

TRADJENTA- linagliptin tablet, film coated
Praxis, LLC

TRADJENTA[®] (linagliptin tablets), for oral use

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited data with TRADJENTA use in pregnant women are not sufficient to inform of drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see *Clinical Considerations*].

In animal reproduction studies, no adverse developmental effects were observed when linagliptin was administered to pregnant rats during the period of organogenesis at doses similar to the maximum recommended clinical dose, based on exposure [see *Data*].

The estimated background risk of major birth defects is 6% to 10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20% to 25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

No adverse developmental outcome was observed when linagliptin was administered to pregnant Wistar Han rats and Himalayan rabbits during the period of organogenesis at doses up to 240 mg/kg/day and 150 mg/kg/day, respectively. These doses represent approximately 943-times (rats) and 1,943-times (rabbits) the 5 mg maximum clinical dose, based on exposure. No adverse functional, behavioral, or reproductive outcome was observed in offspring following administration of linagliptin to Wistar Han rats from gestation day 6 to lactation day 21 at a dose 49-times the maximum recommended human dose, based on exposure.

Linagliptin crosses the placenta into the fetus following oral dosing in pregnant rats and rabbits.

8.2 Lactation

Risk Summary

There is no information regarding the presence of linagliptin in human milk, the effects on the breastfed infant, or the effects on milk production. However, linagliptin is present in rat milk. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADJENTA and any potential adverse effects on the breastfed child from TRADJENTA or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of TRADJENTA have not been established in pediatric patients.

Effectiveness of TRADJENTA was not demonstrated in a 26-week randomized, double-blind, placebo-controlled trial (NCT03429543) in 157 pediatric patients aged 10 to 17 years with inadequately controlled type 2 diabetes mellitus.

8.5 Geriatric Use

In linagliptin studies, 1,085 linagliptin-treated patients were 65 years of age and older and 131 patients were 75 years of age and older. In these linagliptin studies, no overall differences in safety or effectiveness of linagliptin were observed between geriatric patients and younger adult patients.

8.6 Renal Impairment

No dosage adjustment is recommended for patients with renal impairment [see *Clinical Pharmacology* (12.3)].

In the TRADJENTA treatment arm of the CARMELINA trial [see *Clinical Studies* (14)] , 2,200 (63%) patients had renal impairment (eGFR <60 mL/min/1.73 m²). Approximately 20% of the population had eGFR ≥45 to <60 mL/min/1.73 m², 28% of the population had eGFR ≥30 to <45 mL/min/1.73 m² and 15% had eGFR <30 mL/min/1.73 m². The overall incidence of adverse reactions were generally similar between the TRADJENTA and placebo treatment arms.

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with hepatic impairment [see *Clinical Pharmacology* (12.3)] .

10 OVERDOSAGE

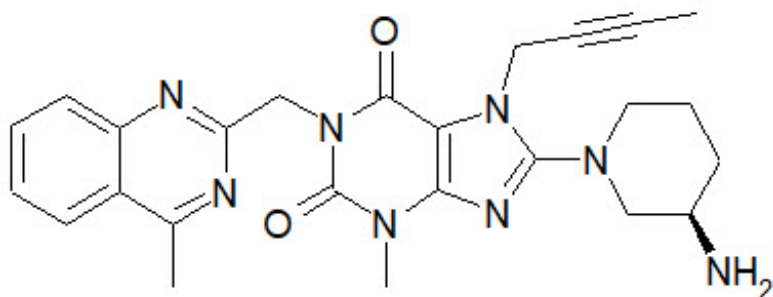
In the event of an overdose with TRADJENTA, consider contacting the Poison Help Line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations. Removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely.

11 DESCRIPTION

TRADJENTA tablets for oral use contain linagliptin, an inhibitor of the DPP-4 enzyme.

The chemical name of linagliptin is 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]-

The molecular formula is C₂₅H₂₈N₈O₂ and the molecular weight is 472.54 g/mol. The structural formula is:



Linagliptin is a white to yellowish, not or only slightly hygroscopic solid substance. It is very slightly soluble in water (0.9 mg/mL). Linagliptin is soluble in methanol (ca. 60 mg/mL), sparingly soluble in ethanol (ca. 10 mg/mL), very slightly soluble in isopropanol (<1 mg/mL), and very slightly soluble in acetone (ca. 1 mg/mL).

Each film-coated tablet of TRADJENTA contains 5 mg of linagliptin free base and the following inactive ingredients: copovidone, corn starch, magnesium stearate, mannitol, and pregelatinized starch. In addition, the film coating contains the following inactive ingredients: hypromellose, polyethylene glycol, red ferric oxide, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP). Thus, linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore, GLP-1 also reduces glucagon secretion from pancreatic alpha-cells, resulting in a reduction in hepatic glucose output.

12.2 Pharmacodynamics

Linagliptin binds to DPP-4 in a reversible manner and thus increases the concentrations of incretin hormones. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion, thus resulting in better regulation of glucose homeostasis. Linagliptin binds selectively to DPP-4 and selectively inhibits DPP-4, but not DPP-8 or DPP-9 activity *in vitro* at concentrations approximating therapeutic exposures.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, 4-way crossover study, 36 healthy subjects were administered a single oral dose of linagliptin 5 mg, linagliptin 100

mg (20 times the recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either the recommended dose of 5 mg or the 100 mg dose. At the 100 mg dose, peak linagliptin plasma concentrations were approximately 38-fold higher than the peak concentrations following a 5 mg dose.

12.3 Pharmacokinetics

The pharmacokinetics of linagliptin has been characterized in healthy subjects and patients with type 2 diabetes mellitus. After oral administration of a single 5 mg dose to healthy subjects, peak plasma concentrations of linagliptin occurred at approximately 1.5 hours post dose (T_{max}); the mean plasma area under the curve (AUC) was 139 nmol*h/L and maximum concentration (C_{max}) was 8.9 nmol/L.

Plasma concentrations of linagliptin decline in at least a biphasic manner with a long terminal half-life (>100 hours), related to the saturable binding of linagliptin to DPP-4. The prolonged elimination phase does not contribute to the accumulation of the drug. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of linagliptin 5 mg, is approximately 12 hours. After once-daily dosing, steady-state plasma concentrations of linagliptin 5 mg are reached by the third dose, and C_{max} and AUC increased by a factor of 1.3 at steady-state compared with the first dose. The intra-subject and inter-subject coefficients of variation for linagliptin AUC were small (12.6% and 28.5%, respectively). Plasma AUC of linagliptin increased in a less than dose-proportional manner in the dose range of 1 to 10 mg. The pharmacokinetics of linagliptin is similar in healthy subjects and in patients with type 2 diabetes mellitus.

Absorption

The absolute bioavailability of linagliptin is approximately 30%. A high-fat meal reduced C_{max} by 15% and increased AUC by 4%; this effect is not clinically relevant. TRADJENTA may be administered with or without food.

Distribution

The mean apparent volume of distribution at steady-state following a single intravenous dose of linagliptin 5 mg to healthy subjects is approximately 1,110 L, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99% at 1 nmol/L to 75%-89% at ≥ 30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70% to 80% of linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment.

Elimination

Linagliptin has a terminal half-life of about 200 hours at steady-state, though the accumulation half-life is about 11 hours. Renal clearance at steady-state was approximately 70 mL/min.

Metabolism

Following oral administration, the majority (about 90%) of linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway. 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 administration of an oral [^{14}C]-linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated via the enterohepatic system (80%) or urine (5%) within 4 days of dosing.

Specific Populations

Patients with Renal Impairment

An open-label pharmacokinetic study evaluated the pharmacokinetics of linagliptin 5 mg in male and female patients with varying degrees of chronic renal impairment. The study included 6 healthy subjects with normal renal function (creatinine clearance [CrCl] ≥ 80 mL/min), 6 patients with mild renal impairment (CrCl 50 to <80 mL/min), 6 patients with moderate renal impairment (CrCl 30 to <50 mL/min), 10 patients with type 2 diabetes mellitus and severe renal impairment (CrCl <30 mL/min), and 11 patients with type 2 diabetes mellitus and normal renal function. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula.

Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects.

In patients with moderate renal impairment under steady-state conditions, mean exposure of linagliptin increased ($\text{AUC}_{\tau,ss}$ by 71% and C_{\max} by 46%) compared with healthy subjects. This increase was not associated with a prolonged accumulation half-life, terminal half-life, or an increased accumulation factor. Renal excretion of linagliptin was below 5% of the administered dose and was not affected by decreased renal function.

Patients with type 2 diabetes mellitus and severe renal impairment showed steady-state exposure approximately 40% higher than that of patients with type 2 diabetes mellitus and normal renal function (increase in $\text{AUC}_{\tau,ss}$ by 42% and C_{\max} by 35%). For both type 2 diabetes mellitus groups, renal excretion was below 7% of the administered dose.

These findings were further supported by the results of population pharmacokinetic analyses.

Patients with Hepatic Impairment

In patients with mild hepatic impairment (Child-Pugh class A), steady-state exposure ($\text{AUC}_{\tau,ss}$) of linagliptin was approximately 25% lower and $C_{\max,ss}$ was approximately 36% lower than in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh class B), AUC_{ss} of linagliptin was about 14% lower and $C_{\max,ss}$ was approximately 8% lower than in healthy subjects. Patients with severe hepatic impairment (Child-Pugh class C) had comparable exposure of linagliptin in terms of AUC_{0-24} and approximately 23% lower C_{\max} compared with healthy subjects. Reductions in the pharmacokinetic parameters seen in patients with hepatic impairment did not result in reductions in DPP-4 inhibition.

Effects of Age, Body Mass Index (BMI), Gender, and Race

Based on the population pharmacokinetic analysis, age, BMI, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of linagliptin [see *Use in Specific Populations* (8.5)] .

Drug Interaction Studies

In vitro Assessment of Drug Interactions

Linagliptin is a weak to moderate inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes and is not an inducer of CYP isozymes, including CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 4A11.

Linagliptin is a P-glycoprotein (P-gp) substrate, and inhibits P-gp mediated transport of digoxin at high concentrations. Based on these results and *in vivo* drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates at therapeutic concentrations.

In vivo Assessment of Drug Interactions

Strong inducers of CYP3A4 or P-gp (e.g., rifampin) decrease exposure to linagliptin to subtherapeutic and likely ineffective concentrations [see *Drug Interactions* (7)]. *In vivo* studies indicated evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp and organic cationic transporter (OCT).

Table 3 describes the effect of coadministered drugs on systemic exposure of linagliptin.

Table 3 Effect of Coadministered Drugs on Systemic Exposure of Linagliptin

Coadministered Drug	Dosing of Coadministered Drug*	Dosing of Linagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.0	
			AUC †	C _{max}
Metformin	850 mg TID	10 mg QD	1.20	1.03
Glyburide	1.75 mg #	5 mg QD	1.02	1.01
Pioglitazone	45 mg QD	10 mg QD	1.13	1.07
Ritonavir	200 mg BID	5 mg #	2.01	2.96
Rifampin**	600 mg QD	5 mg QD	0.60	0.56

*Multiple dose (steady-state) unless otherwise noted

**For information regarding clinical recommendations [see *Drug Interactions* (7.1)].

#Single dose

†AUC = AUC(0 to 24 hours) for single-dose treatments and AUC = AUC(TAU) for multiple-dose treatments

QD = once daily

BID = twice daily

TID = three times daily

Table 4 describes the effect of linagliptin on systemic exposure of coadministered drugs.

Table 4 Effect of Linagliptin on Systemic Exposure of Coadministered Drugs

Coadministered Drug	Dosing of Coadministered Drug*	Dosing of Linagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.0	
			AUC †	C _{max}

				AUC †	C_{max}
Metformin	850 mg TID	10 mg QD	metformin	1.01	0.89
Glyburide	1.75 mg #	5 mg QD	glyburide	0.86	0.86
Pioglitazone	45 mg QD	10 mg QD	pioglitazone	0.94	0.86
			metabolite M-III	0.98	0.96
			metabolite M-IV	1.04	1.05
Digoxin	0.25 mg QD	5 mg QD	digoxin	1.02	0.94
Simvastatin	40 mg QD	10 mg QD	simvastatin	1.34	1.10
			simvastatin acid	1.33	1.21
Warfarin	10 mg #	5 mg QD	R-warfarin	0.99	1.00
			S-warfarin	1.03	1.01
			INR	0.93**	1.04**
			PT	1.03**	1.15**
Ethinylestradiol and levonorgestrel	ethinylestradiol 0.03 mg and levonorgestrel 0.150 mg QD	5 mg QD	ethinylestradiol	1.01	1.08
			levonorgestrel	1.09	1.13

*Multiple dose (steady-state) unless otherwise noted

#Single dose

†AUC=AUC(INF) for single-dose treatments and AUC = AUC(TAU) for multiple-dose treatments

**AUC=AUC(0-168) and C_{max}=E_{max} for pharmacodynamic end points

INR = International Normalized Ratio

PT = Prothrombin Time

QD = once daily

TID = three times daily

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Linagliptin did not increase the incidence of tumors in male and female rats in a 2-year study at doses of 6, 18, and 60 mg/kg. The highest dose of 60 mg/kg is approximately 418 times the clinical dose of 5 mg/day based on AUC exposure. Linagliptin did not increase the incidence of tumors in mice in a 2-year study at doses up to 80 mg/kg (males) and 25 mg/kg (females), or approximately 35- and 270-times the clinical dose based on AUC exposure. Higher doses of linagliptin in female mice (80 mg/kg) increased the incidence of lymphoma at approximately 215-times the clinical dose based on AUC exposure.

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

In fertility studies in rats, linagliptin had no adverse effects on early embryonic development, mating, fertility, or bearing live young up to the highest dose of 240 mg/kg (approximately 943-times the clinical dose based on AUC exposure).

14 CLINICAL STUDIES

14.1 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus

TRADJENTA has been studied as monotherapy and in combination with metformin, sulfonylurea, pioglitazone, and insulin. TRADJENTA has also been studied in patients with type 2 diabetes mellitus and severe chronic renal impairment.

In patients with type 2 diabetes mellitus, treatment with TRADJENTA produced clinically significant improvements in hemoglobin A1c (A1C), fasting plasma glucose (FPG), and 2-hour post-prandial glucose (PPG) compared with placebo.

Monotherapy

A total of 730 patients with type 2 diabetes mellitus participated in 2 double-blind, placebo-controlled studies, one of 18 weeks' and another of 24 weeks' duration, to evaluate the efficacy and safety of TRADJENTA monotherapy. In both monotherapy studies, patients currently on an antihyperglycemic agent discontinued the agent and underwent a diet, exercise, and drug washout period of about 6 weeks that included an open-label placebo run-in during the last 2 weeks. Patients with inadequate glycemic control (A1C 7% to 10%) after the washout period were randomized; patients not currently on antihyperglycemic agents (off therapy for at least 8 weeks) with inadequate glycemic control (A1C 7% to 10%) were randomized after completing the 2-week, open-label, placebo run-in period. In the 18-week trial, only patients ineligible for metformin were recruited. In the 18-week trial, 76 patients were randomized to placebo and 151 to TRADJENTA 5 mg; in the 24-week trial, 167 patients were randomized to placebo and 336 to TRADJENTA 5 mg. Patients who failed to meet specific glycemic goals during the 18-week trial received rescue therapy with pioglitazone and/or insulin; metformin rescue therapy was used in the 24-week trial.

Treatment with TRADJENTA 5 mg daily provided statistically significant improvements in A1C, FPG, and 2-hour PPG compared with placebo (Table 5). In the 18-week trial, 12% of patients receiving TRADJENTA 5 mg and 18% who received placebo required rescue therapy. In the 24-week trial, 10.2% of patients receiving TRADJENTA 5 mg and 20.9% of patients receiving placebo required rescue therapy. The improvement in A1C compared with placebo was not affected by gender, age, race, prior antihyperglycemic therapy, baseline BMI, or a standard index of insulin resistance (HOMA-IR). As is typical for trials of agents to treat type 2 diabetes mellitus, the mean reduction in A1C with TRADJENTA appears to be related to the degree of A1C elevation at baseline. In these 18- and 24-week studies, the changes from baseline in A1C were -0.4% and -0.4%, respectively, for those given TRADJENTA, and 0.1% and 0.3%, respectively, for those given placebo. Change from baseline in body weight did not differ significantly between the groups.

