

PRODUCT MONOGRAPH

Pr **TRAJENTA**[®]

Linagliptin

Tablets 5 mg

Oral Antihyperglycemic Agent
DPP-4 Inhibitor
Incretin Enhancer

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Date of Preparation:
May 14, 2015

Submission Control No: 182036

BICL-CCDS# 0273-06

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Pr **TRAJENTA**[®]

Linagliptin

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 5 mg	<i>Mannitol</i> <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

TRAJENTA[®] (linagliptin) is indicated in adult patients with type 2 diabetes mellitus (T2DM) to improve glycemic control.

Monotherapy

In conjunction with diet and exercise in patients for whom metformin is inappropriate due to contraindications or intolerance.

Combination Therapy

In combination with metformin when diet and exercise plus metformin alone do not provide adequate glycemic control.

In combination with a sulfonylurea when diet and exercise plus a sulfonylurea alone do not provide adequate glycemic control.

In combination with metformin and a sulfonylurea when diet and exercise plus metformin and a sulfonylurea do not provide adequate glycemic control.

Geriatrics (≥ 65 years of age):

TRAJENTA[®] has been studied in a limited number of patients >75 years. (See WARNINGS AND PRECAUTIONS, Special Populations, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Pediatrics (<18 years of age):

Safety and effectiveness of TRAJENTA[®] in pediatric patients have not been studied. Therefore TRAJENTA[®] should not be used in this patient population.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION and PACKAGING section of the product monograph.
- Patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

WARNINGS AND PRECAUTIONS

General

The use of TRAJENTA[®] in combination with insulin is not indicated due to a cardiovascular risk which cannot be excluded (see WARNINGS and PRECAUTIONS, Cardiovascular).

Cardiovascular

Patients with Congestive Heart Failure: A limited number of patients with history of congestive heart failure participated in clinical studies with TRAJENTA[®]. In clinical trials, patients with a clinically significant history of cardiac disease or presence of active cardiac disease within 6 months were excluded. Use in this population is not recommended.

Patients using insulin: TRAJENTA[®] is not indicated in combination with insulin due to an increase in cardiovascular risk, which cannot be excluded. In a Phase III randomized, double-blind, placebo-controlled, parallel group efficacy and safety study of TRAJENTA[®] 5 mg, administered orally once daily for at least 52 weeks in 1255 type 2 diabetic patients in combination with basal insulin therapy, a composite endpoint of cardiovascular and cerebrovascular death, myocardial infarction, and stroke occurred in 0.80% (5 of 627) of patients in the placebo group and in 1.59% (10 of 628) of subjects in the linagliptin group (Hazard Ratio 1.93 [0.66, 5.66]). The incidence of cardiovascular death was 0.16% (1 of 627) in the placebo group and 0.80% (5 of 628) in the linagliptin group (Hazard Ratio 4.79 [0.56, 40.98]). These findings were not statistically significant.

In a pooled analysis of 4 studies with insulin background consisting of 1613 patients on linagliptin and placebo, the difference between the linagliptin and placebo group for cardiovascular risk was not statistically significant. A composite endpoint of cardiovascular and cerebrovascular death, myocardial infarction, and stroke occurred in 1.12% (9 of 802) of patients in the placebo group and in 1.97 (16 of 811) of subjects in the linagliptin group (Hazard Ratio 1.73 [0.77, 3.92]).

Endocrine and Metabolism

Hypoglycemia

Use with Sulfonylureas:

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, CLINICAL TRIAL Adverse Drug Reactions and DOSAGE AND

ADMINISTRATION). Therefore, caution is advised when linagliptin is used in combination with a sulfonyleurea. A dose reduction of the sulfonyleurea may be considered to reduce the risk of hypoglycemia.

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/CYP3A4 inducers

Long term co-treatment with strong inducers of P-gp or CYP3A4 (e.g. rifampicin) may reduce the glycemic lowering effect of TRAJENTA[®]. Where efficacy is insufficient, 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 DRUG INTERACTIONS).

