In addition linagliptin trough concentrations measured in Phase III were similar in patients with mild, moderate or severe renal impairment and patients with normal renal function. There is lack of clinical experience with linagliptin in patients with ESRD and those on dialysis. Therefore, use in these patients should be with caution.

Hepatic Impairment: In patients with mild or moderate 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 dose adjustment for linagliptin is required for patients with mild or moderate hepatic impairment. While Phase I data showed no clinical relevant effect of severe hepatic impairment on linagliptin pharmacokinetics following administration of single 5 mg dose, use in these patients is not recommended due to lack of clinical experience.

STORAGE AND STABILITY

Store at room temperature (15-30°C).

SPECIAL HANDLING INSTRUCTIONS

Store in a safe place and out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TRAJENTA tablets for oral administration contain 5 mg linagliptin.

Non-medicinal ingredients: mannitol, pregelatinised starch, maize starch, copovidone and magnesium stearate. The film coating contains hypromellose, titanium dioxide, talc, macrogol and iron oxide red.

TRAJENTA tablets are available as light red, round, biconvex, bevel-edged film-coated tablets, one side debossed with Boehringer Ingelheim company symbol, the other side debossed with "D5".

TRAJENTA is available in blister packs of 30 and 90 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

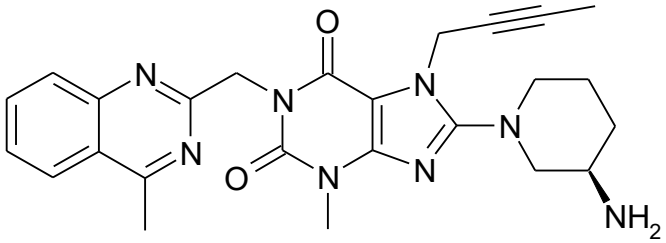
Drug Substance

Common name: linagliptin

Chemical name: 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]-

Molecular formula and molecular mass: $C_{25}H_{28}N_8O_2$, 472.54 g/mol

Structural formula:



Physicochemical properties: White to yellowish crystalline solid substance, very slightly soluble in water, soluble in methanol, sparingly soluble in ethanol, very slightly soluble in isopropanol and in acetone.

pKa: $pKa_1 = 8.6$; $pKa_2 = 1.9$

Partition Co-efficient: Log P = 1.7 (free base); Log D (pH 7.4) = 0.4

Melting Temperature: 202-209EC

CLINICAL TRIALS

Study Demographics and Trial Design

In total 6602 patients with type 2 diabetes and 453 healthy volunteers received treatment with linagliptin in the clinical program.

Table 10 Summary of Patient Demographics for Clinical Trials in Specific Indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender (% F/M)
Monotherapy					
1218.16	Multicentre, randomized, double-blind, placebo-controlled	Linagliptin 5 mg or placebo Oral, 24 weeks	Total: 503 Linagliptin: 336 Placebo: 167	55.7 (24-79)	52/48
1218.50	Multicentre, randomized, double-blind, placebo-controlled in metformin ineligible patients, followed by active-controlled, parallel-group comparison	Linagliptin 5 mg or placebo Linagliptin 5 mg or glimepiride 1, 2, or 4 mg Oral, 18 weeks	Total: 227 Linagliptin: 151 Placebo: 76	56.5 (20-80)	61/39
Add-on Combination Therapy with Metformin					
1218.17	Multicentre, randomized, double-blind, **placebo-controlled**	Linagliptin 5 mg or placebo Oral, 24 weeks	Total: 701 Linagliptin: 524 Placebo: 177	56 (21-79)	46/54
1218.20	Multicentre, randomized, double-blind, **active-controlled**	Linagliptin 5 mg or glimepiride (forced titration from 1 mg to max. 4 mg) Oral, 52 weeks	Total: 1560 Linagliptin: 779 Glimepiride: 781	60 (28-80)	40/60
Add-on Combination Therapy with a Sulfonylurea					
1218.35	Multicentre, randomized, double-blind, placebo-controlled	Linagliptin 5 mg or placebo Oral, 18 weeks	Total: 245 Linagliptin: 161 Placebo: 84	57 (27-79)	47/53
Add-on Combination Therapy with Metformin and a Sulfonylurea					
1218.18	Multicentre, randomized, double-blind, placebo-controlled	Linagliptin 5 mg or placebo Oral, 24 weeks	Total: 1058 Linagliptin: 793 Placebo: 265	58 (23-79)	53/47
Add-on Combination Therapy with Metformin and Empagliflozin					

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender (% F/M)
1275.10	Randomized, multicenter, double-dummy, double-blind, placebo-controlled parallel-group	FDC empa 10 mg/lina 5 mg + metformin	n = 122	56.6 (9.5)	57/43
		Empa 10 + metformin	n = 125	56.8 (9.4)	56/44
		FDC empa 25 mg/lina 5 mg + metformin	n = 110	56.6 (9.8)	47/53
		Empa 25 + metformin	n = 110	56.1 (10.6)	57/43
		Tablets, orally, once daily Randomized treatment: 24 week			
Add-on Combination Therapy with Insulin					
1218.36	Multicentre, randomized, double-blind, placebo-controlled	Linagliptin 5 mg or placebo Oral, 52 weeks	Total: 1261 Linagliptin: 631 Placebo: 630	60 (22-91)	48/52
Open-label Long-term Extension Study					
1218.40	Open-label extension trial without a control group. Patients who completed one of the 4 pivotal trials (1218.15[+], 1218.16, 1218.17 or 1218.18)	Linagliptin 5 mg Oral, 78 weeks	Total: 2121 *Lina "old": 1532 *Lina "new": 589	57.5 (21-80)	48/52

[+] Indication not approved
* Lina "old": patients treated with linagliptin in the preceding trials; Lina "new": patients treated with placebo in the preceding trials
FDC empa 10 mg/lina 5 mg = fixed dose combination empagliflozin 10 mg + linagliptin 5 mg; FDC empa 25 mg/lina 5 mg = fixed dose combination empagliflozin 25 mg + linagliptin 5 mg; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg

Study Results

Linagliptin monotherapy (BI Study 1218.16)

The efficacy and safety of linagliptin monotherapy were 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}, fasting plasma glucose (FPG), 2-hour post-prandial glucose (PPG), and a greater proportion (28%) of patients achieved a target HbA_{1c} of <7.0%, compared to placebo (15%) (see Table 11). Body weight did not differ significantly between the groups.

Linagliptin monotherapy for patients ineligible for metformin (BI Study 1218.50)

The efficacy and safety of linagliptin monotherapy were also evaluated in patients for whom metformin therapy is inappropriate, due to intolerability or contraindication, in a double-blind placebo-controlled study of 18 weeks duration, followed by a 34 week safety extension period (placebo

patients switched to glimepiride). Linagliptin provided significant improvements in HbA_{1c}, fasting plasma glucose (FPG), and a greater portion of patients (28%) achieved a target HbA_{1c} of <7.0%, compared to placebo (15%), (Table 11). Body weight did not differ significantly between the groups during the placebo controlled 18 weeks.