Table 5 Glycemic Parameters in Placebo-Controlled Monotherapy Trials of TRADJENTA*

	18-Week Trial		24-Week Trial	
	TRADJENTA 5 mg	Placebo	TRADJENTA 5 mg	Placebo
A1C (%)				
Number of patients	n = 147	n = 73	n = 333	n = 163
Baseline (mean)	8.1	8.1	8.0	8.0

Change from baseline (adjusted mean***)	-0.4	0.1	-0.4	0.3
Difference from placebo (adjusted mean) (95% CI)	-0.6 (-0.9, -0.3)	--	-0.7 (-0.9, -0.5)	--
Patients [n (%)] achieving A1C <7%**	32 (23.5)	8 (11.8)	77 (25)	17 (12)
FPG (mg/dL)				
Number of patients	n = 138	n = 66	n = 318	n = 149
Baseline (mean)	178	176	164	166
Change from baseline (adjusted mean***)	-13	7	-9	15
Difference from placebo (adjusted mean) (95% CI)	-21 (-31, -10)	--	-23 (-30, -16)	--
2-hour PPG (mg/dL)				
Number of patients	Data not available	Data not available	n = 67	n = 24
Baseline (mean)	--	--	258	244
Change from baseline (adjusted mean***)	--	--	-34	25
Difference from placebo (adjusted mean) (95% CI)	--	--	-58 (-82, -34)	--

*Full analysis population using last observation on trial

**18-week trial: Placebo, n=68; TRADJENTA, n=136

24-week trial: Placebo, n=147; TRADJENTA, n=306

***18-week trial. HbA1c: ANCOVA model included treatment, reason for metformin intolerance and number of prior oral anti-diabetic medicine(s) (OADs) as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment, reason for metformin intolerance and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates. 24-week trial. HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates. PPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline postprandial glucose after two hours as covariate.

Add-on Combination Therapy with Metformin

A total of 701 patients with type 2 diabetes mellitus participated in a 24-week, randomized, double-blind, placebo-controlled trial designed to assess the efficacy of TRADJENTA in combination with metformin. Patients already on metformin (n = 491) at a dosage of at least 1,500 mg per day were randomized after completing a 2-week, open-label, placebo run-in period. Patients on metformin and another antihyperglycemic agent (n = 207) were randomized after a run-in period of approximately 6 weeks on metformin (at a dosage of at least 1,500 mg per day) in monotherapy. Patients were randomized to the addition of either TRADJENTA 5 mg or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with glimepiride rescue.

In combination with metformin, TRADJENTA provided statistically significant improvements in A1C, FPG, and 2-hour PPG compared with placebo (Table 6). Rescue glycemic therapy was used in 7.8% of patients treated with TRADJENTA 5 mg and in 18.9% of patients treated with placebo. A similar decrease in body weight was observed for both treatment groups.

Table 6 Glycemic Parameters in Placebo-Controlled Trial for TRADJENTA in Combination with Metformin*

	TRADJENTA 5 mg + Metformin	Placebo + Metformin
A1C (%)		
Number of patients	n = 513	n = 175
Baseline (mean)	8.1	8.0
Change from baseline (adjusted mean***)	-0.5	0.15
Difference from placebo + metformin (adjusted mean) (95% CI)	-0.6 (-0.8, -0.5)	--
Patients [n (%)] achieving A1C <7%**	127 (26.2)	15 (9.2)
FPG (mg/dL)		
Number of patients	n = 495	n = 159
Baseline (mean)	169	164
Change from baseline (adjusted mean***)	-11	11
Difference from placebo + metformin (adjusted mean) (95% CI)	-21 (-27, -15)	--
2-hour PPG (mg/dL)		
Number of patients	n = 78	n = 21
Baseline (mean)	270	274
Change from baseline (adjusted mean***)	-49	18
Difference from placebo + metformin (adjusted mean) (95% CI)	-67 (-95, -40)	--

*Full analysis population using last observation on trial

**TRADJENTA 5 mg + Metformin, n=485; Placebo + Metformin, n=163

***HbA1c: ANCOVA model included treatment and number of prior oral OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates. PPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline postprandial glucose after two hours as covariate.

A total of 791 patients with type 2 diabetes mellitus and inadequate glycemic control on diet and exercise participated in the 24-week, randomized, double-blind, portion of this placebo-controlled factorial trial designed to assess the efficacy of TRADJENTA as initial therapy with metformin. Patients on an antihyperglycemic agent (52%) underwent a drug washout period of 4 weeks' duration. After the washout period and after completing a 2-week single-blind placebo run-in period, patients with inadequate glycemic control ($A1C \geq 7.0\%$ to $\leq 10.5\%$) were randomized. Patients with inadequate glycemic control ($A1C \geq 7.5\%$ to $< 11.0\%$) not on antihyperglycemic agents at trial entry (48%) immediately entered the 2-week, single-blind, placebo run-in period and then were randomized. Randomization was stratified by baseline $A1C$ ($< 8.5\%$ vs $\geq 8.5\%$) and use of a prior oral antidiabetic drug (none vs monotherapy). Patients were randomized in a 1:2:2:2:2 ratio to either placebo or one of 5 active-treatment arms. Approximately equal numbers of patients were randomized to receive initial therapy with 5 mg of TRADJENTA once daily, 500 mg or 1,000 mg of metformin twice daily, or 2.5 mg of linagliptin twice daily in combination with 500 mg or 1,000 mg of metformin twice daily. Patients who failed to meet specific glycemic goals during the trial were treated with sulfonylurea, thiazolidinedione, or insulin rescue therapy.

Initial therapy with the combination of linagliptin and metformin provided significant improvements in $A1C$ and fasting plasma glucose (FPG) compared to placebo, to metformin alone, and to linagliptin alone (Table 7).

The adjusted mean treatment difference in $A1C$ from baseline to week 24 (LOCF) was -0.5% (95% CI -0.7, -0.3; $p < 0.0001$) for linagliptin 2.5 mg/metformin 1,000 mg twice daily compared to metformin 1,000 mg twice daily; -1.1% (95% CI -1.4, -0.9; $p < 0.0001$) for linagliptin 2.5 mg/metformin 1,000 mg twice daily compared to TRADJENTA 5 mg once daily; -0.6% (95% CI -0.8, -0.4; $p < 0.0001$) for linagliptin 2.5 mg/metformin 500 mg twice daily compared to metformin 500 mg twice daily; and -0.8% (95% CI -1.0, -0.6; $p < 0.0001$) for linagliptin 2.5 mg/metformin 500 mg twice daily compared to TRADJENTA 5 mg once daily.

Lipid effects were generally neutral. No meaningful change in body weight was noted in any of the 6 treatment groups.

