

# Trajenta Duo®



## Composition

1 film-coated tablet	contains	2.5 mg	1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]- (=linagliptin)
	and	500 mg, or 850 mg, or 1000 mg	N,N-dimethylimido-dicarbonimidic diamide hydrochloride (= metformin hydrochloride)

Excipients: L-Arginine, Maize starch, Copovidone, Silica, colloidal anhydrous, Magnesium stearate (E470b), Hypromellose 2910, Propylene glycol, Titanium dioxide (E171), Talc, Iron oxide red/yellow (E172)

## Description

Linagliptin / metformin hydrochloride film-coated tablets, 2.5 mg / 500 mg: Consists of a light yellow, oval, biconvex, tablet. One side is debossed with the code 'D2/500', the other side is debossed with the Boehringer Ingelheim company symbol.

Linagliptin / metformin hydrochloride film-coated tablets, 2.5 mg / 850 mg: Consists of a light orange, oval, biconvex, tablet. One side is debossed with the code 'D2/850', the other side is debossed with the Boehringer Ingelheim company symbol.

Linagliptin / metformin hydrochloride film-coated tablets, 2.5 mg / 1000 mg: Consists of a light pink, oval, biconvex, tablet. One side is debossed with the code 'D2/1000', the other side is debossed with the Boehringer Ingelheim company symbol.

## Properties

Pharmacotherapeutic group: Combinations of oral blood glucose lowering drugs, ATC code: A10BD11

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

in an overall improvement in the glucose homoeostasis. Linagliptin binds selectively to DPP-4 and exhibits a >10000 fold selectivity versus DPP-8 or DPP-9 activity in vitro.

Metformin hydrochloride is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin hydrochloride may act via 3 mechanisms:

- (1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- (2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- (3) and delay of intestinal glucose absorption.

Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin hydrochloride increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

In humans, independently of its action on glycaemia, metformin hydrochloride has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDL cholesterol and triglyceride levels.

## Clinical Trials

### Linagliptin as add-on to metformin therapy

The efficacy and safety of linagliptin in combination with metformin in patients with insufficient glycaemic control on metformin monotherapy was evaluated in a double blind placebo controlled study of 24 weeks duration.

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

In a 24-week placebo-controlled factorial study of initial therapy, linagliptin 2.5 mg twice daily in combination with metformin (500 mg or 1000 mg twice daily) provided significant improvements in glycaemic parameters compared with either monotherapy as summarized in table 3 (mean baseline HbA1c 8.65%).

**Table 1:** Glycaemic Parameters at Final Visit (24-Week Study) for Linagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Diet and Exercise

	Placebo	Linagliptin 5 mg Once Daily*	Metformin 500 mg Twice Daily	Linagliptin 2.5 mg Twice Daily* + Metformin 500 mg Twice Daily	Metformin 1000 mg Twice Daily	Linagliptin 2.5 mg Twice Daily* + Metformin 1000 mg Twice Daily
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<b>HbA1c (%)</b>						
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 HbA1c <7%	7 (10.8)	14 (10.4)	27 (19.1)	42 (30.7)	43 (31.2)	76 (54.3)
Patients (%) receiving rescue medication	29.2	11.1	13.5	7.3	8.0	4.3
<b>FPG (mg/dL)</b>						
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 dose of linagliptin is equal to 5 mg

Mean reductions from baseline in HbA1c were generally greater for patients with higher baseline HbA1c values. Effects on plasma lipids were generally neutral. The decrease in body weight with the combination of linagliptin and metformin was similar to that observed for metformin alone or placebo; there was no change from baseline for patients on linagliptin alone. The incidence of hypoglycaemia was similar across treatment groups (placebo 1.4%, linagliptin 5 mg 0%, metformin 2.1%, and linagliptin 2.5mg plus metformin twice daily 1.4%).

In addition, this study included patients (n=66) with more severe hyperglycemia (HbA<sub>1c</sub> at baseline ≥11%) who were treated with twice daily open-label linagliptin 2.5 mg + metformin 1000 mg. In this group of patients, the mean baseline HbA1c value was 11.8% and mean FPG was 261.8 mg/dL (14.5 mmol/L). A mean decrease from baseline of -3.74% in HbA1c (n=48) and -81.2 mg/dL (-4.5mmol/L) for FPG (n=41) was observed for patients completing the 24 week trial period without rescue therapy (n=48).

In the LOCF analysis including all patients with primary endpoint measurements (n=65) at last observation without rescue therapy changes from baseline were -3.19% for HbA1c and -73.6 mg/dL (-4.1mmol/L) for FPG.