Table 11 Glycemic Parameters in Placebo-Controlled Monotherapy Studies of TRAJENTA in Patients with Type 2 Diabetes

	18-Week Study (BI Study 1218.50)		24-Week Study (BI Study 1218.16)	
	TRAJENTA 5 mg	**Placebo**	**TRAJENTA 5 mg**	**Placebo**
HbA_{1C} (%)	**n = 147**	**n = 73**	**n = 333**	**n = 163**
Baseline (mean)	8.11	8.04	8.0	8.0
Change from baseline (adjusted mean)	-0.39	0.14	-0.44	0.25
Difference from placebo (adjusted mean) (95% CI)	-0.60 (-0.88, -0.32)	--	-0.69 (-0.85, -0.53)	--
Patients (%) achieving HbA_{1C} <7%	41 (28%)	11 (15%)	94 (28.2%)	25 (15.3%)
FPG (mmol/L)	**n = 138**	**n = 66**	**n = 318**	**n = 149**
Baseline (mean)	9.9	9.8	9.1	9.2
Change from baseline (adjusted mean)	-0.74	0.4	-0.47	0.82
Difference from placebo (adjusted mean) (95% CI)	-1.14 (-1.73, -0.55)	--	-1.30 (-1.69, -0.91)	--
2-hour PPG (mmol/L)	**N/A**	**N/A**	**n = 67**	**n = 24**
Baseline (mean)	--	--	14.33	13.56
Change from baseline (adjusted mean)	--	--	-1.86	1.38
Difference from placebo (adjusted mean) (95% CI)	--	--	-3.24 (-4.57, -1.91)	--

N/A: not available

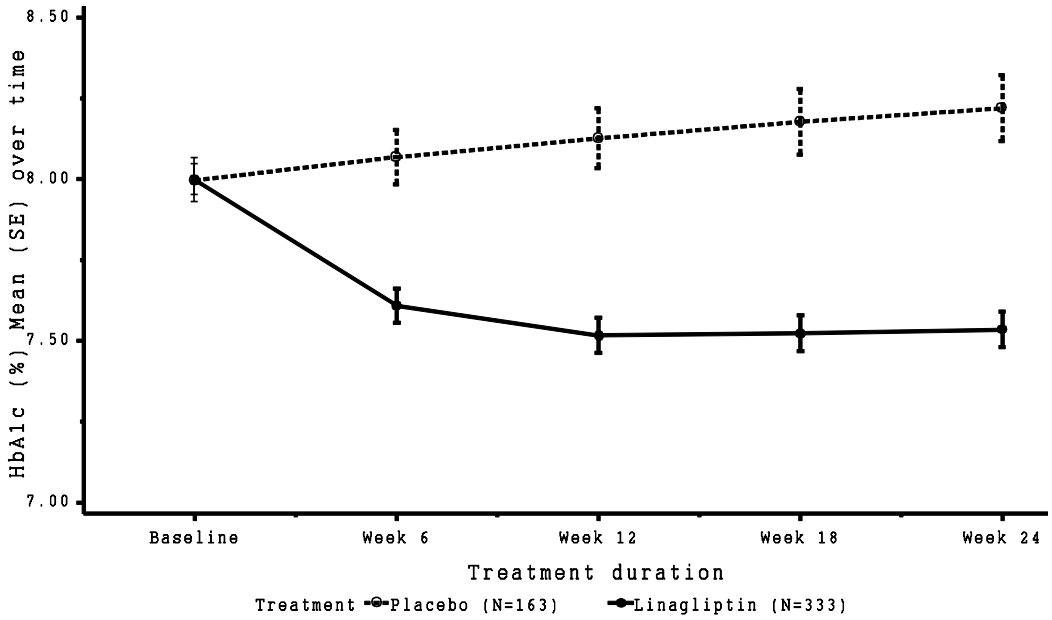


Figure 1 Mean HbA_{1C} (%) over 24 Weeks with TRAJENTA and Placebo in Patients with Type 2 Diabetes (BI Study 1218.16, monotherapy patients)

Linagliptin as add-on to metformin therapy (BI Study 1218.17)

The efficacy and safety of linagliptin in combination with metformin were evaluated in a double-blind placebo-controlled study of 24 weeks duration. Linagliptin provided significant improvements in HbA_{1c}, fasting plasma glucose (FPG), 2-hour post-prandial glucose (PPG) and a greater portion of patients (28%) achieved a target HbA_{1c} of <7.0%, compared to placebo (11%) (Table 12). Body weight did not differ significantly between the groups.

Table 12 Glycemic Parameters at Final Visit (Placebo-Controlled Study) for TRAJENTA in Combination with Metformin (BI study 1218.17)

	TRAJENTA 5 mg + Metformin	**Placebo + Metformin**
HbA_{1C} (%)	**n = 513**	**n = 175**
Baseline (mean)	8.09	8.02
Change from baseline (adjusted mean)	-0.49	0.15
Difference from placebo + metformin (adjusted mean) (95% CI)	-0.64 (-0.78, -0.50)	--
Patients (%) achieving HbA_{1C} <7%	145 (28.3)	20 (11.4)
FPG (mmol/L)	**n = 495**	**n = 159**
Baseline (mean)	9.39	9.10
Change from baseline (adjusted mean)	-0.59	0.58
Difference from placebo + metformin (adjusted mean) (95% CI)	-1.17 (-1.52, -0.83)	--
2-hour PPG (mmol/L)	**n = 78**	**n = 21**
Baseline (mean)	15.0	15.22
Change from baseline (adjusted mean)	-2. 71	1.01
Difference from placebo + metformin (adjusted mean) (95% CI)	-3.72 (-5.26, -2.20)	--

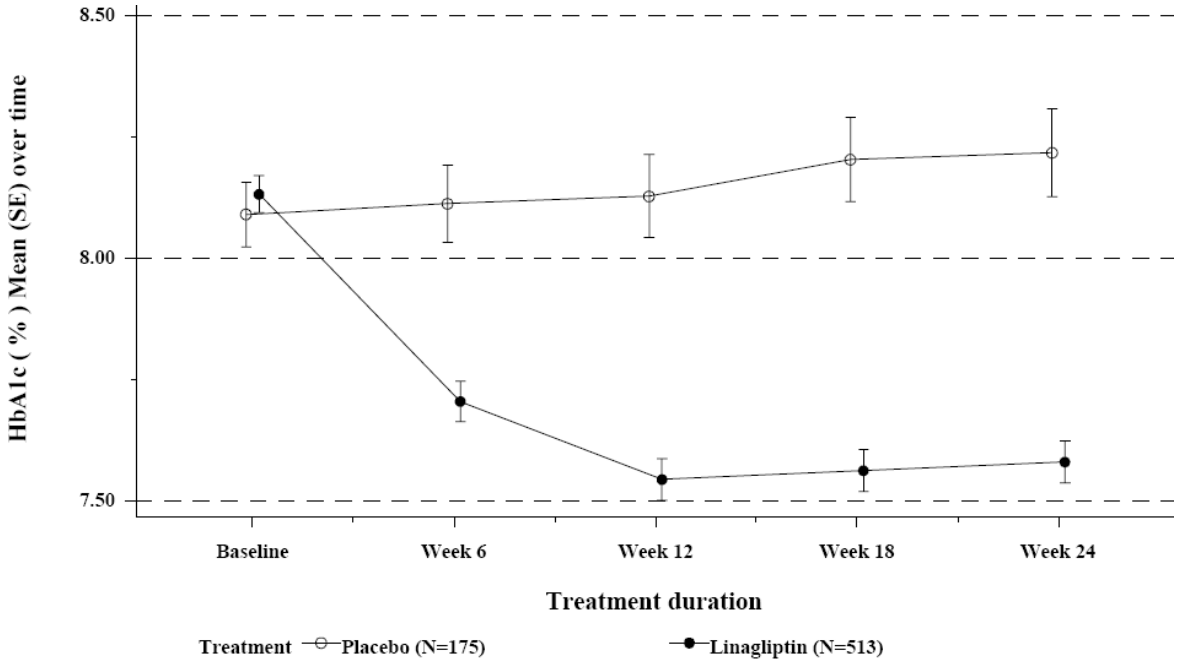


Figure 2 Mean HbA_{1C} (%) over 24 Weeks with TRAJENTA/Metformin and Placebo/Metformin in Patients with Type 2 Diabetes (BI study 1218.17, add-on to metformin patients)