Table 7 Glycemic Parameters at Final Visit (24-Week Trial) for Linagliptin and Metformin, Alone and in Combination in Randomized Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Diet and Exercise**

	Placebo	TRADJENTA 5 mg Once Daily*	Metformin 500 mg Twice Daily	Linagliptin 2.5 mg Twice Daily* + Metformin 500 mg Twice Daily	Metformin 1,000 mg Twice Daily	Linagliptin 2.5 mg Twice Daily* + Metformin 1,000 mg Twice Daily
A1C (%)						
Number of patients	n = 65	n = 135	n = 141	n = 137	n = 138	n = 140
Baseline (mean)	8.7	8.7	8.7	8.7	8.5	8.7

Change from baseline (adjusted mean****)	0.1	-0.5	-0.6	-1.2	-1.1	-1.6
Difference from placebo (adjusted mean) (95% CI)	--	-0.6 (-0.9, -0.3)	-0.8 (-1.0, -0.5)	-1.3 (-1.6, -1.1)	-1.2 (-1.5, -0.9)	-1.7 (-2.0, -1.4)
Patients [n (%)] achieving A1C <7%***	7 (10.8)	14 (10.4)	26 (18.6)	41 (30.1)	42 (30.7)	74 (53.6)
Patients (%) receiving rescue medication	29.2	11.1	13.5	7.3	8.0	4.3
FPG (mg/dL)						
Number of patients	n = 61	n = 134	n = 136	n = 135	n = 132	n = 136
Baseline (mean)	203	195	191	199	191	196
Change from baseline (adjusted mean****)	10	-9	-16	-33	-32	-49
Difference from placebo (adjusted mean) (95% CI)	--	-19 (-31, -6)	-26 (-38, -14)	-43 (-56, -31)	-42 (-55, -30)	-60 (-72, -47)

*Total daily dosage of TRADJENTA is equal to 5 mg

**Full analysis population using last observation on trial

***Metformin 500 mg twice daily, n=140; Linagliptin 2.5 mg twice daily + Metformin 500 mg twice daily, n=136; Metformin 1,000 mg twice daily, n=137; Linagliptin 2.5 mg twice daily + Metformin 1,000 mg twice daily, n=138

****HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

Active-Controlled Trial vs Glimepiride in Combination with Metformin

The efficacy of TRADJENTA was evaluated in a 104-week, double-blind, glimepiride-controlled, non-inferiority trial in patients with type 2 diabetes mellitus with insufficient glycemic control despite metformin therapy. Patients being treated with metformin only entered a run-in period of 2 weeks' duration, whereas patients pretreated with metformin and one additional antihyperglycemic agent entered a run-in treatment period of 6 weeks' duration with metformin monotherapy (dosage of $\geq 1,500$ mg/day) and washout of the other agent. After an additional 2-week placebo run-in period, those with inadequate glycemic control (A1C 6.5% to 10%) were randomized 1:1 to the addition of TRADJENTA 5 mg once daily or glimepiride. Randomization was stratified by baseline HbA1c (<8.5% vs $\geq 8.5\%$), and the previous use of antidiabetic drugs (metformin alone vs metformin plus one other OAD). Patients receiving glimepiride were given an initial dosage of 1 mg/day and then electively titrated over the next 12 weeks to a maximum dosage of 4 mg/day as needed to optimize glycemic control. Thereafter, the glimepiride dosage was to be kept constant, except for down-titration to prevent hypoglycemia.

After 52 and 104 weeks, TRADJENTA and glimepiride both had reductions from baseline in A1C (52 weeks: -0.4% for TRADJENTA, -0.6% for glimepiride; 104 weeks: -0.2% for TRADJENTA, -0.4% for glimepiride) from a baseline mean of 7.7% (Table 8). The mean difference between groups in A1C change from baseline was 0.2% with 2-sided 97.5% confidence interval (0.1%, 0.3%) for the intent-to-treat population using last observation carried forward. These results were consistent with the completers analysis.

Table 8 Glycemic Parameters at 52 and 104 Weeks in Trial Comparing TRADJENTA to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin**

	Week 52		Week 104	
	TRADJENTA 5 mg + Metformin	Glimepiride + Metformin (mean Glimepiride dosage 3 mg)	TRADJENTA 5 mg + Metformin	Glimepiride + Metformin (mean Glimepiride dosage 3 mg)
A1C (%)				
Number of patients	n = 764	n = 755	n = 764	n = 755
Baseline (mean)	7.7	7.7	7.7	7.7
Change from baseline (adjusted mean****)	-0.4	-0.6	-0.2	-0.4
Difference from glimepiride (adjusted mean) (97.5% CI)	0.2 (0.1, 0.3)	--	0.2 (0.1, 0.3)	--
FPG (mg/dL)				
Number of patients	n = 733	n = 725	n = 733	n = 725
Baseline (mean)	164	166	164	166
Change from baseline (adjusted mean****)	-8*	-15	-2 †	-9
Hypoglycemia incidence (%)***				
Number of patients	n = 776	n = 775	n = 776	n = 775
Incidence****	5.3*	31.1	7.5*	36.1

*p<0.0001 vs glimepiride; †p=0.0012 vs glimepiride

**Full analysis population using last observation on trial

***Hypoglycemic incidence included both asymptomatic events (not accompanied by typical symptoms and plasma glucose concentration of ≤70 mg/dL) and symptomatic events with typical symptoms of hypoglycemia and plasma glucose concentration of ≤70 mg/dL.

****HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates. Hypoglycemia incidence (%): Cochran-Mantel-Haenszel test was performed on the patient population contained in the treated set, to compare the proportion of patients with hypoglycemic events between patients treated with linagliptin and patients treated with glimepiride.

Patients treated with linagliptin had a mean baseline body weight of 86 kg and were observed to have an adjusted mean decrease in body weight of 1.1 kg at 52 weeks and 1.4 kg at 104 weeks. Patients on glimepiride had a mean baseline body weight of 87 kg and were observed to have an adjusted mean increase from baseline in body weight of 1.4 kg at 52 weeks and 1.3 kg at 104 weeks (treatment difference $p < 0.0001$ for both timepoints).

Add-On Combination Therapy with Pioglitazone

A total of 389 patients with type 2 diabetes mellitus participated in a 24-week, randomized, double-blind, placebo-controlled trial designed to assess the efficacy of TRADJENTA in combination with pioglitazone. Therapy was stopped in patients on oral antihyperglycemic therapy for a period of 6 weeks (4 weeks followed by a 2-week, open-label, placebo run-in period). Drug-naïve patients entered directly into the 2-week placebo run-in period. After the run-in period, patients were randomized to receive either TRADJENTA 5 mg or placebo, both in addition to pioglitazone 30 mg daily. Patients who failed to meet specific glycemic goals during the studies were treated with metformin rescue. Glycemic endpoints measured were A1C and FPG.

In initial combination with pioglitazone 30 mg, TRADJENTA 5 mg provided statistically significant improvements in A1C and FPG compared to placebo with pioglitazone (Table 9). Rescue therapy was used in 7.9% of patients treated with TRADJENTA 5 mg/pioglitazone 30 mg and 14.1% of patients treated with placebo/pioglitazone 30 mg. Patient weight increased in both groups during the trial with an adjusted mean change from baseline of 2.3 kg and 1.2 kg in the TRADJENTA 5 mg/pioglitazone 30 mg and placebo/pioglitazone 30 mg groups, respectively ($p = 0.0141$).

Table 9 Glycemic Parameters in Placebo-Controlled Trial for TRADJENTA in Combination Therapy with Pioglitazone*

	TRADJENTA 5 mg + Pioglitazone	Placebo + Pioglitazone
A1C (%)		
Number of patients	n = 252	n = 128
Baseline (mean)	8.6	8.6
Change from baseline (adjusted mean**)	-1.1	-0.6
Difference from placebo + pioglitazone (adjusted mean) (95% CI)	-0.5 (-0.7, -0.3)	--
Patients [n (%)] achieving A1C <7%	108 (42.9)	39 (30.5)
FPG (mg/dL)		
Number of patients	n = 243	n = 122
Baseline (mean)	188	186
Change from baseline (adjusted mean**)	-33	-18
Difference from placebo + pioglitazone (adjusted mean) (95% CI)	-14 (-21, -7)	--

*Full analysis population using last observation on trial

**HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG:

ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

Add-On Combination with Sulfonylureas

A total of 245 patients with type 2 diabetes mellitus participated in an 18-week, randomized, double-blind, placebo-controlled trial designed to assess the efficacy of TRADJENTA in combination with sulfonylurea (SU). Patients on sulfonylurea monotherapy (n = 142) were randomized after completing a 2-week, single-blind, placebo run-in period. Patients on a sulfonylurea plus one additional oral antihyperglycemic agent (n = 103) were randomized after a wash-out period of 4 weeks and a 2-week, single-blind, placebo run-in period. Patients were randomized to the addition of TRADJENTA 5 mg or to placebo, each administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with metformin rescue. Glycemic endpoints measured included A1C and FPG.