The efficacy and safety of linagliptin 2.5 mg twice daily versus 5 mg once daily in combination with metformin in patients with insufficient glycaemic control on metformin monotherapy was evaluated in a double blind placebo controlled study of 12 weeks duration. Linagliptin (2.5 mg twice daily and 5 mg once daily) added to metformin provided significant improvements in glycaemic parameters compared to placebo. Linagliptin 5 mg once daily and 2.5 mg twice daily provided comparable (CI: -0.07; 0.19), significant HbA<sub>1c</sub> reductions of -0.80 % (from baseline 7.98%), and -0.74 (from baseline 7.96%) compared to placebo.

The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo (2.2% on linagliptin 2.5 mg twice daily, 0.9% on linagliptin 5 mg once daily, and 2.3% on placebo). Body weight did not differ significantly between the groups.

#### *Linagliptin as add-on to a combination of metformin and sulphonylurea therapy*

A placebo controlled study of 24 weeks in duration was conducted to evaluate the efficacy and safety of linagliptin 5 mg to placebo, in patients not sufficiently controlled with a combination with metformin and a sulphonylurea. Linagliptin provided significant improvements in HbA<sub>1c</sub> (-0.62 % change compared to placebo), from a mean baseline HbA<sub>1c</sub> of 8.14%.

Linagliptin also showed significant improvements in patients achieving a target HbA<sub>1c</sub> of < 7.0% (31.2% on linagliptin vs. 9.2% on placebo), and also for fasting plasma glucose (FPG) with -12.7 mg/dl (-0.7 mmol/L) reduction compared to placebo. Body weight did not differ significantly between the groups.

#### *Linagliptin as add on to a combination of metformin and empagliflozin*

In patients inadequately controlled with metformin and empagliflozin (10 mg (n=247) or 25 mg (n=217)), 24-weeks treatment with add-on therapy of linagliptin 5 mg provided adjusted mean HbA<sub>1c</sub> reductions from baseline by -0.53% (significant difference to add-on placebo -0.32% (95% CI -0.25, -0.13) and -0.58% (significant difference to add-on placebo -0.47% (95% CI -0.66; -0.28), respectively. A statistically significant greater proportion of patients with a baseline HbA<sub>1c</sub> ≥7.0% and treated with linagliptin 5 mg achieved a target HbA<sub>1c</sub> of <7% compared to placebo.

In prespecified subgroups of patients with baseline HbA<sub>1c</sub> greater or equal than 8.5% (n=66 and n=42 patients on metformin plus empagliflozin 10 mg or 25 mg, respectively), the adjusted mean HbA<sub>1c</sub> reductions from baseline to 24 weeks on add-on therapy with linagliptin 5 mg were -0.97% (p=0.0875, for difference to add-on placebo) and -1.16% (p=0.0046 for difference to add-on placebo), respectively.

#### *Linagliptin in combination with metformin and insulin*

A 24-week placebo-controlled study was conducted to evaluate the efficacy and safety of linagliptin (5 mg once daily) added to insulin with or without metformin. 83 % of patients were taking metformin in combination with insulin in this trial. Linagliptin in combination with metformin plus insulin provided significant improvements in HbA<sub>1c</sub> in this subgroup with -0.68% (CI:-0.78; -0.57) adjusted mean change from baseline (mean baseline HbA<sub>1c</sub> 8.28%) compared to placebo in combination with metformin plus insulin. There was no meaningful change from baseline in body weight in either group.

#### *Linagliptin 24 month data, as add- on to metformin in comparison with glimepiride*

In a study comparing the efficacy and safety of the addition of linagliptin 5 mg or glimepiride (a sulphonylurea agent) in patients with inadequate glycaemic control on metformin monotherapy,

linagliptin was similar to glimepiride in reducing HbA1c, with a mean treatment difference in HbA1c from baseline to 104 weeks for linagliptin compared to glimepiride of + 0.20%.

In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, showed a statistically significant improvement with linagliptin compared with glimepiride treatment. The incidence of hypoglycaemia in the linagliptin group (7.5%) was significantly lower than that in the glimepiride group (36.1%).

Patients treated with linagliptin exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glimepiride (-1.39 vs + 1.29 kg).

*Linagliptin as add on therapy in elderly patients (age  $\geq$  70 years) with type 2 diabetes:*

The efficacy and safety of linagliptin in elderly (age  $\geq$  70 years) type 2 diabetes patients was evaluated in a double blind study of 24 weeks duration. Patients received metformin and/or sulphonylurea and/or insulin as background therapy. Doses of background antidiabetic medications were kept stable during the first 12 weeks, after which adjustments were permitted. Linagliptin provided significant improvements in HbA1c of -0.64 % (95% CI -0.81, -0.48;  $p < 0.0001$ ) compared to placebo after 24 weeks, from a mean baseline HbA1c of 7.8%. Linagliptin also showed significant improvements in fasting plasma glucose (FPG) of -20.7mg/dL (95% CI -30.2, -11.2;  $p < 0.0001$ ) compared to placebo (-1.1 mmol/L). Body weight did not differ significantly between the groups. Overall, the incidence of hypoglycaemia was comparable between linagliptin (2 of 45 patients, 4.4%) and placebo (none of 22 patients, 0%) on the background of metformin alone. Hypoglycaemia rates were also comparable on a background of insulin with or without metformin (13 of 35 patients, 37.1% treated with linagliptin and 6 of 15 patients, 40.0% treated with placebo). However, on a background of sulphonylurea with or without metformin, hypoglycaemia was reported in a higher proportion of patients treated with linagliptin (24 of 82 patients, 29.3%) compared to placebo (7 of 42 patients, 16.7%). There was no difference between linagliptin and placebo in severe hypoglycaemic events.