Linagliptin as add-on to a sulfonylurea therapy (BI Study 1218.35)

The efficacy and safety of linagliptin in combination with sulfonylurea were evaluated in a double-blind placebo-controlled study of 18 weeks duration. Linagliptin provided significant improvements in HbA_{1c}, and a greater portion of patients (15%) achieved the target HbA_{1c} of <7.0% compared to placebo (4%) (Table 13). Body weight did not differ significantly between the groups.

Table 13 Glycemic Parameters at Final Visit (18-Week Study) for TRAJENTA in Combination Therapy with Sulfonylurea (BI Study 1218.35)

	TRAJENTA 5 mg + SU	**Placebo + SU**
HbA_{1C} (%)	**n = 158**	**n = 82**
Baseline (mean)	8.6	8.6
Change from baseline (adjusted mean)	-0.54	-0.07
Difference from placebo + SU (adjusted mean) (95% CI)	-0.47 (-0.70, -0.24)	--
Patients (%) achieving HbA_{1C} <7%	15.2	3.7
FPG (mmol/L)	**n = 155**	**n = 78**
Baseline (mean)	10.0	9.5
Change from baseline (adjusted mean)	-0.46	-1.0
Difference from placebo + SU (adjusted mean) (95% CI)	-0.36 (-0.96, 0.24)	--

SU = sulfonylurea

Linagliptin as add-on to a combination of metformin and a sulfonylurea therapy (BI Study 1218.18)

A placebo-controlled study of 24 weeks in duration was conducted to evaluate the efficacy and safety of linagliptin 5 mg compared to placebo, in patients not sufficiently treated with a combination with metformin and a sulfonylurea. Linagliptin provided significant improvements in HbA_{1c}, fasting plasma glucose (FPG), and 2-hour post-prandial glucose (PPG) and a greater portion of patients (31%) achieved a target HbA_{1c} of <7.0% compared to placebo (9%) (Table 14). Body weight did not differ significantly between the groups.

Table 14 Glycemic Parameters at Final Visit (24-Week Study) for TRAJENTA in Combination with Metformin and Sulfonylurea (BI Study 1218.18)

	TRAJENTA 5 mg + Metformin + SU	**Placebo + Metformin + SU**
HbA_{1C} (%)	**n = 778**	**n = 262**
Baseline (mean)	8.15	8.14
Change from baseline (adjusted mean)	-0.72	-0.10
Difference from placebo (adjusted mean) (95% CI)	-0.62 (-0.73, -0.50)	--
Patients n (%) achieving HbA_{1C} <7%	243 (31.2)	24 (9.2)
FPG (mmol/L)	**n = 739**	**n = 248**
Baseline (mean)	8.84	9.03
Change from baseline (adjusted mean)	-0.26	0.45
Difference from placebo (adjusted mean) (95% CI)	-0.71 (-1.0, -0.40)	--

SU = sulfonylurea

Linagliptin (lina) as add-on to a combination of metformin and empagliflozin (BI Study 1275.10)

Following a 16-week open-label period with metformin (≥1500 mg/day) and either empagliflozin 10 mg or empagliflozin 25 mg, patients with T2DM who did not achieve adequate glycemic control were randomized to receive 24-week double-blind treatment. Patients who received open-label treatment with metformin and empagliflozin 10 mg were randomized (1:1) to receive either metformin + FDC empa 10 mg/lina 5 mg or metformin + empagliflozin 10 mg, while patients who received open-label treatment with metformin and empagliflozin 25 mg were randomized (1:1) to receive either metformin + FDC empa 25 mg/lina 5 mg or metformin + empagliflozin 25 mg. The study was not designed to evaluate the efficacy of FDC empa 25 mg/lina 5 mg in patients with T2DM inadequately controlled with FDC empa 10 mg/lina 5 mg.

Approximately 19% of randomized patients were aged ≥65 years (3% aged ≥75 years). Approximately 97% were White and 3% were Black/African American. Approximately 60% of patients had been diagnosed with T2DM for longer than 5 years, and approximately 9% for less than or equal to 1 year. The mean body mass index (BMI) of patients randomized to receive metformin + FDC empa 10

mg/lina 5 mg or metformin + empagliflozin 10 mg was 31.0 kg/m^2. The mean BMI of patients randomized to receive metformin + FDC empa 25 mg/lina 5 mg or metformin + empagliflozin 25 mg was 31.4 kg/m^2.

The primary endpoint of the study was the difference in change from baseline HbA_{1c} at week 24. The key secondary endpoint was change from baseline FPG, at week 24. Metformin + FDC empa 10 mg/lina 5 mg and metformin + FDC empa 25 mg/lina 5 mg each provided statistically significant improvements in HbA_{1c} and FPG after 24 weeks of treatment compared to metformin + empagliflozin 10 mg or metformin + empagliflozin 25 mg, respectively (see Table 15).

The proportion of patients with a baseline HbA_{1c} ≥7.0% who achieved a target HbA_{1c} of <7% at week 24 was 25.9% in the metformin + FDC empa 10 mg/lina 5 mg group compared to 10.9% in the metformin + empagliflozin 10 mg group.

The proportion of patients with a baseline HbA_{1c} ≥7.0% who achieved a target HbA_{1c} of <7% at week 24 was 36.0% in the metformin + FDC empa 25 mg/lina 5 mg group compared to 15.0% in the metformin + empagliflozin 25 group.

Table 15 Efficacy Parameters in the Clinical Study Comparing FDC empa /lina + Metformin to Empagliflozin + Metformin in Patients with T2DM Inadequately Controlled on Empagliflozin + Metformin (Study 1275.10)

	FDC empa 10 mg/lina 5mg + Metformin	Empa 10 + Metformin	FDC empa 25 mg/lina 5mg + Metformin	Empa 25 + Metformin
Efficacy Parameter				
HbA_{1c} (%) – 24 weeks[2]				
N[1]	122	125	109	108
Baseline (mean)	8.04	8.03	7.82	7.88
Change from baseline (adjusted mean)	-0.53	-0.21	-0.58	-0.10
Difference from Empa + Metformin (adjusted mean) (95% CI)	-0.32 (-0.52, -0.13) p<0.001	--	-0.47 (-0.66, -0.28) p<0.001	--
FPG (mmol/L) – 24 weeks[2]				
N[1]	120	123	107	107
Baseline (mean)	8.76	8.64	8.45	8.61
Change from baseline (adjusted mean)	-0.44	0.21	-0.68	-0.24
Difference from Empa + Metformin (adjusted mean) (95% CI)	-0.65 (-1.15, -0.16) p<0.05	--	-0.44 (-0.87, -0.01) p<0.05	--

Abbreviations: FDC empa 10 mg/lina 5 mg = fixed dose combination empagliflozin 10 mg + linagliptin 5 mg; FDC empa 25 mg/lina 5 mg = fixed dose combination empagliflozin 25 mg + linagliptin 5 mg; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg

[1]N = Full Analysis Set (FAS): treated patients with a pre-randomization baseline and at least one on-treatment HbA_{1c} assessment

[2]MMRM (mixed model repeated measures) model on FAS (observed case includes baseline HbA_{1c}, baseline eGFR (modification of diet in renal disease), geographical region, visit treatment, and treatment by visit interaction. For FPG, baseline FPG is also included.