In combination with a sulfonylurea, TRADJENTA provided statistically significant improvements in A1C compared with placebo following 18 weeks' treatment; the improvements in FPG observed with TRADJENTA were not statistically significant compared with placebo (Table 10). Rescue therapy was used in 7.6% of patients treated with TRADJENTA 5 mg and 15.9% of patients treated with placebo. There was no significant difference between TRADJENTA and placebo in body weight.

Table 10 Glycemic Parameters in Placebo-Controlled Trial for TRADJENTA in Combination with Sulfonylurea*

	TRADJENTA 5 mg + SU	Placebo + SU
A1C (%)		
Number of patients	n = 158	n = 82
Baseline (mean)	8.6	8.6
Change from baseline (adjusted mean***)	-0.5	-0.1
Difference from placebo + SU (adjusted mean) (95% CI)	-0.5 (-0.7, -0.2)	--
Patients [n (%)] achieving A1C <7%**	23 (14.7)	3 (3.7)
FPG (mg/dL)		
Number of patients	n = 155	n = 78
Baseline (mean)	180	171
Change from baseline (adjusted mean***)	-8	-2
Difference from placebo + SU (adjusted mean) (95% CI)	-6 (-17, 4)	--

SU = sulfonylurea

*Full analysis population using last observation on trial

**TRADJENTA 5 mg + SU, n=156; Placebo + SU, n=82

***HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects,

as well as baseline HbA1c and baseline FPG as continuous covariates

Add-On Combination Therapy with Metformin and a Sulfonylurea

A total of 1,058 patients with type 2 diabetes mellitus participated in a 24-week, randomized, double-blind, placebo-controlled trial designed to assess the efficacy of TRADJENTA in combination with a sulfonylurea and metformin. The most common sulfonylureas used by patients in the trial were: glimepiride (31%), glibenclamide (26%), and gliclazide (26%, not available in the United States). Patients on a sulfonylurea and metformin were randomized to receive TRADJENTA 5 mg or placebo, each administered once daily. Patients who failed to meet specific glycemic goals during the trial were treated with pioglitazone rescue. Glycemic endpoints measured included A1C and FPG.

In combination with a sulfonylurea and metformin, TRADJENTA provided statistically significant improvements in A1C and FPG compared with placebo (Table 11). In the entire trial population (patients on TRADJENTA in combination with sulfonylurea and metformin), a mean reduction from baseline relative to placebo in A1C of -0.6% and in FPG of -13 mg/dL was seen. Rescue therapy was used in 5.4% of patients treated with TRADJENTA 5 mg and in 13% of patients treated with placebo. Change from baseline in body weight did not differ significantly between the groups.

Table 11 Glycemic Parameters in Placebo-Controlled Trial for TRADJENTA in Combination with Metformin and Sulfonylurea*

	TRADJENTA 5 mg + Metformin + SU	Placebo + Metformin + SU
A1C (%)		
Number of patients	n = 778	n = 262
Baseline (mean)	8.2	8.1
Change from baseline (adjusted mean***)	-0.7	-0.1
Difference from placebo (adjusted mean) (95% CI)	-0.6 (-0.7, -0.5)	--
Patients [n (%)] achieving A1C <7%**	217 (29.2)	20 (8.1)
FPG (mg/dL)		
Number of patients	n = 739	n = 248
Baseline (mean)	159	163
Change from baseline (adjusted mean***)	-5	8
Difference from placebo (adjusted mean) (95% CI)	-13 (-18, -7)	--

SU = sulfonylurea

*Full analysis population using last observation on trial

**TRADJENTA 5 mg + Metformin + SU, n=742; Placebo + Metformin + SU, n=247

***HbA1c: ANCOVA model included treatment as class-effects and baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment as class-effects, as well as baseline HbA1c and baseline FPG as continuous

covariates.

Add-On Combination Therapy with Insulin

A total of 1,261 patients with type 2 diabetes mellitus inadequately controlled on basal insulin alone or basal insulin in combination with oral drugs participated in a randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy of TRADJENTA as add-on therapy to basal insulin over 24 weeks. Randomization was stratified by baseline HbA1c (<8.5% vs ≥8.5%), renal function impairment status (based on baseline eGFR), and concomitant use of oral antidiabetic drugs (none, metformin only, pioglitazone only, metformin + pioglitazone). Patients with a baseline A1C of ≥7% and ≤10% were included in the trial including 709 patients with renal impairment (eGFR <90 mL/min), most of whom (n=575) were categorized as mild renal impairment (eGFR 60 to <90 mL/min). Patients entered a 2 week placebo run-in period on basal insulin (e.g., insulin glargine, insulin detemir, or NPH insulin) with or without metformin and/or pioglitazone background therapy. Following the run-in period, patients with inadequate glycemic control were randomized to the addition of either 5 mg of TRADJENTA or placebo, administered once daily. Patients were maintained on a stable dosage of insulin prior to enrollment, during the run-in period, and during the first 24 weeks of treatment. Patients who failed to meet specific glycemic goals during the double-blind treatment period were rescued by increasing background insulin dosage.

TRADJENTA used in combination with insulin (with or without metformin and/or pioglitazone), provided statistically significant improvements in A1C and FPG compared to placebo (Table 12) after 24 weeks of treatment. The mean total daily insulin dosage at baseline was 42 units for patients treated with TRADJENTA and 40 units for patients treated with placebo. Background baseline diabetes mellitus therapy included use of: insulin alone (16.1%), insulin combined with metformin only (75.5%), insulin combined with metformin and pioglitazone (7.4%), and insulin combined with pioglitazone only (1%). The mean change from baseline to Week 24 in the daily dosage of insulin was +1.3 IU in the placebo group and +0.6 IU in the TRADJENTA group. The mean change in body weight from baseline to Week 24 was similar in the two treatment groups.

Table 12 Glycemic Parameters in Placebo-Controlled Trial for TRADJENTA in Combination with Insulin*

	TRADJENTA 5 mg + Insulin	Placebo + Insulin
A1C (%)		
Number of patients	n = 618	n = 617
Baseline (mean)	8.3	8.3
Change from baseline (adjusted mean***)	-0.6	0.1
Difference from placebo (adjusted mean) (95% CI)	-0.7 (-0.7, -0.6)	--
Patients [n (%)] achieving A1C <7%**	116 (19.5)	48 (8.1)
FPG (mg/dL)		
Number of patients	n = 613	n = 608
Baseline (mean)	147	151

Change from baseline (adjusted mean***)	-8	3
Difference from placebo (adjusted mean) (95% CI)	-11 (-16, -6)	--

*Full analysis population using last observation carried forward (LOCF) method on trial

**TRADJENTA + Insulin, n=595; Placebo + Insulin, n=593

***HbA1c: ANCOVA model included treatment, categorical renal function impairment status and concomitant OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment, categorical renal function impairment status and concomitant OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

The difference between treatment with linagliptin and placebo in terms of adjusted mean change from baseline in HbA1c after 24 weeks was comparable for patients with no renal impairment (eGFR ≥ 90 mL/min, n=539), with mild renal impairment (eGFR 60 to < 90 mL/min, n= 565), or with moderate renal impairment (eGFR 30 to < 60 mL/min, n=124).

Renal Impairment

A total of 133 patients with type 2 diabetes mellitus participated in a 52 week, double-blind, randomized, placebo-controlled trial designed to evaluate the efficacy and safety of TRADJENTA in patients with both type 2 diabetes mellitus and severe chronic renal impairment. Participants with an estimated (based on the four variables modified diet in renal disease [MDRD] equation) GFR value of < 30 mL/min were eligible to participate in the trial. Randomization was stratified by baseline HbA1c ($\leq 8\%$ and $> 8\%$) and background antidiabetic therapy (insulin or any combination with insulin, SU or glinides as monotherapy and pioglitazone or any other antidiabetics excluding any other DPP-4 inhibitors). For the initial 12 weeks of the trial, background antidiabetic therapy was kept stable and included insulin, sulfonylurea, glinides, and pioglitazone. For the remainder of the trial, dosage adjustments in antidiabetic background therapy were allowed. At baseline in this trial, 62.5% of patients were receiving insulin alone as background diabetes mellitus therapy, and 12.5% were receiving sulfonylurea alone.