In a pooled analysis of elderly (age  $\geq$  70 years) patients with type 2 diabetes (n=183) who were taking both metformin and basal insulin as background therapy, linagliptin in combination with metformin plus insulin provided significant improvements in HbA1c parameters with -0.81% (CI: -1.01, -0.61) adjusted mean change from baseline (mean baseline HbA1c 8.13%) compared to placebo in combination with metformin plus insulin. There was no clinically meaningful difference in the incidence of hypoglycaemic events, in patient's  $\geq$  70 years (37.2% on linagliptin in combination with metformin plus insulin vs. 39.8% on placebo in combination with metformin plus insulin).

*Linagliptin and initial combination with Linagliptin and Metformin in recently diagnosed treatment naïve patients with marked hyperglycaemia:*

The efficacy and safety of the initial combination of linagliptin 5 mg once daily and metformin twice daily (up-titrated in the first 6 weeks to 1500 mg or 2000 mg/d) compared to linagliptin 5 mg once daily has been studied in a 24 week trial in recently diagnosed treatment naïve patients with T2DM and marked hyperglycaemia (baseline HbA1c 8.5–12.0%). After 24 weeks both linagliptin monotherapy as well as the initial combination of linagliptin and metformin significantly reduced HbA1c levels by -2.0% and -2.8% respectively, from a baseline HbA1c of 9.69% and 9.73% respectively (per protocol completers cohort). The treatment difference of -0.8% (95% CI -1.1 to -0.5) showed superiority for the initial combination over monotherapy ( $p < 0.0001$ ). Notably, 40% and 61% of patients in the monotherapy and combination arms achieved HbA1c  $< 7.0\%$ .

### **Linagliptin cardiovascular and renal safety study (CARMELINA)**

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

The mean HbA<sub>1c</sub> at baseline was 8.0%.

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

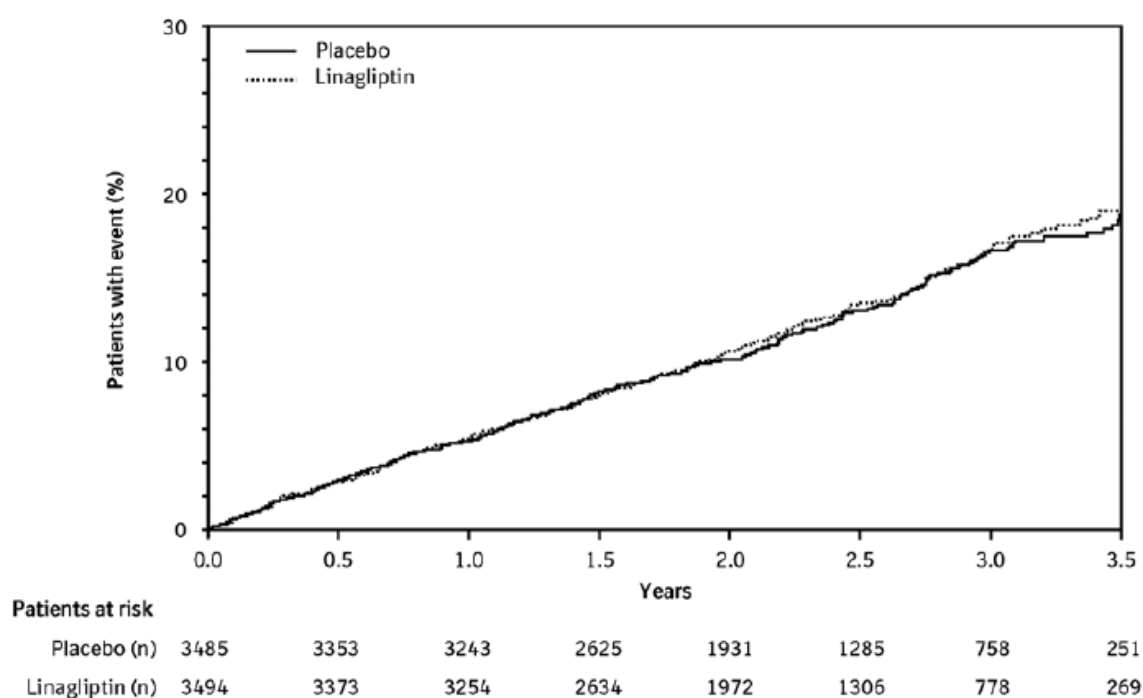
After a median follow up of 2.2 years, linagliptin, when added to standard of care, did not increase the risk of major adverse cardiovascular events or renal outcome events (Table 2 and Figure 1). There was no increased risk in hospitalization for heart failure which was an additional adjudicated endpoint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