Linagliptin as add-on to insulin therapy (BI Study 1218.36)

The efficacy and safety of linagliptin 5 mg as add-on therapy to a stable dose of basal insulin regimen was evaluated in a total of 1261 patients with type 2 diabetes mellitus inadequately controlled (HbA_{1c}

level of ≥7.0 to ≤10%) on insulin alone or in combination with other antihyperglycemic agents in a randomized double-blind placebo-controlled study of at least 52 weeks duration. Patients using prandial insulin alone or in pre-mixed formulations or insulin delivered by pump were not included in this study. The mean treatment difference in HbA_{1c} between linagliptin versus placebo from baseline to Week 24 (LOCF) was -0.65% (95% CI -0.74, -0.55; p<0.0001) from a mean baseline HbA_{1c} of 8.3%. Linagliptin also showed modest but significant improvements in fasting plasma glucose (FPG) of -0.62 mmol/L (95% CI -0.90, -0.35; p<0.0001) compared to placebo, and a greater portion of patients achieved a target HbA_{1c} of <7.0%, compared to placebo. Body weight did not differ significantly between the groups. After 24 weeks of treatment, the mean daily insulin dose at baseline was 42 units in patients treated with TRAJENTA and 40 units in placebo-treated patients. The mean change from baseline to Week 24 in daily dose of insulin was 1.3 IU in the placebo group and 0.6 IU in the TRAJENTA group.

Based on subgroup analyses of background antidiabetic medications (Table 16), there was a slightly greater efficacy in patients taking insulin and metformin than insulin alone. Of 197 patients on a background of insulin alone (no concomitant oral antidiabetic agents), the mean placebo-adjusted change from baseline in HbA_{1c} at Week 24 (LOCF) was -0.54 (p<0.0001). Based on a subgroup analysis of 932 patients on a background of insulin plus metformin only, the mean placebo-adjusted reduction from baseline in HbA_{1c} at Week 24 (LOCF) was -0.67 (p<0.0001).

Table 16 Glycemic Parameters in Placebo-Controlled Study for TRAJENTA in Combination with Insulin Alone or Insulin with Metformin* at 24 Weeks

Background Therapy	**Insulin Alone**		**Insulin + Metformin only**	
	TRAJENTA 5 mg + Insulin	Placebo + Insulin	TRAJENTA 5 mg + Metformin + Insulin	Placebo + Metformin + Insulin
HbA_{1C} (%)				
Number of patients	95	102	469	463
Basesline (mean)	8.39	8.35	8.29	8.26
Change from baseline (adjusted mean)	-0.49[1]	0.05[1]	-0.64[1]	0.04[1]
Difference from placebo (adjusted mean) (95% CI)	-0.54[1] (-0.77, -0.30) p<0.0001	--	-0.67[1] (-0.79, -0.56) p<0.0001	--
Patients (%) achieving HbA_{1C} <7%	13.7	7.8	22.4	9.7
FPG (mmol/L)				
Number of patients	94	99	466	458
Baseline (mean)	7.90	8.19	8.24	8.47
Change from baseline (adjusted mean)	-0.22[2]	0.06[2]	-0.57[2]	0.17[2]
Difference from placebo (adjusted mean) (95%CI)	-0.27[2] (-0.96, 0.41) p=0.4321	--	-0.74[2] (-1.05, -0.44) p<0.0001	--

*Full analysis population using last observation carried forward (LOCF)
[1] ANCOVA model includes treatment, continuous baseline HbA_{1c} and renal impairment category
[2] ANCOVA model includes treatment, continuous baseline HbA_{1c}, continuous baseline FPG and renal impairment category

Linagliptin as add-on to metformin in comparison with glimepiride (BI Study 1218.20)
In a study comparing the efficacy and safety of the addition of linagliptin 5 mg or glimepiride (a sulfonylurea agent) in patients with inadequate glycemic control on metformin monotherapy, linagliptin was similar to glimepiride in reducing HbA_{1c}, with a mean treatment difference in HbA_{1c} from baseline to 104 weeks for linagliptin compared to glimepiride of +0.2%.

Open-label long-term extension add-on combination with various antidiabetic medications (BI Study 1218.40)
Data on long-term efficacy (over 12 months) is supported by the results of an open-label extension trial conducted in patients who completed the 24-week treatment period of 4 placebo-controlled studies (1218.15*, 1218.16, 1218.17 and 1218.18). In this extension trial, all patients received 5 mg linagliptin as monotherapy or as add-on to the background therapy they took in the previous trial. The treatment duration in this study was 78 weeks, i.e., patients who completed this study have received 5 mg for either 78 weeks (those who received placebo in the initial trial) or 102 weeks (those who received linagliptin in the initial trial). The HbA_{1c} reduction achieved at the end of week 24 was maintained during the open-label extension study.
*not an approved indication

Subgroups of the Pooled Analysis
The analysis of the influence of renal impairment (eGFR, estimated according to the MDRD formula) was limited to patients with normal renal function (≥90 mL/min) and patients with mild (60 to <90 mL/min) and moderate (30 to <60 mL/min) renal impairment. The number of patients with moderate renal impairment was comparatively low (n=109 in total; 29 placebo, 80 linagliptin) and the pooled analysis did not comprise any patient with severe renal impairment (<30 mL/min). The treatment effect of linagliptin in terms of adjusted mean differences to placebo in HbA_{1c} was similar in patients with normal renal function (-0.61%), and patients with mild (-0.63%) or moderate (-0.57%) renal impairment. The p-value for the treatment-by-subgroup interaction was 0.9096. Thus, it can be concluded that mild and moderate renal impairment did not influence the treatment effect of linagliptin.

Study in Special Population
Patients with Renal Impairment – 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) (BI Study 1218.43): The efficacy and safety of linagliptin were also evaluated in type 2 diabetes patients with severe renal impairment in a double-blind study versus placebo where patients were on a variety of background therapies including insulin and/or oral antihyperglycemic drug. A total of 133 patients participated (linagliptin: n=68, placebo: n=65). Patients on dialysis were excluded from entry into the study. The predominant background therapy was insulin (82%). The study had an initial 12 week period during which background glycemic therapies were kept stable. There was a follow up 40 week period during which dose adjustments in antidiabetes background therapies were allowed.

Linagliptin provided significant improvements in HbA_{1c} (-0.59% change compared to placebo at Week 12), from a mean baseline HbA_{1c} of 8.2%. Improvements in HbA_{1c} following treatment with linagliptin were sustained up to Week 52.