Hepatic/Biliary/Pancreatic

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

Pancreatitis

There have been reports of acute and chronic pancreatitis, in patients taking TRAJENTA[®] during the clinical trials and post marketing reports of acute pancreatitis in patients taking TRAJENTA[®]. Reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, were noted in patients taking other members of this class. 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.

Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, angioedema, bronchial reactivity, rash, and urticaria, were observed with TRAJENTA[®] in clinical trials and/or post marketing reports. 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).

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.

Immune

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.

Peri-operative considerations

See Endocrine and Metabolism section - Loss of control of blood glucose.

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).

Skin

Ulcerative and necrotic skin lesions have been reported with other members of this 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.

Special Populations

Reproduction: 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).

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. Linagliptin was not teratogenic in rats and rabbits. At doses of 240 mg/kg/day in rats and 150 mg/kg/day in rabbits, increased resorption rate and intrauterine deaths were noted. There were slight delays in skeletal ossification or increased incidence of visceral and skeletal variations. AUCs were approximately 1000 to 2000 times human exposure (see TOXICOLOGY).

Nursing Women: TRAJENTA[®] should not be used during breast-feeding. There are no data in nursing women. Linagliptin is secreted in the milk of lactating rats. It is not known whether linagliptin is secreted 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 studied. Therefore TRAJENTA[®] should not be used in this patient population.

Geriatrics (≥ 65 years of age):

TRAJENTA[®] has been studied in limited number of patients >75 years. No overall difference in safety and efficacy between elderly and younger patients was observed. Greater sensitivity of some older individuals cannot be ruled out.

Monitoring and Laboratory Tests

Response to TRAJENTA[®] treatment should be monitored by periodic measurements of blood glucose and HbA_{1c} levels. Hepatic function should be assessed before starting treatment and periodically thereafter.

When TRAJENTA[®] is co-administered with strong inducers of P-gp or CYP3A4, the physician should monitor glucose more closely. 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 DRUG INTERACTIONS).

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% placebo). 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 (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia). In the pooled placebo controlled trials, nasopharyngitis was observed more frequently with linagliptin compared to placebo (5.9% vs. 4.7% placebo).

The incidence of serious adverse events was low in both treatment groups (4.8% linagliptin 5mg vs. 5.9% placebo).

The main causes for discontinuation for TRAJENTA[®] were diarrhea (0.2% vs. 0.1% placebo), glomerular filtration rate decreased (0.3% vs. 0.2% placebo), hyperglycemia (0.2% vs. 0.8% placebo) and hypoglycemia (0.2% 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% 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 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 of 2364 patients (1356 patient years of exposure) treated with placebo.

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, 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 \geq 12 weeks.

Adverse events were analysed and displayed based on the respective treatment regimens (monotherapy, add on to metformin, add on to sulfonylurea and add on to metformin plus sulfonylurea).

Adverse reactions classified by SOC and MedDRA preferred terms reported in \geq 2% of patients treated with TRAJENTA[®] 5 mg daily as monotherapy or in combination with sulfonylurea 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 $\geq 2\%$ 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

SOC Adverse Reaction	Linagliptin monotherapy *		Linagliptin + Metformin #		Linagliptin + Sulphonylurea		Linagliptin + Metformin + Sulphonylurea	
	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 (%)
Infections & infestations								
Nasopharyngitis	--	--	--	--	7 (4.3)	1 (1.2)	--	--
Respiratory, thoracic & mediastinal disorders								
Cough	--	--	--	--	--	--	19 (2.4)	3 (1.1)
Metabolism & nutrition disorders								
Hypertriglyceri- daemia [†]	--	--	--	--	4 (2.4)	0 (0.0)	--	--
Gastrointestinal disorders								
Constipation	--	--	--	--	--	--	--	--

* 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%)

The incidence of adverse events, reported regardless of causality assessment, in $\geq 2\%$ of patients and occurring more frequently in patients treated with TRAJENTA[®] 5 mg over placebo, as add-on to metformin, or add-on to sulphonylurea, or add-on to metformin plus sulphonylurea are shown in Table 2 to Table 6.