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

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

\*PY=patient years

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

**Figure 1:** Time to first occurrence of 3P-MACE in CARMELINA**Table 3:** Hospitalization for heart failure and mortality by treatment group in the CARMELINA study

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

\*PY=patient years

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

#### **Linagliptin cardiovascular safety study (CAROLINA)**

CAROLINA was a randomized study in 6033 patients with early type 2 diabetes and increased CV risk or established complications who were treated with linagliptin 5 mg (3023) or glimepiride 1-4 mg (3010)

added to standard of care (including background therapy with metformin in 83% of patients) targeting regional standards for HbA<sub>1c</sub> and CV risk factors. The mean age for study population was 64 years and included 2030 (34%) patients  $\geq$  70 years of age. The study population included 2089 (35%) patients with cardiovascular disease and 1130 (19%) patients with renal impairment with an eGFR  $<$  60ml/min/1.73m<sup>2</sup> at baseline. The mean HbA<sub>1c</sub> at baseline was 7.15%.

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

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

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

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

\* PY=patient years

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

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

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

### Pharmacokinetics

Bioequivalence studies in healthy subjects demonstrated that the TRAJENTA DUO (linagliptin/metformin hydrochloride) combination tablets are bioequivalent to co-administration of linagliptin and metformin hydrochloride as individual tablets.

Administration of TRAJENTA DUO 2.5 /1000 mg with food resulted in no change in overall exposure of linagliptin. With metformin there was no change in AUC, however mean peak serum concentration of



metformin was decreased by 18% when administered with food. A delayed time to peak serum concentrations by 2 hours was observed for metformin under fed conditions. These changes are not likely to be clinically significant.

The following statements reflect the pharmacokinetic properties of the individual active substances of TRAJENTA DUO.

#### Linagliptin

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

Plasma concentrations of linagliptin decline in a bi-phasic manner with a long terminal half-life (terminal half-life for linagliptin more than 100 hours), that is mostly related to the saturable, tight binding of linagliptin to DPP-4 and does not contribute to the accumulation of the drug. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of 5 mg linagliptin, is approximately 12 hours. After once-daily dosing, steady-state plasma concentrations of 5 mg linagliptin are reached by the third dose.

Plasma AUC of linagliptin increased approximately 33% following 5 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for linagliptin AUC were small (12.6% and 28.5%, respectively).

Plasma AUC of linagliptin increased in a less than dose-proportional manner. The pharmacokinetics of linagliptin was generally similar in healthy subjects and in patients with type 2 diabetes.

#### *Absorption*

The absolute bioavailability of linagliptin is approximately 30%. Because coadministration of a high-fat meal with linagliptin had no clinically relevant effect on the pharmacokinetics, linagliptin may be administered with or without food. *In vitro* studies indicated that linagliptin is a substrate of P-glycoprotein and of CYP3A4. Ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, led to a twofold increase in exposure (AUC) and multiple co-administration of linagliptin with rifampicin, a potent inducer of P-gp and CYP3A, resulted in an about 40% decreased linagliptin steady-state AUC, presumably by increasing/decreasing the bioavailability of linagliptin by inhibition/induction of P-glycoprotein.

#### *Distribution*

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

#### *Biotransformation*

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

### *Elimination*

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

## **Special populations**

### *Renal Impairment*

A multiple-dose, open-label study was conducted to evaluate the pharmacokinetics of linagliptin (5 mg dose) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with renal impairment classified on the basis of creatinine clearance as mild (50 to <80 mL/min), moderate (30 to <50 mL/min), and severe (<30 mL/min), as well as patients with ESRD on hemodialysis. In addition patients with T2DM and severe renal impairment (<30 mL/min) were compared to T2DM patients with normal renal function.

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

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

Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects. In moderate renal impairment, a moderate increase in exposure of about 1.7 fold was observed compared with control.

Exposure in T2DM patients with severe RI was increased by about 1.4 fold compared to T2DM patients with normal renal function. Steady-state predictions for AUC of linagliptin in patients with ESRD indicated comparable exposure to that of patients with moderate or severe renal impairment.

In addition, linagliptin is not expected to be eliminated to a therapeutically significant degree by hemodialysis or peritoneal dialysis. Therefore, no dosage adjustment of linagliptin is necessary in patients with any degree of renal impairment.

In addition, mild renal impairment had no effect on linagliptin pharmacokinetics in patients with type 2 diabetes as assessed by population pharmacokinetic analyses.