Elderly Patients – Linagliptin as add-on therapy in elderly patients (age ≥70 years) with type 2 diabetes (BI Study 1218.63): The efficacy and safety of linagliptin in elderly type 2 diabetes patients has been evaluated in a 24-week, randomized, double-blind, placebo-controlled study. A total of 241 patients aged ≥70 years and inadequately controlled on a stable treatment regimen of metformin and/or a sulfonylurea and/or basal insulin and with an HbA_{1c} of ≥7.0% were randomized (2:1) to receive either linagliptin 5 mg once daily (n=162) or placebo (n=79). Linagliptin provided significant improvements in HbA_{1c} (-0.64% [95% CI -0.81, -0.48; p<0.0001]) and fasting plasma glucose (-1.15 mmol/L [95% CI -1.7, -0.62; p<0.0001]) compared to placebo after 24 weeks, from a mean baseline HbA_{1c} of 7.8%. Body weight did not differ significantly between the groups.

CARMELINA – Cardiovascular Safety and Renal Microvascular Outcome Study (BI Study 1218.22): The CARMELINA trial was a randomized, double-blind, placebo-controlled, parallel-group, time- and event-driven, multicentre study investigating the effect of TRAJENTA on cardiovascular (CV) risk in adult patients with type 2 diabetes (T2D) mellitus with increased CV risk evidenced by a history of established macrovascular or renal disease. Patients were eligible to enter the trial if they were adults, had inadequately controlled T2D mellitus (HbA_{1c} ≥6.5% and ≤10.0%), and had either albuminuria and previous macrovascular disease (39% of enrolled population), or evidence of impaired renal function (42%), or both (18%). The study included 6979 patients (37% female, 63% male) in the treated set population who were treated with linagliptin 5 mg once daily (n=3494) or placebo (n=3485) added to standard of care targeting regional standards for HbA_{1c}, CV risk factors and renal disease. The mean duration of study follow-up was 2.2 years. The proportion of subjects who completed the study was 98.7%.

Approximately 80% of the study population was Caucasian, 9% was Asian, and 6% was Black. The mean age was 66 years. The mean HbA_{1c} at baseline was 8.0% and mean duration of diabetes was 15 years. At baseline, 96.8% of patients were treated with one or more antidiabetic medications including metformin (54%), insulin (57%), and sulfonylurea (32%). Patients were also taking antihypertensives (96%), lipid lowering drugs (76%) with 72% of statin, and aspirin (62%). The study population included 4081 (58.5%) patients with ischemic heart disease, 1873 (26.8%) with a history of heart failure, 1211 (17%) patients ≥75 years of age, and 4348 (62%) patients with renal impairment (eGFR <60 mL/min/1.73 m^2). The mean baseline renal function was eGFR 54.6 mL/min/1.73 m^2 and 27% of patients had mild renal impairment (eGFR ≥60 to <90 mL/min/1.73 m^2). Approximately 47% of the population had moderate renal impairment (28% with an eGFR ≥30 to <45 mL/min/1.73 m^2 and 19% with an eGFR ≥45 to <60 mL/min/1.73 m^2). Patients with severe renal impairment were not to be enrolled in the study but 15% of the poluation had an eGFR <30 mL/min/1.73 m^2.

The primary CV endpoint was the time to first occurrence of any of the following adjudication-confirmed components of the primary composite endpoint (3-point MACE): CV death, non-fatal myocardial infarction, or non-fatal stroke. The key secondary endpoint was time to the first occurrence of any of the following adjudication-confirmed components of composite renal endpoint 1: renal death, sustained end stage renal disease (ESRD), sustained decrease of 40% or more in eGFR. Other CV endpoints included a composite of the first occurrence of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina pectoris (4-point MACE); as well as first occurrence of the following independent CV endpoints: CV death, myocardial infarction (fatal + non-fatal), stroke (fatal + non-fatal), hospitalization for unstable angina, hospitalization for heart

failure, and all-cause mortality. A composite endpoint of first occurrence of CV death or hospitalization for congestive heart failure was also assessed.

TRAJENTA, when added to standard of care, did not increase the risk of major adverse CV events or renal outcome events (Table 17 and Figure 3). 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 T2D (Table 18 and Figure 4). Superiority to placebo was not demonstrated for any endpoint in hypothesis testing of 3-point MACE or other pre-specified CV endpoints.

Table 17 Major Adverse Cardiovascular Events (MACE) and Renal Outcome Events Reported in the CARMELINA Study

	Linagliptin 5 mg N=3494		**Placebo N=3485**		**Hazard Ratio vs. Placebo** (95% CI)	**p-value**[†]
	Subjects with Events N (%)	Incidence Rate per 1000 Patient-Years	Subjects with Events N (%)	Incidence Rate per 1000 Patient-Years		
Primary CV Composite Endpoint MACE	434 (12.4)	57.7	420 (12.1)	56.3	1.02 (0.89, 1.17)	<0.0002 0.6301[††] 0.7398
• CV death	255 (7.3)	32.6	264 (7.6)	34.0	0.96 (0.81, 1.14)	0.6282
• Non-fatal myocardial infarction	156 (4.5)	20.6	135 (3.9)	18.0	1.15 (0.91,1.45)	0.2345
• Non-fatal stroke	65 (1.9)	8.5	73 (2.1)	9.6	0.88 (0.63,1.23)	0.4495
Secondary Renal Composite Endpoint (renal death, ESRD, 40% sustained decrease in eGFR)	327 (9.4)	48.9	306 (8.8)	46.6	1.04 (0.89, 1.22)	0.6918[††]

Abbreviations: CV = cardiovascular; ESRD = end-stage renal disease; eGFR = estimated glomerular filtration rate; CI = confidence of interval
[†] Based on a Cox model stratified by region. For composite endpoints, the p-values correspond to a test of non-inferiority seeking to show that the hazard ratio is less than 1.3. For all other endpoints, the p-values correspond to a test of differences in hazard rates (two-sided p-values for superiority)
[††] One-sided p-values for superiority