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 $\geq 2\%$ and for linagliptin in excess over placebo, irrespective of causality by system organ class and preferred term

System Organ Class/ Preferred term	Pbo 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 $\geq 2\%$ and for linagliptin in excess over placebo, irrespective of causality by system organ class and preferred term

System Organ Class/ Preferred term	Pbo 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 $\geq 2\%$ and for linagliptin in excess over placebo, irrespective of causality by system organ class and preferred term

System Organ Class/ Preferred term	Pbo 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 $\geq 2\%$ and for linagliptin in excess over placebo, irrespective of causality by system organ class and preferred term

System Organ Class/ Preferred term	Pbo 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)
Hypoglycaemia	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 (BI study 1218.20, 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 $\geq 2\%$ 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)

Less common Clinical Trial Adverse Drug Reactions

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®.

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*

*BI assessed ADRs

Abnormal Hematologic and Clinical Chemistry Findings

Changes in laboratory findings were similar in patients treated with TRAJENTA® 5 mg compared to patients treated with placebo. Measured laboratory values to assess the following were evaluated: hematology, electrolytes, liver enzymes, renal function, cholesterol (including bilirubin), and uric acid. Changes in these values, that occurred more frequently, in the TRAJENTA® group and $\geq 1\%$ more than in the placebo group were increases in uric acid (1.3% in the placebo group, 2.7 % in the TRAJENTA® group).

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: pancreatitis

Immune system disorders: angioedema, urticaria, hypersensitivity, mouth ulceration

Skin and subcutaneous tissue disorders: rash

DRUG INTERACTIONS

Overview

The propensity of linagliptin to be involved in clinically meaningful drug-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.

Linagliptin is metabolized by the CYP isozyme CYP 3A4 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 CYP 1A1, 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 also WARNINGS AND PRECAUTIONS, Endocrine and Metabolism and Monitoring and Laboratory Tests).

Drug-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 also WARNINGS AND PRECAUTIONS, Endocrine and Metabolism and Monitoring and Laboratory Tests).

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

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

When TRAJENTA[®] is used in combination with a sulfonylurea alone or plus metformin, patients should be advised to take precautions to avoid hypoglycemia while driving or using machinery.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Recommended Dose and Dosage Adjustment

Adults

The recommended dose is 5 mg once daily. TRAJENTA[®] can be taken with or without a meal.

Renal Impairment

No dose adjustment is required for patients with renal impairment.

Use of TRAJENTA[®] in patients with ESRD and those on dialysis should be with caution.

Hepatic Impairment

No dose adjustment is required for patients with mild and moderate hepatic impairment.

Use of TRAJENTA[®] in patients with severe hepatic insufficiency is not recommended.

Geriatrics (≥ 65 years of age):

No dose adjustment is necessary.

Pediatrics (< 18 years of age):

Safety and effectiveness of TRAJENTA[®] in pediatric patients have not been studied. Therefore TRAJENTA[®] should not be used in this patient population.

Missed Dose

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

OVERDOSAGE

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

Symptoms

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

Therapy

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

Pharmacodynamics

Linagliptin binds selectively to DPP-4 and exhibits a >10,000-fold selectivity vs., 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 7 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-∞} 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-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-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

Pediatric (<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.

Geriatric (≥ 65 years of age): No dose 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 dose 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 dose 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 dose 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 End Stage Renal Disease (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 (ESRD) 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.

Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula:

$$\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{[72 \times \text{serum creatinine (mg/dL)}]} \{ \times 0.85 \text{ for female patients} \}$$

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 $\text{AUC}_{\tau, \text{ss}}$ 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. Use in these patients should be with caution.