### *Hepatic Insufficiency*

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

### *Body Mass Index (BMI)*

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

*Gender*

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

*Geriatric*

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

*Paediatric*

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

*Race*

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

Metformin*Absorption:*

After an oral dose of metformin,  $T_{max}$  is reached in 2.5 hours. Absolute bioavailability of a 500mg or 850mg metformin hydrochloride tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin hydrochloride absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin hydrochloride absorption is non-linear.

At the recommended metformin hydrochloride doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/ml. In controlled clinical trials, maximum metformin hydrochloride plasma levels ( $C_{max}$ ) did not exceed 5 microgram/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin hydrochloride. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these decreases is unknown.

*Distribution:*

Plasma protein binding is negligible. Metformin hydrochloride partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution ( $V_d$ ) ranged between 63-276 L.

**Metabolism:**

Metformin hydrochloride is excreted unchanged in the urine. No metabolites have been identified in humans.

**Elimination:**

Renal clearance of metformin hydrochloride is  $> 400$  ml/min, indicating that metformin hydrochloride is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin hydrochloride in plasma.

**Special populations****Paediatric**

Single dose study: After single doses of metformin 500 mg, paediatric patients have shown a similar pharmacokinetic profile to that observed in healthy adults.

Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration ( $C_{max}$ ) and systemic exposure ( $AUC_{0-t}$ ) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

**Renal impairment**

The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/ tolerability consideration (see section Dosage and administration).

**Indications**

TRAJENTA DUO is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate [see *Dosage and Administration and Clinical Studies*].

**Dosage and administration****Adults with normal renal function ( $GFR \geq 90$ ml/min)**

The recommended dose is 2.5/500 mg, 2.5/ 850 mg or 2.5/1000 mg twice daily.

The dosage should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability. Maximum recommended daily dose of TRAJENTA DUO is 5 mg of linagliptin and 2000 mg of metformin (see table 4 for additional dosing information).

TRAJENTA DUO should be given with meals to reduce the gastrointestinal undesirable effects associated with metformin.

For patients currently not treated with metformin

For patients currently not treated with metformin, the recommended starting dose is 2.5 mg linagliptin/500mg metformin hydrochloride twice daily.

For patients inadequately controlled on maximal tolerated dose of metformin monotherapy

**For patients not adequately controlled on metformin alone, the usual starting dose of TRAJENTA DUO should provide linagliptin dosed as 2.5 mg twice daily (5 mg total daily dose) plus the dose of metformin already being taken.**

For patients switching from co-administration of linagliptin and metformin

**For patients switching from co-administration of linagliptin and metformin to the fixed dose combination, TRAJENTA DUO should be initiated at the dose of linagliptin and metformin already being taken.**

For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a sulphonylurea

**The dose of TRAJENTA DUO should provide linagliptin dosed as 2.5 mg twice daily (5 mg total daily dose) and a dose of metformin similar to the dose already being taken.**

**When TRAJENTA DUO is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycaemia (see section Special warnings and precautions).**

For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin

**The dose of TRAJENTA DUO should provide linagliptin dosed as 2.5 mg twice daily (5 mg total daily dose) and a dose of metformin similar to the dose already being taken.**

**When TRAJENTA DUO is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia (see section Special warnings and precautions).**

For the different doses on metformin, TRAJENTA DUO is available in strengths of 2.5 mg linagliptin plus 500 mg metformin hydrochloride, 850 mg metformin hydrochloride or 1000 mg metformin hydrochloride.

### **Renal insufficiency**

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter.

In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

Factors that may increase the risk of lactic acidosis (see Warnings and Precautions) should be reviewed before considering initiation of metformin in patients with GFR<60 ml/min.

Table 5 Posology for renally impaired patients\*

eGFR ml/min	Metformin	Linagliptin
60 - 89	Maximum daily dose is 3000 mg*.  Dose reduction may be considered in relation to declining renal function.	No dose adjustment is required.
45 - 59	Maximum daily dose is 2000 mg.  The starting dose is at most half of the maximum dose.	No dose adjustment is required.
30 - 44	Maximum daily dose is 1000 mg*.  The starting dose is at most half of the maximum dose.	No dose adjustment is required.
<30	Metformin is contraindicated.	No dose adjustment is required.

\*If no adequate strength of TRAJENTA DUO is available, individual monocomponents should be used instead of the fixed dose combination.

### Hepatic impairment

TRAJENTA DUO is contraindicated in patients with hepatic impairment due to the metformin component. (see section Contraindications).

### Elderly

As metformin is excreted via the kidney, and elderly patients have a tendency for decreased renal function, **elderly patients taking TRAJENTA DUO should have their renal function monitored regularly** (see section Special warnings and precaution). Experience in patients older than >75 years of age is limited.

### Children and adolescents

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

### Missed dose

If a dose is missed, it should be taken as soon as the patient remembers.

However, a double dose should not be taken at the same time. In that case the missed dose should be skipped.