After 12 weeks of treatment, TRADJENTA 5 mg provided statistically significant improvement in A1C compared to placebo, with an adjusted mean change of -0.6% compared to placebo (95% confidence interval -0.9, -0.3) based on the analysis using last observation carried forward (LOCF). With adjustments in antidiabetic background therapy after the initial 12 weeks, efficacy was maintained for 52 weeks, with an adjusted mean change from baseline in A1C of -0.7% compared to placebo (95% confidence interval -1.0, -0.4) based on analysis using LOCF.

14.2 Cardiovascular Safety Trials in Patients with Type 2 Diabetes Mellitus

CARMELINA

The cardiovascular risk of TRADJENTA was evaluated in CARMELINA, a multi-national, multi-center, placebo-controlled, double-blind, parallel group trial comparing TRADJENTA (N=3,494) to placebo (N=3,485) in adult patients with type 2 diabetes mellitus and a history of established macrovascular and/or renal disease. The trial compared the risk of major adverse cardiovascular events (MACE) between TRADJENTA and placebo when

these were added to standard of care treatments for diabetes mellitus and other cardiovascular risk factors. The trial was event driven, the median duration of follow-up was 2.2 years and vital status was obtained for 99.7% of patients.

Patients were eligible to enter the trial if they were adults with type 2 diabetes mellitus, with HbA1c of 6.5% to 10%, and had either albuminuria and previous macrovascular disease (39% of enrolled population), or evidence of impaired renal function by eGFR and Urinary Albumin Creatinine Ratio (UACR) criteria (42% of enrolled population), or both (18% of enrolled population).

At baseline the mean age was 66 years and the population was 63% male, 80% White, 9% Asian, 6% Black or African American, and 36% were of Hispanic or Latino ethnicity. Mean HbA1c was 8.0% and mean duration of type 2 diabetes mellitus was 15 years. The trial population included 17% patients ≥ 75 years of age and 62% patients with renal impairment defined as eGFR < 60 mL/min/1.73 m². The mean eGFR was 55 mL/min/1.73 m² and 27% of patients had mild renal impairment (eGFR 60 to < 90 mL/min/1.73 m²), 47% of patients had moderate renal impairment (eGFR 30 to < 60 mL/min/1.73 m²) and 15% of patients had severe renal impairment (eGFR < 30 mL/min/1.73 m²). Patients were taking at least one antidiabetic drug (97%), and the most common were insulin and analogues (57%), metformin (54%) and sulfonylurea (32%). Patients were also taking antihypertensives (96%), lipid lowering drugs (76%) with 72% on statin, and aspirin (62%).

The primary endpoint, MACE, was the time to first occurrence of one of three composite outcomes which included cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The trial was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio of MACE.

The results of CARMELINA, including the contribution of each component to the primary composite endpoint, are shown in Table 13. The estimated hazard ratio for MACE associated with TRADJENTA relative to placebo was 1.02 with a 95% confidence interval of (0.89, 1.17). The upper bound of this confidence interval, 1.17, excluded the risk margin of 1.3. The Kaplan-Meier curve depicting time to first occurrence of MACE is shown in Figure 1.

Table 13 Major Adverse Cardiovascular Events (MACE) by Treatment Group in the CARMELINA Trial

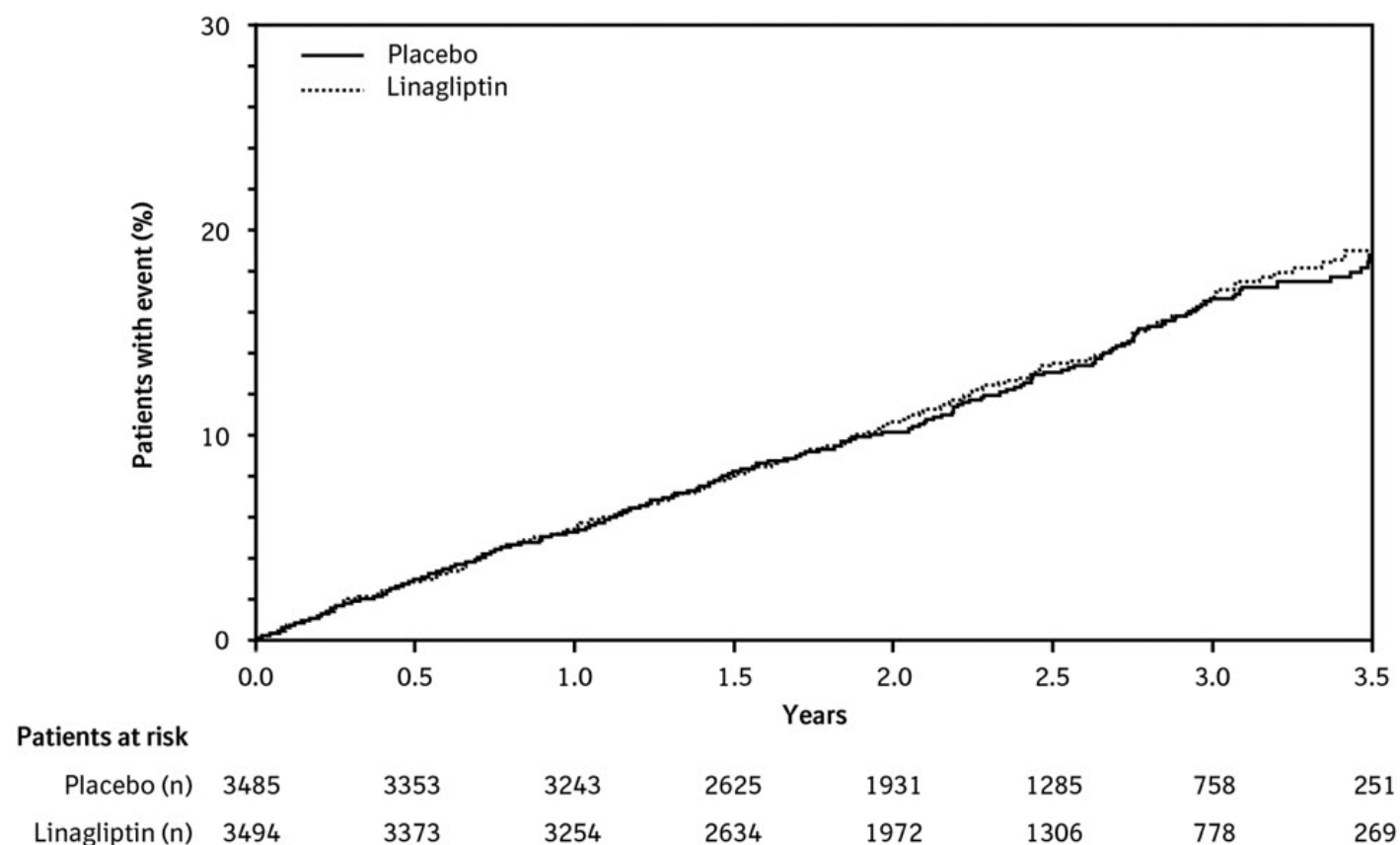
	TRADJENTA 5 mg n = 3,494		Placebo n = 3,485		Hazard Ratio
	Number of Subjects (%)	Incidence Rate per 1,000 PY*	Number of Subjects (%)	Incidence Rate per 1,000 PY*	(95% CI)
Composite of first event of CV death, non-fatal myocardial infarction (MI), or non-fatal stroke (MACE)	434 (12.4)	57.7	420 (12.1)	56.3	1.02 (0.89, 1.17)
CV death**	255 (7.3)	32.6	264 (7.6)	34.0	0.96 (0.81, 1.14)
					1.15 (0.91, 1.45)

Non-fatal MI**	156 (4.5)	20.6	135 (3.9)	18.0	1.15 (0.91, 1.45)
Non-fatal stroke**	65 (1.9)	8.5	73 (2.1)	9.6	0.88 (0.63, 1.23)

*PY=patient years

**A patient may have experienced more than one component; therefore, the sum of the components is larger than the number of patients who experienced the composite outcome.