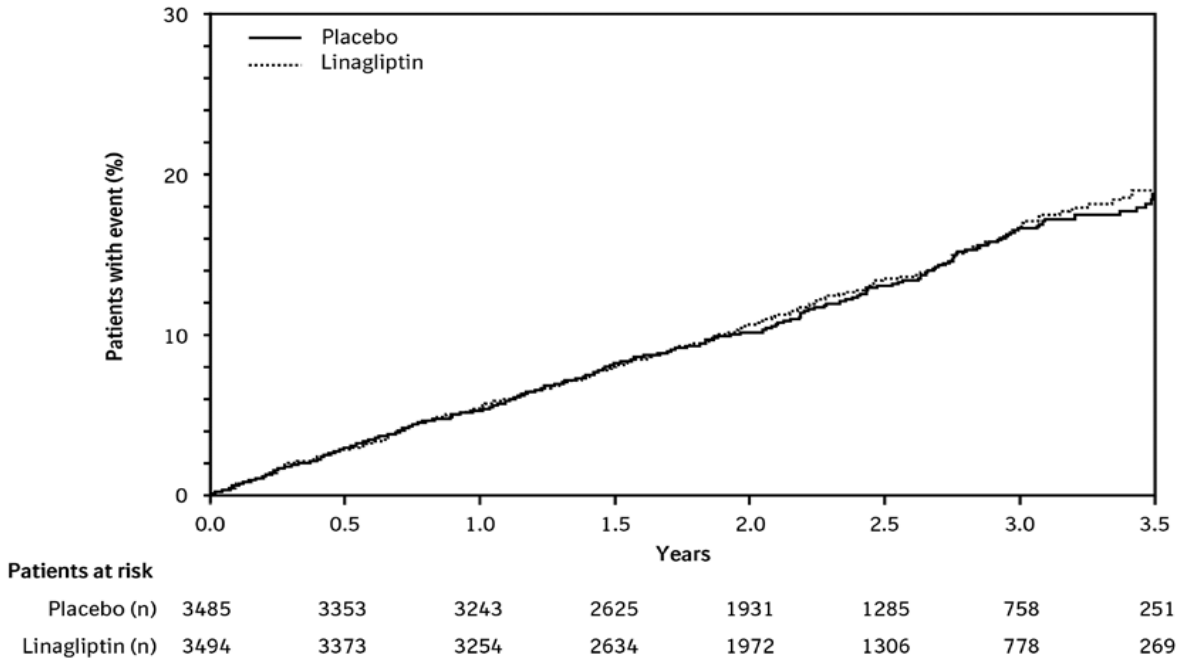


Figure 3 Time to First Occurrence of 3-Point MACE in CARMELINA

Table 18 Other Cardiovascular and Mortality Outcomes in the CARMELINA Study

	Linagliptin 5 mg N=3494		**Placebo N=3485**		**Hazard Ratio vs. Placebo** (95% CI)	**p-value**[†]
	Subjects with Events N (%)	Incidence Rate per 1000 Patient-Years	Subjects with Events N (%)	Incidence Rate per 1000 Patient-Years		
All myocardial infarction (fatal and non-fatal)	165 (4.7)	21.8	146 (4.2)	19.4	1.12 (0.90, 1.40)	0.3021
All stroke (fatal and non-fatal)	81 (2.3)	10.6	88 (2.5)	11.6	0.91 (0.67, 1.23)	0.5336
Hospitalization for unstable angina	42 (1.2)	5.5	48 (1.4)	6.3	0.87 (0.57, 1.31)	0.4956
All-cause mortality	367 (10.5)	46.9	373 (10.7)	48.0	0.98 (0.84, 1.13)	0.7402
Hospitalization for heart failure	209 (6.0)	27.7	226 (6.5)	30.4	0.90 (0.74, 1.08)	0.2635
CV death/ Hospitalization for heart failure	406 (11.6)	53.7	422 (12.1)	56.6	0.94 (0.82, 1.08)	0.3881
All cause mortality/ Hospitalization for heart failure	499 (14.3)	65.9	518 (14.9)	69.4	0.95 (0.84, 1.07)	0.4012

Abbreviations: CV = cardiovascular; CI = confidence of interval

[†] Based on a Cox model stratified by region. The p-values correspond to a test of differences in hazard rates (two-sided p-values for superiority)

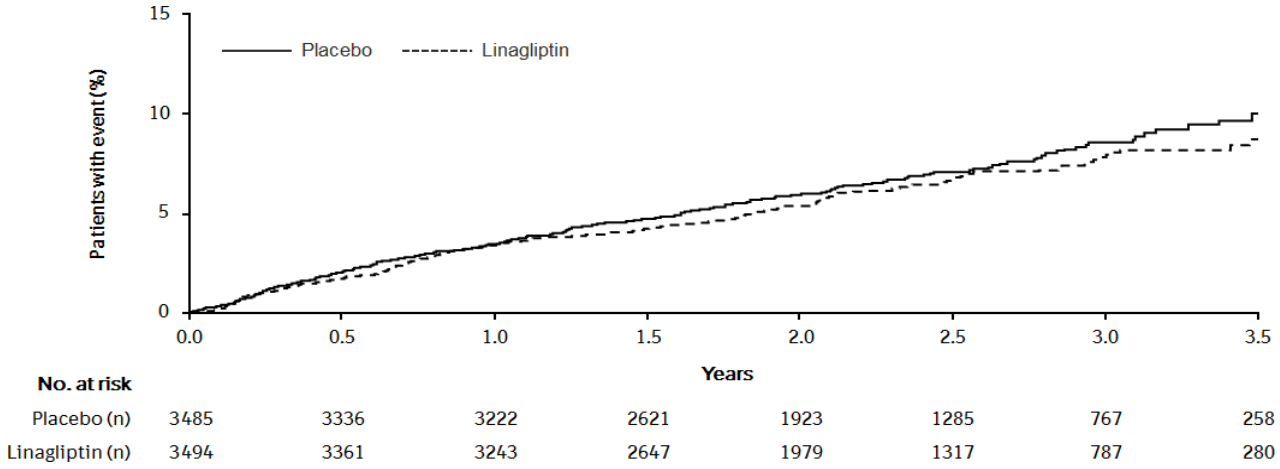


Figure 4 Kaplan-Meier Estimation of Time to First Hospitalisation for Heart Failure – TS

CAROLINA – Cardiovascular Safety Outcome Study (BI Study 1218.74): The CAROLINA trial was a randomized, double-blind, active-controlled, parallel-group, time- and event-driven, multicentre study investigating the effect of TRAJENTA (linagliptin) in comparison with a sulfonylurea agent (glimepiride) on cardiovascular (CV) risk in adult patients with type 2 diabetes (T2D) mellitus and high risk of CV events, mainly characterised by previous vascular disease or multiple CV risk factors. Patients were eligible to enter the trial if they were adults, had inadequately controlled T2D mellitus (defined as HbA_{1c} 6.5% to ≤8.5% or 6.5% to 7.5% depending on whether treatment-naïve, on monotherapy or on combination therapy), and were defined to be at high CV risk with previous vascular disease, evidence of vascular-related end-organ damage, ≥70 years of age, and at least 2 of multiple CV risk factors (duration of diabetes >10 years, hypertension, current smoker, dyslipidemia). The study included 6033 patients (40% female, 60% male) with early T2D mellitus and increased CV risk or established complications who were treated with linagliptin 5 mg once daily (n=3023) or glimepiride 1 mg to 4 mg (n=3010) added to standard of care targeting regional standards for HbA_{1c} and CV risk factors. The median duration of study follow-up was 6.25 years. The proportion of subjects who completed the study was 96%.

At baseline, the mean age was 64 years with 34% of patients ≥70 years of age. Approximately 73% of the study population was Caucasian, 18% was Asian, and 5% was Black. The mean HbA_{1c} at baseline was 7.15% and mean duration of diabetes was 7.6 years. The trial population included 2089 (35%) patients with CV disease and 1130 (19%) patients with renal impairment with an eGFR <60 mL/min/1.73m^2. At baseline, 91% of patients were treated with one or more antidiabetic medications including metformin (83%) and sulfonylurea (28%). Patients were also taking antihypertensives (89%), lipid lowering drugs (70%) with 65% of statin, and aspirin (47%).

The study was designed to demonstrate non-inferiority of treatment with linagliptin in comparison with glimepiride (predominantly on metformin background treatment) for the primary CV endpoint which was the time to first occurrence of any of the following adjudication-confirmed components of

the primary composite endpoint (3-point MACE): CV death, non-fatal myocardial infarction, or non-fatal stroke.

According to the pre-specified risk margin of 1.3, TRAJENTA did not increase the risk of major adverse CV events compared to glimepiride (Table 19). TRAJENTA, when added to standard of care, was non-inferior compared to glimepiride. Superiority to glimepiride was not demonstrated for any endpoint in hypothesis testing of 3-point MACE.