### Contraindications

- **Hypersensitivity to active ingredients linagliptin and/or metformin hydrochloride or to any of the excipients**
- **Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)**
- **Diabetic pre-coma**
- Severe renal failure (CrCl < 30 mL/min or eGFR < 30 ml/min/1.73m<sup>2</sup>)
- **Acute conditions with the potential to alter renal function** such as: dehydration, severe infection, shock, intravascular administration of iodinated contrast agents (see section Special warnings and precautions)

- **Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease)** such as: decompensated heart failure, cardiac or respiratory failure, recent myocardial infarction, shock
- **Hepatic impairment**
- **Acute alcohol intoxication**
- **Alcoholism**

### Special warnings and precautions

#### General

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

#### Pancreatitis

Acute pancreatitis has been observed in patients taking linagliptin.. After initiation of linagliptin, patients should be observed carefully for signs and symptoms of pancreatitis. **If pancreatitis is suspected, linagliptin 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 linagliptin.

#### Hypoglycaemia

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

**Sulphonylureas are known to cause hypoglycaemia. Therefore, caution is advised when TRAJENTA DUO is used in combination with a sulphonylurea. A dose reduction of the sulphonylurea may be considered.**

**Insulin is known to cause hypoglycaemia. Therefore, caution is advised when TRAJENTA DUO is used in combination with insulin. A dose reduction of insulin may be considered.**

Metformin alone does not cause hypoglycaemia under usual circumstances of use, **but hypoglycaemia could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulphonylureas and insulin) or ethanol.**

#### Lactic acidosis

**Lactic acidosis, a very rare, but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.**

**In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.**

**Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients.**

Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see also section Contraindications and Interactions).

**Patients and/or care-givers should be informed of the risk of lactic acidosis.**

**Lactic acidosis is characterised by acidotic dyspnea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention.**

Diagnostic laboratory findings are decreased blood pH (<7.35), increased, plasma lactate levels above (>5 mmol/L), and an increased anion gap and lactate/pyruvate ratio.

#### Administration of iodinated contrast agent

**Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis.**

**In patients with eGFR > 60 ml/min/1.73m<sup>2</sup>, Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections Posology and Interactions.**

**In patients with moderate renal impairment, Metformin must be discontinued 48 hours before administration of iodinated contrast media and not be reinstituted until at least 48 hours afterwards and only after renal function has been re-evaluated and has not deteriorated further.**

#### Renal function:

**GFR should be assessed before treatment initiation and regularly thereafter, see section Posology. TRAJENTA DUO is contraindicated in patients with GFR<30 ml/min and should be temporarily discontinued in the presence of conditions that alter renal function, see section Contraindications.**

#### Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. **In patients with stable chronic heart failure, TRAJENTA DUO may be used with a regular monitoring of cardiac and renal function.**

**For patients with acute and unstable heart failure, TRAJENTA DUO is contraindicated due to the metformin component (see section Contraindications).**

#### Surgery

**As TRAJENTA DUO contains metformin the treatment must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.**



### Bullous pemphigoid

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

### **Vitamin B12**

**The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.**

### *Change in clinical status of patients with previously controlled type 2 diabetes*

As TRAJENTA DUO contains metformin, a patient with previously well controlled type 2 diabetes on TRAJENTA DUO who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis.

Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, TRAJENTA DUO must be stopped immediately and other appropriate corrective measures initiated.

### **Drug Interactions**

#### **Pharmacokinetic Interactions**

##### **General**

Co-administration of multiple doses of linagliptin (10 mg once daily) and metformin (850 mg twice daily) did not meaningfully alter the pharmacokinetics of either linagliptin or metformin in healthy volunteers. Pharmacokinetic drug interaction studies with TRAJENTA DUO have not been performed; however, such studies have been conducted with the individual active substances of TRAJENTA DUO: linagliptin and metformin.

##### **Linagliptin**

##### *In vitro assessment of drug interactions:*

Linagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes. It is not an inducer of CYP isozymes.

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

##### *In vivo assessment of drug interactions:*

**Clinical data described below suggest that the risk for clinically meaningful interactions by coadministered medicinal products is low. No clinically significant interactions requiring dose adjustment were observed.**

Linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glibenclamide, simvastatin, 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).

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

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

**Thiazolidinediones:** 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, indicating that linagliptin is not an inhibitor of CYP2C8-mediated metabolism *in vivo* and supporting 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 multiple 200 mg oral doses of ritonavir increased the AUC and  $C_{max}$  of linagliptin approximately twofold and threefold, respectively. Simulations of steady-state plasma concentrations of linagliptin with and without ritonavir indicated that the increase in exposure will 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. Multiple co-administration of linagliptin with rifampicin, resulted in a 39.6% and 43.8% decreased linagliptin steady-state AUC and  $C_{max}$  and about 30% decreased DPP-4 inhibition at trough. Thus linagliptin in combination with strong P-gp inducers is expected to be clinically efficacious, although full efficacy might not be achieved.