Figure 1 Kaplan-Meier: Time to First Occurrence of MACE in the CARMELINA Trial



CAROLINA

The cardiovascular risk of TRADJENTA was evaluated in CAROLINA, a multi-center, multi-national, randomized, double-blind, parallel group trial comparing TRADJENTA (N=3,023) to glimepiride (N=3,010) in adult patients with type 2 diabetes mellitus and a history of established cardiovascular disease and/or multiple cardiovascular risk factors. The trial compared the risk of major adverse cardiovascular events (MACE) between TRADJENTA and glimepiride when these were added to standard of care treatments for diabetes mellitus and other cardiovascular risk factors. The trial was event driven, the median duration of follow-up was 6.23 years and vital status was obtained for 99.3% of patients.

Patients were eligible to enter the trial if they were adults with type 2 diabetes mellitus with insufficient glycemic control (defined as HbA1c of 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 cardiovascular risk with previous vascular disease, evidence of vascular related end-organ damage, age ≥ 70 years, and/or two cardiovascular risk factors (duration of diabetes mellitus >10 years, systolic blood pressure >140 mmHg, current smoker, LDL cholesterol ≥ 135 mg/dL).

At baseline the mean age was 64 years and the population was 60% male, 73% White, 18% Asian, 5% Black or African American, and 17% were of Hispanic or Latino ethnicity. The mean HbA1c was 7.15% and mean duration of type 2 diabetes mellitus was 7.6 years. The trial population included 34% patients ≥ 70 years of age and 19% patients with renal impairment defined as eGFR <60 mL/min/1.73 m². The mean eGFR was 77 mL/min/1.73m². Patients were taking at least one antidiabetic drug (91%) and the most common were metformin (83%) and sulfonylurea (28%). Patients were also taking antihypertensives (89%), lipid lowering drugs (70%) with 65% on statin, and aspirin (47%).

The primary endpoint, MACE, was the time to first occurrence of one of three composite outcomes which included cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The trial was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the upper bound of the 95% CI for the hazard ratio of MACE.

The results of CAROLINA, including the contribution of each component to the primary composite endpoint, are shown in Table 14. The Kaplan-Meier curve depicting time to first occurrence of MACE is shown in Figure 2.

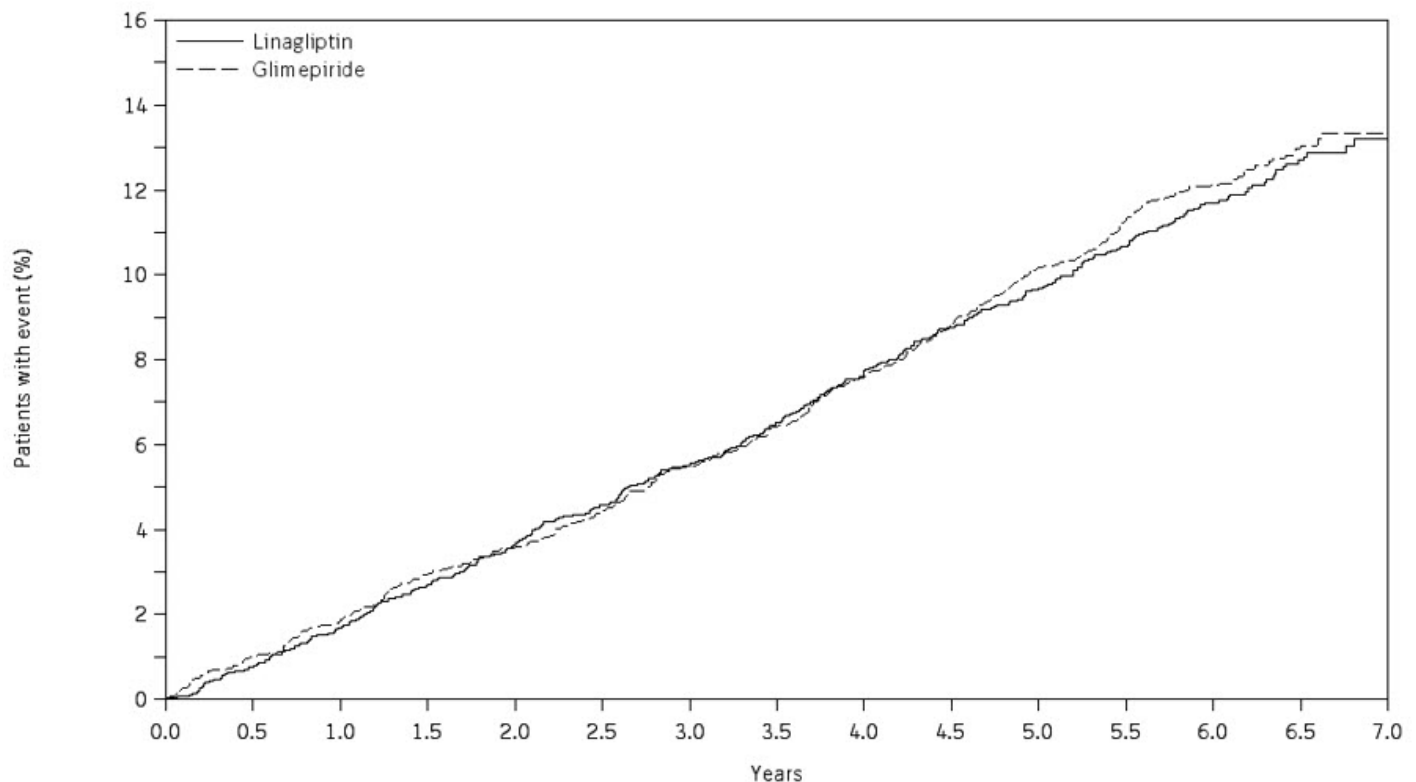
Table 14 Major Adverse Cardiovascular Events (MACE) by Treatment Group in the CAROLINA Trial

	TRADJENTA 5 mg n=3,023		Glimepiride (1 mg to 4 mg) n=3,010		Hazard Ratio
	Number of Subjects (%)	Incidence Rate per 1,000 PY*	Number of Subjects (%)	Incidence Rate per 1,000 PY*	(95% CI)
Composite of first event of CV death, non-fatal myocardial infarction (MI), or non-fatal stroke (MACE)	356 (11.8)	20.7	362 (12.0)	21.2	0.98 (0.84, 1.14)
CV death**	169 (5.6)	9.2	168 (5.6)	9.2	1.00 (0.81, 1.24)
Non-fatal MI**	145 (4.8)	8.3	142 (4.7)	8.2	1.01 (0.80, 1.28)
Non-fatal stroke**	91 (3.0)	5.2	104 (3.5)	6.0	0.87 (0.66, 1.15)

*PY=patient years

**A patient may have experienced more than one component; therefore, the sum of the components is larger than the number of patients who experienced the composite outcome

Figure 2 Time to First Occurrence of 3P-MACE in CAROLINA



Patients at risk

Linagliptin (n)	3023	2957	2901	2846	2803	2762	2725	2679	2627	2582	2534	2451	1830	1040	213
Glimepiride (n)	3010	2940	2890	2833	2797	2757	2710	2662	2618	2569	2509	2414	1865	1020	207

16 HOW SUPPLIED/STORAGE AND HANDLING

TRADJENTA tablets are available as light red, round, biconvex, bevel-edged, film-coated tablets containing 5 mg of linagliptin. TRADJENTA tablets are debossed with "D5" on one side and the Boehringer Ingelheim symbol on the other side.

They are supplied as follows:

Bottles of 30 (NDC 0597-0140-30)

Bottles of 90 (NDC 0597-0140-90)

Cartons containing 10 blister cards of 10 tablets each (10 × 10) (NDC 0597-0140-61), institutional pack.

If repackaging is required, dispense in a tight container as defined in USP.

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Pancreatitis

Inform patients that acute pancreatitis has been reported during use of TRADJENTA. Inform patients that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue TRADJENTA promptly and contact their healthcare provider if persistent severe abdominal pain occurs [see *Warnings and Precautions* (5.1)] .