Table 19 Major Adverse Cardiovascular Events (MACE) Reported in the CAROLINA Study

	Linagliptin 5 mg N=3023		**Glimepiride N=3010**		**Hazard Ratio vs. Glimepiride** (95% CI)	**p-value**[†]
	Subjects with Events N (%)	Incidence Rate per 1000 Patient-Years	Subjects with Events N (%)	Incidence Rate per 1000 Patient-Years		
Primary CV Composite Endpoint MACE	356 (11.8)	20.7	362 (12.0)	21.2	0.98 (0.84, 1.14)	<0.0001 0.3813[††] 0.7625
• CV death	169 (5.6)	9.2	168 (5.6)	9.2	1.00 (0.81, 1.24)	0.9863
• Non-fatal myocardial infarction	145 (4.8)	8.3	142 (4.7)	8.2	1.01 (0.80, 1.28)	0.9060
• Non-fatal stroke	91 (3.0)	5.2	104 (3.5)	6.0	0.87 (0.66, 1.15)	0.3352

Abbreviations: CV = cardiovascular; CI = confidence of interval
[†] Based on a Cox model stratified by region. For composite endpoints, the p-values correspond to a test of non-inferiority seeking to show that the hazard ratio is less than 1.3. For all other endpoints, the p-values correspond to a test of differences in hazard rates (two-sided p-values for superiority)
[††] One-sided p-values for superiority

DETAILED PHARMACOLOGY

Dipeptidyl Peptidase 4 (DPP-4, EC 3.4.14.5) is a membrane bound protease expressed in many tissues including kidneys, liver, intestine, lymphocytes and vascular endothelial cells. A significant level of DPP-4 activity is also observed in plasma, which likely originates from multiple tissues that express the enzyme. The most important physiological substrates of DPP-4 are the incretins Glucagon-Like Peptide-1 (GLP-1) and Glucose-dependent Insulinotropic Peptide (GIP). DPP-4 catalyzes the degradation and inactivation of incretion and inhibition of DPP-4 increases the duration of these short lived endogenous incretin hormones. Both GLP-1 and GIP exert potent glucose-dependent insulinotropic actions and thereby contribute to the maintenance of post-meal glycemic control.

Linagliptin is a potent inhibitor (IC50 = 1 nM) of human Dipeptidyl Peptidase 4 (DPP-4) and exhibits high selectivity versus a variety of proteases including DPP-8 and DPP-9 (>10,000-fold). In obese and diabetic animals (Zucker *fa/fa* rat, Zucker Diabetic Fatty Rat (ZDF) and *db/db* mice) linagliptin enhanced glucose-induced elevations of intact GLP-1 and insulin and lowered glucose levels with an ED50 of 1 mg/kg and below. These data indicate that linagliptin is an efficacious anti-diabetic drug.

The main metabolite of linagliptin CD 1790 neither inhibited DPP-4 activity nor interacted with a variety of receptors, channels and enzymes.

Linagliptin has a pharmacological profile that suggests good tolerability. Safety pharmacology studies did not indicate a risk of arrhythmia including those associated with a prolongation of the QT interval. No relevant effects on cardiovascular parameters were observed in safety pharmacology and toxicology studies in the Cynomolgus monkey at oral dosages up to and including 300 mg/kg/day (2523-fold clinical C_{max}). The safety pharmacology assessment of neurological (CNS) and respiratory effects in rats after oral administration did not identify any effects on behaviour, spontaneous locomotor activity or body temperature at 600 mg/kg. Transient decreases in respiratory rate were observed at this dose. There were no effects on respiratory effects at 60 mg/kg.

TOXICOLOGY

General toxicity

Linagliptin was well tolerated and the minimum lethal dose after a single oral dose was 1000 mg/kg in rats and mice. Repeat oral dosing was associated with lethality/moribund euthanasia at ≥600 mg/kg (> 3000 times human clinical exposure) in rats, 600 mg/kg (>3000 times human clinical exposure) in mice, 150 mg/kg (>1500 times human clinical exposure) in dogs and one monkey at 100 mg/kg (>750 times human clinical exposure). In dogs, a pseudo-allergic reaction occurred at ≥15 mg/kg and C_{max} 3690 nmol/L (>300 times human clinical C_{max}). The reaction was characterized by reddening and swelling of ears, circumocular region, as well as upper lips and vomiting. The reaction typically occurred 10 to 90 min post dose and then disappeared gradually and correlated reasonably with increases in circulating histamine concentrations. Linagliptin was associated with changes that appear secondary to irritation with high local concentrations of linagliptin in the GI tract after oral administration or in the biliary tract associated with excretion of drug. These ranged from minimal to slight epithelial hypertrophy/hyperplasia to ulcers and affected the gastro intestinal tract, gallbladder and biliary epithelium with or without peribiliary changes in mice (≥120 mg/kg, >400 times human clinical exposure), rats (≥300 mg/kg, >1500 times human clinical exposure), dogs (≥45 mg/kg, >200 times human clinical exposure) and monkeys (≥25 mg/kg, >100 times human clinical exposure). Linagliptin administration also results in metabolic effects that appear secondary to prolonged action of incretins as a result of DPP-4 inhibition. These include increased glycogen deposits in the hepatocytes of rat, mouse and monkey and decreases in cholesterol and triglycerides. The changes in the liver were not adverse at lower doses but at 300 mg/kg in the mouse and 100 mg/kg in the rat, there were either histological indication of adverse liver effects and/or increases in plasma markers for hepato-biliary perturbation. There were effects on kidney function or integrity in mouse, rat and monkey. In the monkey, there were no microscopic changes in the kidney but increases in plasma creatinine, kidney weight and urinary protein at ≥150 mg/kg(>1500 times human clinical exposure). In the rat, plasma creatinine and urea, increases in kidney weight and/or microscopic tubular damage were noted at ≥100 mg/kg. In the mouse, overt kidney toxicity was evident at 600 mg/kg. Linagliptin is an inducer of phospholipidosis in the rat. At 600 mg/kg, foam cells in liver, lung, lymph nodes, spleen, thymus and bone marrow were noted. Also in the rat at doses of ≥100 mg/kg, foci of foam cells were noted in the lung and at 60 mg/kg (approximately 400 times human clinical exposure) in the carcinogenicity study, there was an increased incidence of cholesterol cleft granuloma. There were no indications of effects on the immune system at doses up to 100 mg/kg (approximately 800 times human clinical exposure) for 52 weeks in the monkey, at doses up to 300 mg/kg (approximately 1800

times human clinical exposure) for 26 weeks in the rat, or in the mouse at 600 mg/kg (approximately 3300 times human clinical exposure) for 13 weeks. Increased apoptosis in the thymus, spleen and lymph nodes in rats and monkeys occurred at high doses and were attributed to stress and nonspecific toxicity. The NOAEL after 52 weeks dosing was 10 mg/kg/day in the monkey and 30 mg/kg/day in a 26 week study in rats. At these doses, AUC values were 40 times human clinical exposure in the monkey and 66 times in the rat.

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 tumors in any organ up to 60 mg/kg/day. This dose results in exposures approximately 400 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 240 times human clinical exposure.

Genotoxicity

The mutagenic and clastogenic potential of linagliptin were tested in an *in vitro* Ames bacterial assay, an *in vitro* cytogenetics assay in primary human lymphocytes, and an *in vivo* oral micronucleus assay in rats. Linagliptin was not mutagenic or clastogenic in these studies. The major metabolite was not mutagenic in an *in vitro* Ames bacterial assay or clastogenic in human lymphocytes.