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

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

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

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

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

## **Metformin**

Concomitant use not recommended

Alcohol

**Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic insufficiency.**

Iodinated contrast agents

In patient with  $\text{eGFR} > 60 \text{ ml/min/1.73m}^2$ , metformin must be discontinued prior to, or at the time of the imaging procedure and not be restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see section Posology and Special Warnings and Precautions).

In patients with moderate renal impairment, metformin must be discontinued 48 hours before administration of iodinated contrast media and not be reinstituted until at least 48 hours afterwards and only after renal function has been re-evaluated and has not deteriorated further (see section Interactions).

## **Combination requiring precautions for use**

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

## **Organic cation transporters (OCT)**

Metformin is a substrate of both transporters OCT1 and OCT2. Co-administration of metformin with:

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

## **Fertility, pregnancy and lactation**

### Pregnancy

There are no adequate and well-controlled studies in pregnant women with TRAJENTA DUO or its individual components. Non-clinical reproduction studies in pregnant rats performed with the combined products in TRAJENTA DUO did not indicate a teratogenic effect attributed to the **co-administration of linagliptin and metformin**.

There are limited data from the use of **linagliptin** in pregnant women. Non-clinical studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

There are limited data from the use of **metformin** in pregnant women. Metformin was not teratogenic in rats at a dose of 200 mg/kg/day associated with 4 times human exposure. At higher doses (500 and 1000 mg/kg/day, associated with 11 and 23 times human exposure), teratogenicity of metformin was observed in the rat.

As a precautionary measure, it is preferable to avoid the use of TRAJENTA DUO during pregnancy.

When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with TRAJENTA DUO but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of fetal malformations associated with abnormal blood glucose levels.

### Lactation

No studies on lactating animals have been performed with the combination of metformin and linagliptin. Non-clinical studies with the individual active substances have shown excretion of both metformin and linagliptin into milk in lactating rats. Metformin is excreted with milk in humans. It is not known whether linagliptin is excreted into human milk. TRAJENTA DUO should not be used during breast-feeding.

### Fertility

No studies on the effect on human fertility have been conducted for TRAJENTA DUO. No adverse effects of linagliptin on fertility were observed in non-clinical studies up to the highest tested dose of 240 mg/kg/day (> 900 times human exposure).

### **Effects on ability to drive and use machines**

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

### **Side effects**

The safety of linagliptin 2.5 mg twice daily (or its bioequivalent of 5 mg once daily) plus metformin has been evaluated in over 6800 patients with type 2 diabetes mellitus.

In placebo-controlled studies, more than 1800 patients were treated with the therapeutic dose of either 2.5 mg linagliptin twice daily (or its bioequivalent of 5 mg linagliptin once daily) in combination with metformin for  $\geq 12/24$  weeks.

In the pooled analysis of the placebo-controlled trials, the overall incidence of AEs in patients treated with placebo and metformin was comparable to linagliptin 2.5 mg and metformin (54.3% and 49.0%). Discontinuation of therapy due to AEs was comparable in patients who received placebo and metformin to patients treated with linagliptin and metformin (3.8% and 2.9%).

Due to the impact of the background therapy on adverse events (e.g. on hypoglycaemias), adverse events were analysed and displayed based on the respective treatment regimens, add-on to metformin, and add-on to metformin plus sulphonylurea.

The placebo-controlled studies included 7 studies where linagliptin was given as add-on to metformin and 1 study where linagliptin was given as add-on to metformin + sulphonylurea.

### **Tabulated summary of adverse reactions**

The following adverse reactions derived from the use of the linagliptin/metformin combination or the use of the monocomponents (linagliptin or metformin) in clinical trials or from post-marketing experience are shown in the table below. Undesirable effects previously reported with one of the individual components may be potential undesirable effects with TRAJENTA DUO even if not observed in clinical trials with this product.

<i>MedDRA System Organ Class terminology</i>	<i>Linagliptin and Metformin Adverse reactions</i>
Infections and infestations	<b>Nasopharyngitis</b> <sup>1,3</sup>
Immune system disorders	<b>Hypersensitivity</b> <sup>1; 3</sup> <b>Angioedema</b> <sup>4</sup> <b>Urticaria</b> <sup>2; 4</sup>
Metabolism and nutrition disorders	<b>Lactic acidosis</b> <sup>2</sup> <b>Vitamin B<sub>12</sub> decrease/deficiency</b> <sup>2</sup> <b>Hypoglycaemia (when linagliptin and metformin were combined with a sulphonylurea)</b>
Nervous system disorders	<b>Taste disturbance</b> <sup>2</sup>
Respiratory, thoracic and mediastinal disorders	<b>Cough</b> <sup>1; 3</sup>
Gastrointestinal disorders**	<b>Decreased appetite</b> <sup>3; 5</sup> <b>Diarrhoea</b> <sup>3; 5</sup> <b>Constipation (when linagliptin and metformin were combined with insulin)</b> <b>Nausea</b> <sup>3; 5</sup> <b>Pancreatitis</b> <sup>1,3</sup> <b>Vomiting</b> <sup>3; 5</sup> <b>Abdominal pain</b> <sup>2</sup> <b>Mouth ulceration</b> <sup>4</sup>
Hepato-biliary disorders	<b>Liver function test abnormal</b> <sup>2</sup> <b>Hepatitis</b> <sup>2</sup>
Skin and subcutaneous tissue disorders	<b>Pruritus</b> <sup>3; 5</sup> <b>Erythema</b> <sup>2</sup> <b>Rash</b> <sup>4</sup> <b>Bullous pemphigoid</b> <sup>4; 5</sup>
Investigations	<b>Lipase increased</b> <sup>3;†</sup> <b>Amylase increased</b> <sup>1, ψ</sup>