Hepatic Impairment:

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

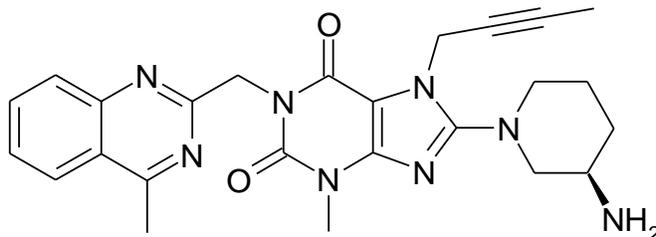
Drug Substance

Common name: linagliptin

Chemical name: 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidiny]-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: $pK_{a1} = 8.6$; $pK_{a2} = 1.9$

Partition Co-efficient: $\text{Log } P = 1.7$ (free base); $\text{Log } D$ (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 8 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, randomised, 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, randomised, double-blind, placebo-controlled in metformin ineligible patients, followed by active-controlled, parallel-group comparison	linagliptin 5 mg or placebo and 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, randomised, 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, randomised, 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, randomised, 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, randomised, double-blind, placebo-controlled	linagliptin 5 mg or placebo Oral, 24 weeks	Total: 1058 Linagliptin: 793 Placebo: 265	58 (23-79)	53/47
Open-label Long-term Extension Study					

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender (% F/M)
1218.40	Open-label extension trial without a control group. Patients who completed one of the 4 pivotal trial (1218.15 ⁺ , 1218.16, 1218.17 or 1218.18)	linagliptin 5 mg Oral, 78 weeks	Total: 2121 Lina “old”*: 1532 Lina “new”: 589 *Lina “old”: patients treated with linagliptin in the preceding trials; Lina “new”: patients treated with placebo in the preceding trials	57.5 (21-80)	48/52

⁺ Indication not approved

Study results

Linagliptin monotherapy (BI Study 1218.16)

The efficacy and safety of linagliptin monotherapy was evaluated in a double blind placebo controlled study of 24 weeks duration. Treatment with once daily linagliptin at 5 mg provided a significant improvement in HbA_{1c}, 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 9). 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 was 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 8). Body weight did not differ significantly between the groups during the placebo controlled 18 weeks.

Table 9 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)	
	5 mg	Placebo	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 A1C <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)	Data not available	Data not available	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)	

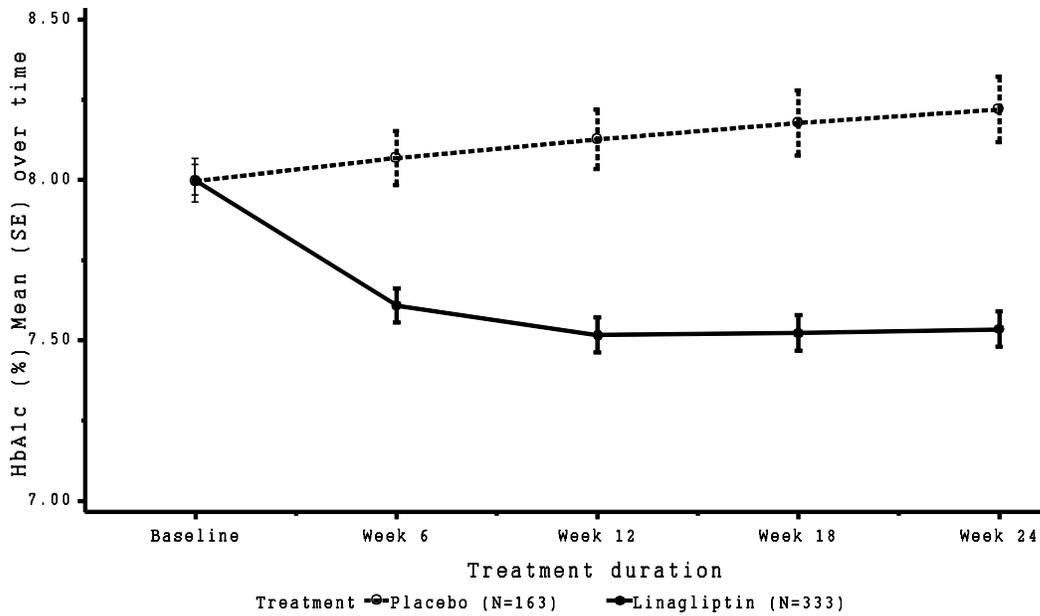


Figure 1 Mean HbA_{1c} (%) over 24 Weeks with TRAJENTA[®] and Placebo in Patients with Type 2 Diabetes (BI Study 1218.16, monotherapy patients)

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

The efficacy and safety of linagliptin in combination with metformin was 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 10). Body weight did not differ significantly between the groups.