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 900 times human clinical exposure of 5 mg/day based on AUC comparisons).

In the studies on embryo-fetal development in rats and rabbits, linagliptin was not teratogenic at dosages up to and including 240 mg/kg/day (approximately 900 times human clinical exposure) in the rat and 150 mg/kg/day (approximately 1900 times human clinical exposure) in the rabbit. In the rat, at 240 mg/kg minor maternal toxicity was noted and there was a slight increased resorption rate, slight retardation of skeletal ossification, and also slightly increased incidence of flat and thickened ribs. Administration of 25 and 150 mg/kg to pregnant rabbits resulted in decreased mean body weight gain and decreased food consumption at 150 mg/kg. At 150 mg/kg, linagliptin treatment was associated with intrauterine death, runts (fetuses weighing less than 65% of the weighted control mean values) and an increased incidence of visceral and skeletal variations. A NOAEL of 30 mg/kg/day (approximately 50 times human clinical exposure) and 25 mg/kg/day (approximately 80 times human clinical exposure) was derived for embryo-fetal toxicity in the rat and the rabbit, respectively.

In a pre and postnatal development toxicity study in rats, treatment of the pregnant dams (the F_0 generation) at 300 mg/kg (approximately 1500 times human clinical exposure) during gestation and lactation caused decreased maternal body weight gain and food consumption observed during gestation and lactation. The F1 generation of dams treated at 300 mg/kg also showed reduced body weight during lactation and weaning. Their physical postnatal development proceeded in a normal

range, except for delayed descensus testis and delayed preputial separation. These effects correlated with reduced body weight and were attributed to general growth retardation. The NOAEL was 30 mg/kg for both maternal and offspring toxicity (approximately 50 times human clinical exposure).

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PART III: CONSUMER INFORMATION

Pr Trajenta®
Linagliptin Tablets

This leaflet is part III of a three-part "Product Monograph" published when TRAJENTA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TRAJENTA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
TRAJENTA, along with diet and exercise to improve control of blood sugar in adults with type 2 diabetes, is used:
- alone in patients who cannot take metformin, or
- in combination with metformin, or
- in combination with a sulfonylurea, or
- in combination with metformin and a sulfonylurea, or
- in combination with metformin and empagliflozin, or
- in combination with insulin (with or without metformin).

What it does:
TRAJENTA is a member of a class of medicines called DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors). TRAJENTA helps to improve the levels of insulin when blood sugar level is high, especially after a meal. TRAJENTA also helps to decrease the amount of sugar made by the body.

When it should not be used:
You should not take TRAJENTA if:
- you are allergic (hypersensitive) to linagliptin or any of the non-medicinal ingredients listed below.
- 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).

What the medicinal ingredient is:
linagliptin

What the important non-medicinal ingredients are:
TRAJENTA tablets contain the following non-medicinal ingredients: mannitol, pregelatinised starch, maize starch, copovidone, magnesium stearate. In addition, the film coating contains the following inactive ingredients: hypromellose, titanium dioxide, talc, macrogol, iron oxide red.

What dosage forms it comes in:
TRAJENTA is supplied as tablets containing 5 mg linagliptin. The tablets are round, light red in colour and have the marking “D5” on one side.

WARNINGS AND PRECAUTIONS

BEFORE you use TRAJENTA talk to your doctor or pharmacist if:
- you take sulfonylurea or insulin. Your doctor may reduce your dose of these products when you take them with TRAJENTA. This can help avoid low blood sugar. Your physician may consider lowering the dose of the sulfonylurea or insulin.
- you have had allergic reactions to any other medicines that you take to control the amount of sugar in your blood;
- you are pregnant or planning to become pregnant;
- you are breast-feeding or plan to breast-feed;
- you have or have had pancreas problems such as inflammation of the pancreas (pancreatitis);
- you have risk factors for pancreatitis such as:
  - gallstones (solid particles that form in the gall bladder),
  - a history of alcoholism,
  - high triglyceride levels;
- you have congestive heart failure, history of any heart problems or other risk factors for heart failure including kidney problems;
- you have any skin problems;
- you have liver problems.

TRAJENTA is not recommended for children and adolescents under 18 years.

Cases of inflammation of the pancreas (**pancreatitis**) have been reported in patients taking TRAJENTA. Pancreatitis can be severe and lead to death.

Cases of **severe skin reactions** including **bullous pemphigoid** can occur and have been reported in patients taking TRAJENTA. You may need treatment in a hospital. You may need to see a dermatologist to diagnose and treat these skin reactions.

Driving and using machines: TRAJENTA can cause low blood sugar. This is more likely when you take it with sulfonylurea or with insulin. Before doing these kinds of tasks wait until you know how you respond to TRAJENTA.

INTERACTIONS WITH THIS MEDICATION

Tell your physician or pharmacist about all the drugs you take. This includes prescription and non-prescription drugs, vitamins, and herbal supplements. TRAJENTA may interact with other medications. This may cause serious side effects. This can be less control of your blood sugar or low blood sugar.

PROPER USE OF THIS MEDICATION

Take all medicines to control blood sugar as prescribed. Your doctor may lower the amount of sulfonylurea or insulin that you take.

Usual Adult Dose:

5 mg tablet, once a day. You can take TRAJENTA with or

without food.

Overdose:

If you think you have taken too much TRAJENTA, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

- If you forget to take a dose of TRAJENTA, take it as soon as you remember. If you do not remember until it is the time for your next dose, skip the missed dose and go back to your regular schedule.
- Do not take a double dose of TRAJENTA on the same day.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

These are not all the possible side effects that you may have when taking TRAJENTA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects with TRAJENTA include:
- Cough
- Inflamed nose or throat (nasopharyngitis), sore throat, cold symptoms, stuffy or runny nose
- High blood triglyceride
- High blood lipase or amylase
- Constipation
- Hives or nettle rash (urticaria)
- Rash, itching
- Mouth sores (mouth ulceration)

Your doctor may do blood tests before you start TRAJENTA and while you take it. They may check your blood sugar, liver function, and how well your kidneys are working. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Very Common			
Hypoglycemia (low blood sugar – when used with a sulfonylurea): shaking, sweating, anxiety, blurred vision, tingling lips, paleness, mood change, vagueness or confusion		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Uncommon			
Hypersensitivity (allergic reactions): rash, hives, and swelling of the face, lips, mouth, tongue or throat that may cause difficulty in breathing or swallowing and wheezing and shortness of breath			✓
Rare			
Pancreatitis (inflammation of the pancreas): prolonged severe abdominal pain which may be accompanied by vomiting; pain may spread out towards the back			✓
Severe skin reactions including bullous pemphigoid: redness, peeling skin, and/or blistering of the skin, lips, eyes or mouth			✓
Very Rare			
Rhabdomyolysis (breakdown of damaged muscle): muscle spasms, weakness, red-brown (tea-coloured) urine			✓
Unknown			
Arthralgia: severe joint pain		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

HOW TO STORE IT

Store at room temperature (15°C to 30°C).

Keep TRAJENTA and all medicines safely away from children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about TRAJENTA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp), the manufacturer's website (https://www.boehringer-ingelheim.ca), or by calling the manufacturer, Boehringer Ingelheim (Canada) Ltd., at 1-800-263-5103, extension 84633.

This leaflet was prepared by Boehringer Ingelheim (Canada) Ltd. The information in this leaflet is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

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