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Inform patients that the incidence of hypoglycemia is increased when TRADJENTA is used in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin [see *Warnings and Precautions* (5.2)] .

Hypersensitivity Reactions

Inform patients that serious allergic reactions, such as anaphylaxis, angioedema, and exfoliative skin conditions, have been reported during postmarketing use of TRADJENTA. If symptoms of allergic reactions (such as rash, skin flaking or peeling, urticaria, swelling of the skin, or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking TRADJENTA and seek medical advice promptly [see *Warnings and Precautions* (5.3)] .

Severe and Disabling Arthralgia

Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs [see *Warnings and Precautions* (5.4)].

Bullous Pemphigoid

Inform patients that bullous pemphigoid has been reported during use of TRADJENTA. Instruct patients to seek medical advice if blisters or erosions occur [see *Warnings and Precautions* (5.5)].

Heart Failure

Inform patients of the signs and symptoms of heart failure. Before initiating TRADJENTA, patients should be asked about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment. Instruct patients to contact their healthcare provider as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight or swelling of the feet [see *Warnings and Precautions* (5.6)].

Missed Dose

Instruct patients to take TRADJENTA only as prescribed. If a dose is missed, it should be taken as soon as the patient remembers. Advise patients not to double their next dose.

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SPL10196B

MEDICATION GUIDE
TRADJENTA[®] (TRAD gen ta)
(linagliptin tablets)
for oral use

What is the most important information I should know about TRADJENTA?
TRADJENTA can cause serious side effects, including:

- **Inflammation of the pancreas (pancreatitis)** which may be severe and lead to death. Certain medical problems make you more likely to get pancreatitis.
Before you start taking TRADJENTA, tell your healthcare provider if you have ever had:

- inflammation of your pancreas (pancreatitis)
- a history of alcoholism
- stones in your gallbladder (gallstones)
- high blood triglyceride levels

Stop taking TRADJENTA and call your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

What is TRADJENTA?

- TRADJENTA is a prescription medicine used along with diet and exercise to lower blood sugar in adults with type 2 diabetes mellitus.
- TRADJENTA is not for people with type 1 diabetes mellitus.
- If you have had pancreatitis in the past, it is not known if you have a higher chance of getting pancreatitis while you take TRADJENTA.
- It is not known if TRADJENTA is safe and effective in children.

Who should not take TRADJENTA?

Do not take TRADJENTA if you:

- are allergic to linagliptin or any of the ingredients in TRADJENTA. See the end of this Medication Guide for a complete list of ingredients in TRADJENTA.
Symptoms of a serious allergic reaction to TRADJENTA may include:
 - skin rash, itching, flaking or peeling
 - raised red patches on your skin (hives)
 - swelling of your face, lips, tongue and throat that may cause difficulty in breathing or swallowing
 - difficulty with swallowing or breathing

If you have any of these symptoms, stop taking TRADJENTA and call your healthcare provider right away or go to the nearest hospital emergency room.

What should I tell my healthcare provider before taking TRADJENTA?

Before taking TRADJENTA, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had inflammation of your pancreas (pancreatitis).
- are pregnant or plan to become pregnant. It is not known if TRADJENTA will harm your unborn baby. If you are pregnant, talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if TRADJENTA passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby if you take TRADJENTA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

TRADJENTA may affect the way other medicines work, and other medicines may affect how TRADJENTA works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take TRADJENTA?

- Take TRADJENTA exactly as your healthcare provider tells you to take it.
- Take 1 tablet 1 time each day with or without food.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take two doses of TRADJENTA at the same time.
- Your healthcare provider may tell you to take TRADJENTA along with other diabetes medicines. Low blood sugar can happen more often when TRADJENTA is taken with certain other diabetes medicines. See "**What are the possible side effects of TRADJENTA?**"

If you take too much TRADJENTA, call your healthcare provider or local poison control center or go to the nearest hospital emergency room right away.

What are the possible side effects of TRADJENTA?

TRADJENTA may cause serious side effects, including:

- See "**What is the most important information I should know about TRADJENTA?**"
- **Low blood sugar (hypoglycemia).** If you take TRADJENTA with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take TRADJENTA. Signs and symptoms of low blood sugar may include:
 - headache ◦ drowsiness ◦ weakness ◦ dizziness ◦ confusion
 - irritability ◦ hunger ◦ fast heartbeat ◦ sweating ◦ shaking or feeling jittery
- **Allergic (hypersensitivity) reactions.** Serious allergic reactions have happened in people who are taking TRADJENTA. Symptoms may include:

◦ difficulty with swallowing or

- swelling of your face, lips, tongue, throat, and other areas on your skin
- raised, red areas on your skin (hives)
- difficulty with swallowing or breathing
- skin rash, itching, flaking, or peeling
- If you have any of these symptoms, stop taking TRADJENTA and call your healthcare provider right away or go to the nearest hospital emergency room.
- **Joint pain.** Some people who take TRADJENTA, may develop joint pain that can be severe. Call your healthcare provider if you have severe joint pain.
- **Skin reaction.** Some people who take medicines called DPP-4 inhibitors like TRADJENTA, may develop a skin reaction called bullous pemphigoid that can require treatment in a hospital. Tell your healthcare provider right away if you develop blisters or the breakdown of the outer layer of your skin (erosion). Your healthcare provider may tell you to stop taking TRADJENTA.
- **Heart failure.** Heart failure means your heart does not pump blood well enough. **Before you start taking TRADJENTA,** tell your healthcare provider if you have ever had heart failure or have problems with your kidneys. Contact your healthcare provider right away if you have any of the following symptoms:
 - increasing shortness of breath or trouble breathing, especially when you lie down
 - swelling or fluid retention, especially in the feet, ankles or legs
 - an unusually fast increase in weight
 - unusual tiredness
 These may be symptoms of heart failure.

The most common side effects of TRADJENTA include:

- stuffy or runny nose and sore throat
- cough
- diarrhea

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of TRADJENTA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TRADJENTA?

- Store TRADJENTA at room temperature between 68°F and 77°F (20°C and 25°C).
- **Keep TRADJENTA and all medicines out of the reach of children.**

General information about the safe and effective use of TRADJENTA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TRADJENTA for a condition for which it was not prescribed. Do not give TRADJENTA to other people, even if they have the same symptoms you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about TRADJENTA that is written for health professionals.

What are the ingredients in TRADJENTA?

Active Ingredient:linagliptin

Inactive Ingredients:copovidone, corn starch, magnesium stearate, mannitol, and

pregelatinized starch. The film coating contains the following inactive ingredients: hypromellose, polyethylene glycol, red ferric oxide, talc, and titanium dioxide.

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For more information about TRADJENTA, including current prescribing information and Medication Guide, go to **www.TRADJENTA.com**, scan the code, or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257.



This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: June
2023

PRINCIPAL DISPLAY PANEL - 5 mg Tablet Blister Card Carton

NDC 0597-0140-61

DISPENSE THE ACCOMPANYING
MEDICATION GUIDE TO EACH PATIENT

Tradjenta[®]
(linagliptin
tablets)

5 mg per tablet

Recommended Dosage: Take one
tablet daily. See Prescribing
Information.

100 tablets
10 blister cards of 10 tablets

This unit dose package is not
child-resistant. If dispensed for
outpatient use, a child-resistant
container should be utilized.

Rx only

Boehringer
Ingelheim



TRADJENTA

linagliptin tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:59368-388
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name		Basis of Strength	Strength	
LINAGLIPTIN (UNII: 3X29Z EJ4R2) (LINAGLIPTIN - UNII:3X29Z EJ4R2)		LINAGLIPTIN	5 mg	
Product Characteristics				
Color	red (Light Red)	Score	no score	
Shape	ROUND	Size	8mm	
Flavor		Imprint Code	D5;	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59368-388-01	7 in 1 CARTON	05/09/2011	08/31/2026
1		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA		NDA201280	05/09/2011	

Labeler - Praxis, LLC (016329513)

Establishment

Name	Address	ID/FEI	Business Operations
Praxis, LLC		016329513	label(59368-388) , pack(59368-388) , manufacture(59368-388)

Revised: 1/2023

Praxis, LLC