Table 10 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)	

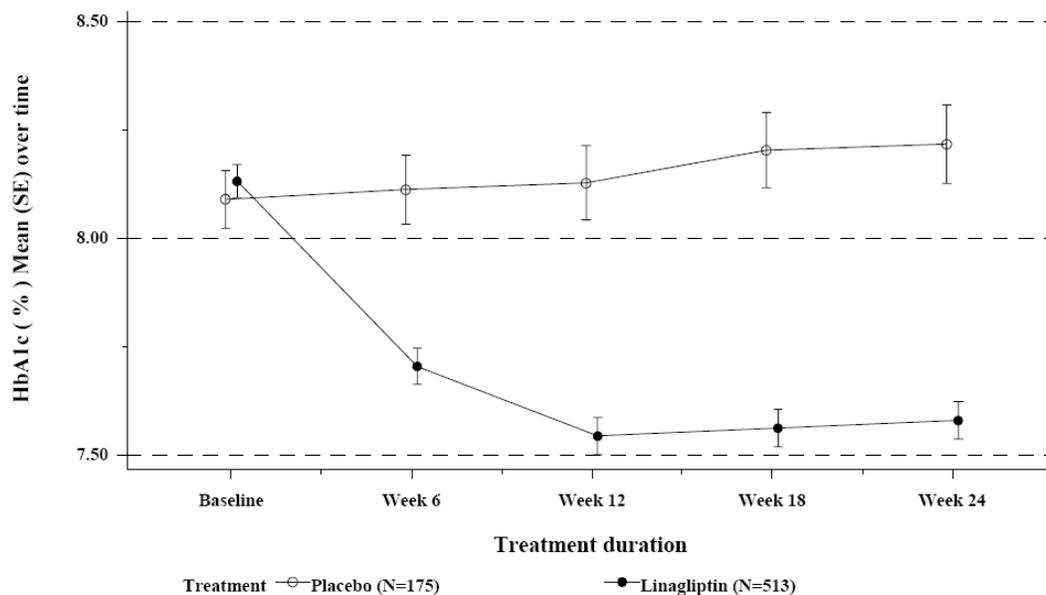


Figure 2 Mean HbA_{1c} (%) over 24 Weeks with TRAJENTA[®]/ Metformin and Placebo/ Metformin in Patients with Type 2 Diabetes (BI study 1218.17, add on to metformin patients)

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

The efficacy and safety of linagliptin in combination with sulfonylurea was 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 11). Body weight did not differ significantly between the groups.

Table 11 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 A1C <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 13). Body weight did not differ significantly between the groups.

Table 12 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 A1C <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 24 month data, 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 (1218.40) 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.

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)

The efficacy and safety of linagliptin was also evaluated in type 2 diabetes patients with severe renal impairment in a double blind study versus placebo 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*. 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 A_{1c} following treatment with linagliptin were sustained up to Week 52.

The reported safety and laboratory results were comparable between linagliptin and placebo except for the adverse events belonging to “renal impairment” which were more frequent in linagliptin (16.2% in linagliptin vs. 6.2% in placebo), but absolute numbers were small. Since severe renal impairment was an inclusion criterion for the study, these adverse events 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.

*not an approved indication

Cardiovascular risk

In a prospective meta-analysis of independently adjudicated cardiovascular events from 19 phase III clinical studies of 12-104 weeks duration (18 placebo-controlled trials of at least 12 weeks in duration, 1 glimepiride-controlled trial of 104 weeks in duration) involving 9297 patients with type 2 diabetes (2675 on placebo, 5847 on linagliptin, 775 on glimepiride), linagliptin treatment was not associated with an increase in cardiovascular risk. A composite endpoint-consisting of: the occurrence or time to first occurrence of CV death, non-fatal myocardial infarction, and non-fatal stroke, was non-significantly lower for linagliptin versus combined active and placebo comparators [Hazard ratio 0.74(95% confidence interval 0.49, 1.14)]. Comparisons of linagliptin with placebo only were not statistically significant [Hazard ratio 1.10 (95% confidence interval 0.61; 2.01)], whereas comparisons of linagliptin with glimepiride were statistically significant (Hazard ratio 0.47; 95% confidence interval 0.23; 0.97).