<sup>1</sup> Adverse reactions reported also in patients treated with linagliptin monotherapy

<sup>2</sup> Adverse reactions of metformin as monotherapy; refer to the Summary of Product Characteristics for metformin for additional information

<sup>3</sup> Adverse reactions of FDC linagliptin + metformin (pooled analysis of placebo-controlled studies)

<sup>4</sup> Adverse reactions identified from post-marketing experience with linagliptin

<sup>5</sup> Adverse reactions reported in patients who received FDC linagliptin + metformin and also in patients who received metformin monotherapy

<sup>\*\*</sup> Gastrointestinal disorders such as abdominal pain and nausea, vomiting, diarrhoea, decreased appetite occur most frequently during initiation of therapy with metformin hydrochloride and resolve spontaneously in most cases. To prevent them, it is recommended that metformin hydrochloride be taken in 2 daily doses during or after meals if administered as monotherapy.

<sup>§</sup> See also *Linagliptin cardiovascular and renal safety study (CARMELINA)* below

<sup>†</sup> Based on lipase increase >3 times ULN

<sup>ψ</sup> In the CAROLINA study comparing linagliptin with active comparator glimepiride (see section Clinical Trials) laboratory analysis of amylase showed increases to >3xULN in 0.99% of patients treated with linagliptin and in 0.54% of patients treated with glimepiride

In placebo-controlled studies the most frequently reported related adverse reaction for linagliptin+metformin was diarrhoea (1.6%) with comparably low rate on metformin+placebo (2.4%).

#### Adverse reactions reported when linagliptin and metformin were combined with SU:

When linagliptin and metformin were administered in combination with a sulphonylurea, hypoglycaemia was the most commonly reported adverse event (linagliptin plus metformin plus sulphonylurea 23.9% vs 16.0% in the placebo group) and identified as an additional adverse reaction under these conditions. None of the hypoglycaemias episodes were classified as severe (requiring assistance).

#### Adverse reactions reported when linagliptin and metformin were combined with insulin:

When linagliptin and metformin were administered in combination with insulin, hypoglycaemia was the most commonly reported adverse event, but occurred at comparable rate when placebo and metformin were combined with insulin (linagliptin plus metformin plus insulin 29.5% vs 30.9% in the placebo plus metformin plus insulin group) with a low rate of severe (requiring assistance) episodes (1.5% vs. 0.9%).

The combination of linagliptin and metformin when administered in combination with insulin may be associated with an increased risk of hepatic events

#### *Linagliptin cardiovascular outcome and renal safety study (CARMELINA)*

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

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

In the overall study observation period adjudicated acute pancreatitis was reported in 0.3% of patients treated with linagliptin and in 0.1% of patients treated with placebo.

In the CARMELINA study, bullous pemphigoid was reported in 0.2% of patients treated with linagliptin and in no patient treated with placebo.

## Overdose

### Symptoms

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

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin hydrochloride or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital.

### Therapy

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring and institute clinical measures as required. The most effective method to remove lactate and metformin hydrochloride is haemodialysis.

### **Availability**

Film-coated tablets of 2.5mg/500mg, 2.5mg/850mg and 2.5mg/1000mg

### **Pack sizes**

Ten x 1 film-coated tablet per aluminium blister strips.  
Cartons containing 6 blister strips (6 x 10 film-coated tablets).  
60's film-coated tablets in a HDPE bottle.

### **Storage conditions**

Do not store above 30°C.  
Store in the original package in order to protect from moisture.

Please refer to the packaging for information on shelf-life.

### **Manufactured by**

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

Or

Boehringer Ingelheim Promeco, S.A. DE C.V.  
Calle del Maíz No. 49  
Col. Barrio Xaltocan  
C.P.16090 Xochimilco  
Mexico City  
Mexico

for

Boehringer Ingelheim International GmbH

Ingelheim am Rhein  
Germany

Date of revision: 2 October 2022

**Store in a safe place out of the reach of children!**