In the final active-controlled 104 week trial of linagliptin (N=776) versus glimepiride (N=775) as add-on therapies to metformin, the incidence of the composite endpoint of CV death, non-fatal myocardial infarction, and non-fatal stroke was 1.42% for linagliptin and 2.97% for glimepiride.

A prospective meta-analysis of independently adjudicated cardiovascular events from 19 phase III clinical studies of 12-104 weeks in duration (18 placebo-controlled trials of at least 12 weeks in duration, 1 glimepiride-controlled trial of 104 weeks in duration) was performed:

Endpoint	Hazard Ratios (95% Confidence Intervals)		
	Linagliptin (N=5847) vs. Combined Placebo + Glimepiride (N=3450)	Linagliptin (N=5071) vs. Placebo (N=2675)	Linagliptin (N=776) vs. Glimepiride (N=775)
Expanded MACE: <ul style="list-style-type: none"> • CV death • non-fatal myocardial infarction • non-fatal stroke • hospitalization due to unstable angina 	0.78 (0.55, 1.12)	1.09 (0.68, 1.75)	0.45 (0.23, 0.90)
Core MACE: <ul style="list-style-type: none"> • CV death • non-fatal myocardial infarction • non-fatal stroke 	0.74 (0.49, 1.14)	1.10 (0.61, 2.01)	0.47 (0.23, 0.97)

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 incretin 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 F₀ 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

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 are taking insulin because TRAJENTA is not approved for use with insulin;
- you are taking an anti-diabetic medicine known as 'sulfonylurea', your doctor may want to reduce your dose of sulfonylurea when you take it together with TRAJENTA in order to avoid low blood sugar;
- 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 congestive heart failure or any heart problems;
- you have any skin problems;
- you have liver problems.

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

INTERACTIONS WITH THIS MEDICATION

Talk to your doctor or pharmacist about all the medicines you take. This includes prescription and non-prescription medicines, and herbal supplements.

PROPER USE OF THIS MEDICATION**Usual dose:**

The adult dose is one 5 mg tablet, once daily, taken with or without food.

Overdose:

In case of drug overdose, contact a health care practitioner, 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. However, if it is nearly time for the next dose, skip the missed dose.
- Do not take a double dose to make up for a forgotten dose. Never take two doses on the same day.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, TRAJENTA can cause side effects. Side effects with TRAJENTA include:

Very Common:

- Low blood sugar (hypoglycemia) when taken with a sulfonylurea. You should stop taking TRAJENTA and see your doctor immediately if you experience symptoms of low blood sugar such as trembling, sweating, anxiety, blurred vision, tingling lips, paleness, mood change, vagueness or confusion.

Uncommon:

- Cough
- Inflamed nose or throat (nasopharyngitis)
- High blood triglyceride
- Severe allergic reaction (hypersensitivity)
- Swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema)
- Hives or nettle rash (urticaria)

Rare:

- Inflammation of pancreas (pancreatitis)
- Rash
- Mouth ulceration

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

This is not a complete list of side effects. For any unexpected effects while taking TRAJENTA, contact your doctor or pharmacist.

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
Uncommon	Allergic reactions including such symptoms as hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing (angioedema, urticaria), and wheezing and shortness of breath (bronchial hyperreactivity)		√	√
Rare	Pancreatitis: symptoms of pancreatitis (prolonged severe abdominal pain which may be accompanied by vomiting)		√	√

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 (when used with a sulfonylurea)		√	√

HOW TO STORE IT

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

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.boehringer-ingenelheim.ca> or by contacting the sponsor, Boehringer Ingelheim (Canada) Ltd., at: 1-800-263-5103, ext. 84633 (Medical Information).

Please check our website to see if more up-to-date information has been posted.

This leaflet was prepared by Boehringer Ingelheim (Canada) Ltd.

Last revised: May 14, 2015

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Co-promoted with:
Eli Lilly Canada Inc.
Toronto, ON, Canada M1N 2E8